

Advances in
**Heterocyclic
Chemistry**

Volume 93



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Preface

Volume 93 of *Advances in Heterocyclic Chemistry* commences with a survey of current Tröger's base chemistry by B. Dolensky, J. Elguero, V. Král, C. Pardo, and M. Valík in a joint publication from the Institute of Chemical Technology (Prague) and the Institute of Medicinal Chemistry, CSIC and the Department of Organic Chemistry of the Universidad Complutense (both of Madrid, Spain). Tröger's base was discovered in 1887, but the subject has undergone a significant revival in the last 20 years and it is on this period that the present review concentrates.

A.V. Gulevskaya and A.F. Pozharskii (Rostov State University, Russia) write on nucleophilic aromatic substitution of hydrogen, concentrated on the use of this reaction for heterocyclic ring annulation. It covers particularly the recent extension of the general S_NH reaction to effect ring annulation.

In a joint publication from Zelinsky Institute (Moscow) and East Ukrainian National University (Lugansk), V.P. Litvinov, V.V. Dotsenko, and S.G. Krivokolysko survey the chemistry of the six isomeric thienopyridines. This chemistry has attracted increasing attention recently.

Volume 93 closes with the eleventh installment in the series by A.P. Sadimenko (University of Fort Hare, Republic of South Africa). The present contribution deals with the organometallic chemistry of polypyridine ligands, which has attracted much recent interest, with almost half the references being from the last 10 years.

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Current Tröger's Base Chemistry

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I. Introduction

Carl Julius Ludwig Tröger (10 October 1862–29 July 1942) was born in Leipzig. When he was 25 years old he published what was to become one of the most important papers in stereochemistry: the synthesis of 2,8-dimethyl-6*H*-12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine, a compound now universally known as Tröger base (TB) **1** (Figure 1) (1887JPR225). The next milestone in the history of Tröger's base occurred in 1944. That year, just some years after the arrival of Vladimir Prelog to the Eidgenössische Technische Hochschule (ETH) (Figure 2, Sarajevo 1906,

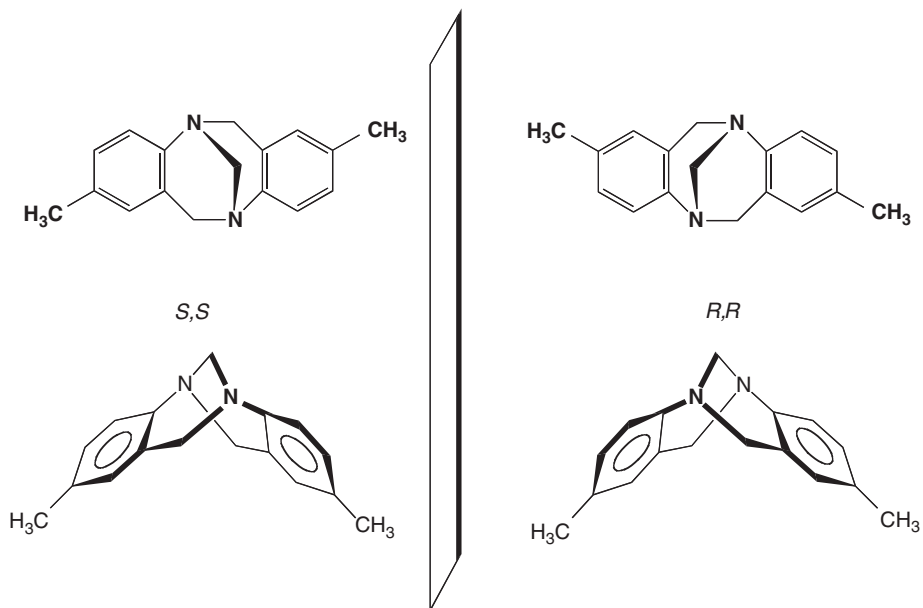


Figure 1. Tröger's base 1 showing its two enantiomers

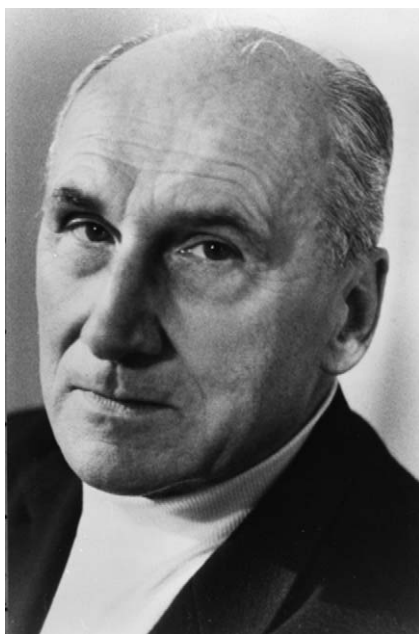


Figure 2. Vladimir Prelog

Zürich 1998, Nobel Prize in Chemistry 1975), he published the first of the many landmarks in stereochemistry that are identified with his name: the resolution of Tröger's base **1** into its mirror-image components by chromatography on a column of lactose hydrate (44HCA1127).

This review will summarize all references on Tröger's bases (TBs) until the end of 2005. There have been previous reviews on these compounds, one of the most significant being that of Demeunynck and Tatibouët (99MI1). In that review, 73 references were commented including those by the authors (generally published with Lhomme) that are of great importance in what concerns the biological aspects. There are other reviews on these compounds and some books in which TBs are discussed, such as those of Vögtle (92MI237), Bag (95MI279), and Sokolov (01RCB1339), as well as the books by Eliel and Wilen (94MI1), and Atwood (96MI1, 04MI1). Quite recently, some of us published a review entitled "Tröger's Base Derivatives – New Life for Old Compounds" (05SUP347) covering the topic with 116 references including several of 2005.

II. Historical Developments

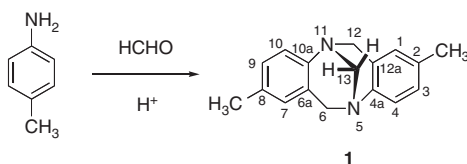
Tröger's base **1**, originally prepared from *p*-toluidine, and its derivatives have been known from 1887. Spielman elucidated the structure (35JA583), Wagner proposed a mechanism of formation (34JA1938, 35JA1296, 41JA832, 54JOC1862), whereas Prelog (44HCA1127) explored its chirality, and their coworkers pioneered the chemistry of **1** and its analogs. TB derivatives were initially viewed as anomalous chiral substances with two nitrogen-containing stereogenic centers. Until the 1980s, TB **1** was used mainly for the evaluation of new separation techniques (see Section V.B.2). Interest in TB derivatives has since grown, as the field of supramolecular chemistry, specifically molecular recognition, has evolved.

III. The Revival of Tröger's Bases

From 1985 onwards, Wilcox (Figure 3) published a series of 19 papers (85TL5749, 86AX(C)224, 86AX(C)253, 86AX(C)376, 86TL5563, 87JA1865, 88JA6204, 88JOC98, 89JA8055, 89MI1, 90JOC363, 91JA678, 91JA8554, 92JA1398, 92JA10189, 93CSR383, 94JA4497, 98JA11192, 02H515) that revisited the field of TBs. His contribution includes the famous Wilcox molecular torsion balance (94JA4497, 98JA11192) that allows measuring "intermolecular" interactions (see Section VI.E). Other groups that have contributed significantly to this field are those of Lhomme, Tatibouët, and Demeunynck in France (94MI637, 95TL1271, 96SC4375, 97BSF495, 97T2891, 97TL1567, 98MI128, 99CC161, 99MI1, 99MRC73, 00BBR(273)681, 01CSR70, 02EJM315, 02TL261, 04TL2863), Wärnmark in Sweden (98TL4565, 01S1873, 02JOC6008, 02S2761, 03EJO3179, 03JHC373, 04JOC5196, 05OL2019), Crossley in Australia (95JCS(CC)1077, 95JCS(CC)1925, 96TL6807, 97TA1161, 98CC11, 00PCCP4281, 01JCS(P1)2294, 05OBC852), and groups in Czech Republic (02CCC609, 03TL2083, 05OL67, 05SUP347, 05TA1969) and Spain (93AQ141,



Figure 3. Craig S. Wilcox

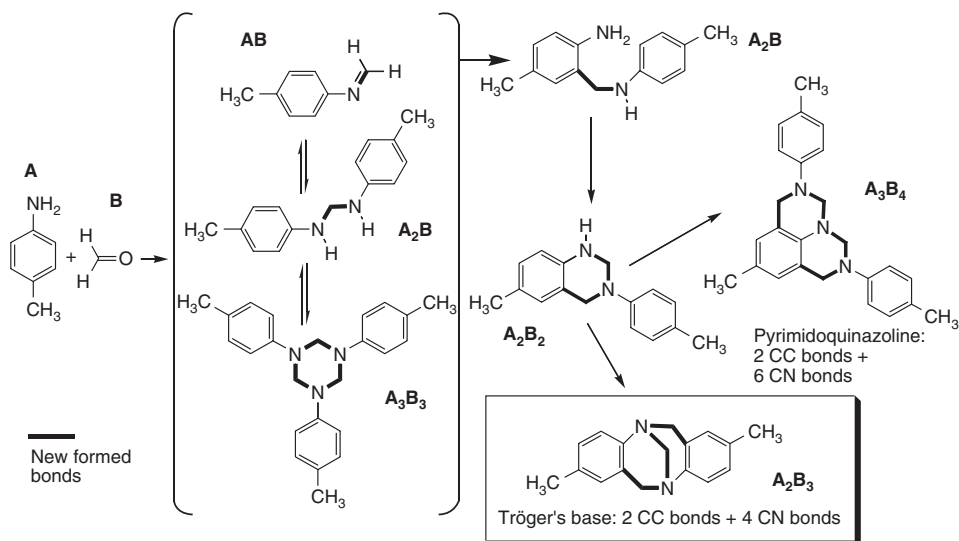
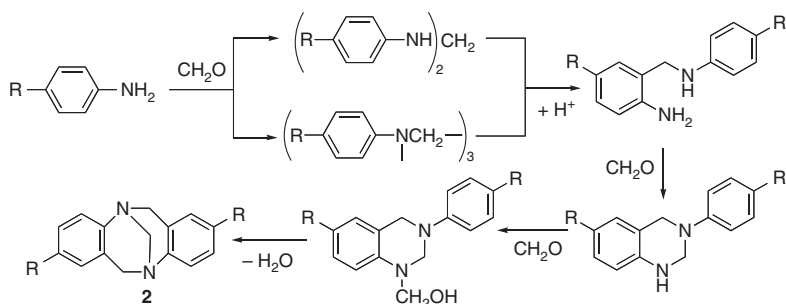


Scheme 1. Tröger's reaction of 1887

93JCS(CC)1713, 96MRC318, 96MRC708, 97T2233, 01JOC1607, 02MRC743, 03ARK(i)1, 04ARK(iv)86, 04EJO1097, 04MC235, 05HCA1199, 05MRC665, 06TA191). Analytical aspects were recently covered by Guiochon and Miyabe in USA (93JCH(637)13, 93JCH(637)19, 93JCH(637)37, 93MI2787, 98CHI375, 98JCH(813A)1, 99JCH(849A)445, 00AC5162, 00JCH(890A)211, 00MI617, 00MI719, 02JCH(944A)3, 02JCH(955A)35, 04MI611), and optical properties by Schanne-Klein and Hache in France (02CPL(362)103, 02CR(P)429, 02SM(127)63, 03JPC(B)5261, 03MI487, 04CP197).

In principle any aromatic or heteroaromatic amine can serve as a possible precursor of TBs. In **Scheme 1**, the synthesis of the original TB **1** from *p*-toluidine is represented.

Actually, this seemingly simple reaction is, from a mechanistic point of view, a rather complicated multicomponent reaction that involves two *p*-toluidine **A** and three formaldehyde **B** molecules (41JA832). Although TB **1** (**A**₂**B**₃) is the main product, other heterocycles have also been isolated (**Scheme 2**), some with more complex “stoichiometries” such as **A**₃**B**₄.

Scheme 2. Reaction of *p*-toluidine with formaldehyde

Scheme 3. Wagner's proposed mechanism of TB formation

IV. The Synthesis and Mechanism of Formation of Tröger's Bases

In 1887, Julius Tröger (1887JPR225) discovered that the condensation of *p*-toluidine and HCHO in the presence of HCl yielded a product of molecular formula $C_{17}H_{18}N_2$. The structure of this compound was the subject of investigation for nearly half a century (34JA1938). The correct structure **1** was established by Spielman in 1935 (35JA583). A few months later, Wagner reported the sequence of reactions by which **1** is formed (35JA1296) (**2**, $R = CH_3$, Scheme 3). Compound **1** has been prepared by many authors, for instance by Hesse and Hagel (76LA996). Other authors reported isolating the carbinolamines (N- CH_2OH) precursors of TBs **2** (05TL2149). This generated much interest, including re-examinations of mechanisms involving aromatic amine and HCHO condensations, over the next three decades (41JA832, 54JOC1862, 64MI389). The first synthesis of polysubstituted Tröger's

base analogs was published in 1948 by Smith and Schubert (48JA2656). These authors also demonstrated the necessity of strong acid conditions for the formation of Tröger's bases; dihydroquinazolines and tetrahydro-quinazolines being the major products in diluted hydrochloric acid. Quinazoline intermediates of the type A_2B_2 (Scheme 2) have been isolated (99H2193).

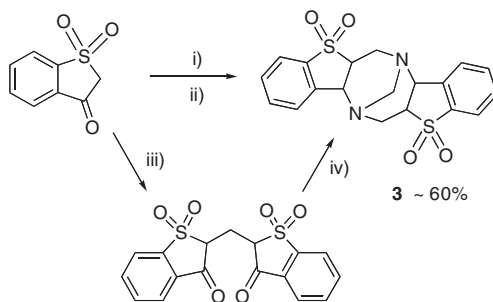
The formation of the methano[1,5]diazocine skeleton of TB involves an electrophilic substitution reaction. The various electrophilic reactive centers in the starting aromatic amine can, however, promote polymerization. To inhibit polymerization it is necessary for the aniline derivatives to have the *para* position blocked. In principle, the starting aromatic amines can be fully substituted except for one *ortho* position that is required for the desired cyclization reaction. Electronic and steric effects of ring substituents have been reported to influence the regiochemistry (88JOC98, 96TL6807, 97T2233, 99MRC73, 02JCS(P1)1963, 03TL2083), and yield (88JOC98) of this and related reactions.

The general preparation of TB derivatives is based on an acid-induced reaction of an aromatic amine with HCHO (88JOC98) or a formaldehyde equivalent, such as paraformaldehyde, hexamethylene-tetraamine (HMT) (91JA8554) or dimethoxymethane (95SC1849). Differences in methodology (93JCS(CC)1713, 95SC1849, 97T2233, 01S1873) and reaction conditions (03JHC373) afford varying yields of TBs. For example, 4-bromo-2-methylaniline furnished the corresponding TB derivative in 85% yield, using paraformaldehyde as a reactive agent. The corresponding yields on replacing paraformaldehyde with HMT or dimethoxymethane were 69% and 43%, respectively. The more common procedure with HCHO afforded no detectable product (01S1873). Using hexahydro-1,3,5-triazines or transforming them into iminium salts by a gas–solid reaction is an interesting procedure to prepare symmetric TBs, including **1** and the unsubstituted TB from anilines (00JPR(342)269).

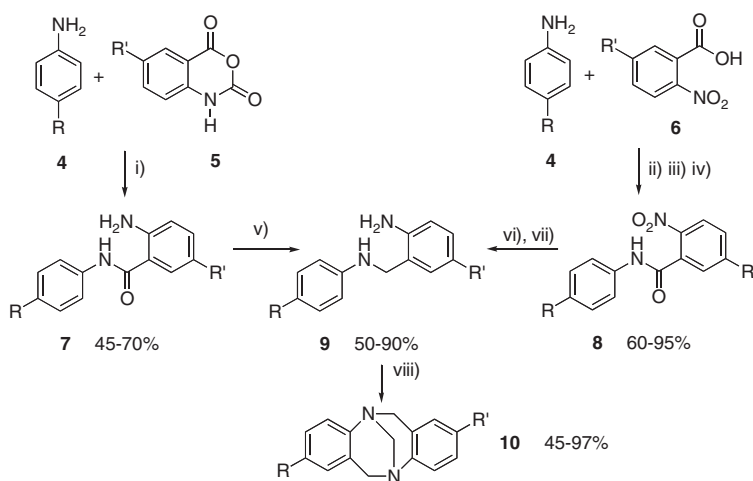
Alternative synthetic techniques towards TB derivatives were reported by Becker (93TL1889) and Čekavičius (01TL4239). Becker prepared a highly functionalized TB derivative by heating methyl 5-chloro-4-[(ethoxyoxoacetyl)amino]-2-methoxybenzoate in DMSO at 180°C. Čekavičius reported that the novel heterocyclic system **3** arose via the intermolecular Mannich reaction of 1,1-dioxo-1,2-dihydro-benzof[b]thiophen-3-one (Scheme 4).

A strategy for producing unsymmetrical TB derivatives is based on the Wilcox synthetic protocol (Scheme 5). The reaction of aniline **4** with the derivative of isatoic anhydride, 3,1-benzoxazine-2,4(1*H*)-dione **5**, or 2-nitrobenzoic acid **6** affords aminoamide **7** and nitroamide **8**, respectively. The reduction of **7** or **8** followed by a final cyclization reaction of bisamine **9** yields unsymmetrical TB derivatives **10** (90JOC363).

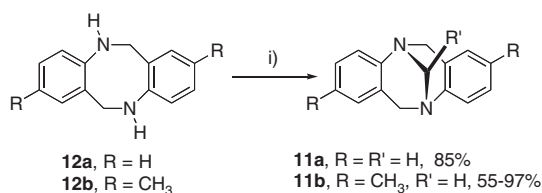
The unsubstituted TB **11a** cannot be prepared directly nor via the multistep sequence described in Scheme 5. As mentioned previously, the main complication in TB formation from aniline is oligomerization through the unsubstituted *para* position. Cooper and Partridge (55JCS991) overcame this problem with the use of intermediate 5,6,11,12-tetrahydrophenomazine **12a** (Scheme 6), which provided **11a** in 85% yield. In addition, 5,6,11,12-tetrahydro-2,8-dimethylphenomazine **12b** was



Scheme 4. Mannich reaction in the preparation of TB derivative **3**. Reaction conditions: (i) $(\text{CH}_2)_6\text{N}_4$, $\text{CH}_3\text{CO}_2\text{NH}_4$, $\text{CH}_3\text{CO}_2\text{H}$ or $\text{CF}_3\text{CO}_2\text{H}$; (ii) $(\text{CH}_2\text{O})_n$, $\text{CH}_3\text{CO}_2\text{NH}_4$, $\text{CH}_3\text{CO}_2\text{H}$; (iii) $(\text{CH}_2\text{O})_n$, EtOH; (iv) $(\text{CH}_2)_6\text{N}_4$, $\text{CH}_3\text{CO}_2\text{NH}_4$, $\text{CH}_3\text{CO}_2\text{H}$



Scheme 5. Preparation of asymmetric TB derivatives. Reaction conditions: (i) EtOH, reflux; (ii) DCC, DMF; (iii) benzene, oxallyl chloride; (iv) DMF, pyridine, rt; (v) BH_3 -THF, reflux; (vi) PtO_2 or Pd, H_2 , MeOH; (vii) LiAlH_4 , THF or Et_2O , reflux; (viii) HCHO, HCl



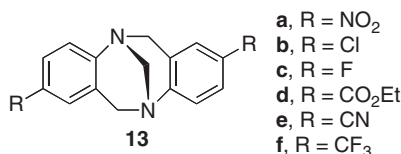
Scheme 6. Preparation of a TB derivative substituted at the endomethylene bridge. Reaction conditions: (i) $\text{R}'\text{CHO}$

used in the preparation of TB derivatives **11b** substituted at the endomethylene bridge ($R' = \text{alkyl or aryl}$) (57JCS2888).

A. MONO TRÖGER'S BASES

1. Simple Substituents

Recently Li et al. (05S1228) reported a new method to prepare TBs using DMSO and HCl as a formaldehyde equivalent. Although Becker, Finnegan and Collins had already used DMSO as a formaldehyde equivalent, their conditions were drastic (185–190°C) (93TL1889). With DMSO/HCl a series of TBs were prepared in good to moderate yields, including the 2,8-dinitro derivative **13a** and other TBs **13b–13f** bearing electron-withdrawing substituents. The interesting compound **13a**, a useful precursor for many syntheses, has also been prepared by another route (03TL2133), by reacting diglycolic acid or iminodiacetic acid with *p*-nitroaniline in PPA at 80°C for 12 h.



2. Heterocyclic Substituents

The intercalating ability of heterocyclic polyaromatics with DNA prompted the preparation and binding studies of methandiazocine-derivatized phenanthroline and acridine derivatives. These compounds are of great promise as DNA probes because of their different possible modes of interaction with DNA and due to their chiral properties. A preliminary molecular modeling study suggested that the binding of such probes to DNA should be enantioselective (94MI637). The geometry of the TB unit affords these molecules a helical shape, which can be similar or opposite to the helicity of DNA (99CC161). Yashima et al. (91CL1017) described for the first time the preparation of such a TB derivative (**14**, Figure 4) by the acid-induced reaction of 5-amino-1,10-phenanthroline with HCHO. A study of interactions with DNA revealed significantly higher changes in circular dichroism (CD) upon the addition of **14** as compared to the parent 1,10-phenanthroline. Moreover, the copper(I) complex of **14** caused nearly complete conversion of covalently closed-circular pUC18 plasmid into open-circular DNA.

Demeunynck et al. have investigated this aspect of TB chemistry in detail. The benzophenanthroline **15** (95TL1271), asymmetric and symmetric acridines **16** (95TL1271, 97T2891, 99MRC73) and acridino-phenanthroline **17a** (99MRC73) analogs were prepared and studied extensively by ¹H-NMR spectroscopy (Figure 4). This served to show the opposite relative chemical shifts of the *endo/exo* protons of the cyclic diazocine unit (99MRC73) (see Figure 21, Section VI.D).

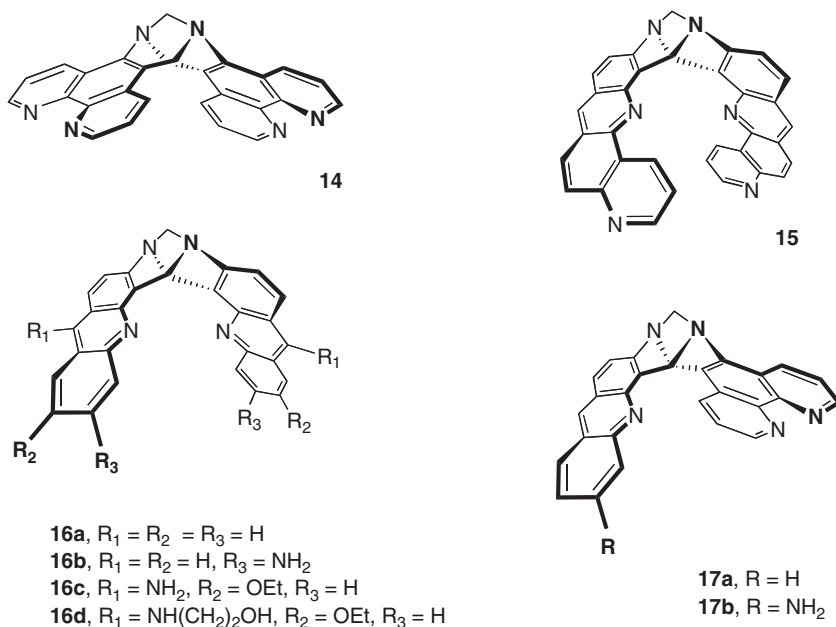


Figure 4. Heterocyclic polyaromatic TB analogs containing phenanthroline or acridine

The UV-visible spectrum of **16b** in the presence of calf thymus DNA shows changes in function of pH (99CC161). The authors noted that the interaction with DNA should be accompanied by protonation of the acridine moiety. The same conclusion was drawn from an analysis of the CD spectra of **16b** recorded in the presence of calf thymus DNA and in 3 M HCl solution. The liquid-liquid partitioning of racemic **16b** between an aqueous solution of calf thymus B-DNA and BuOH revealed that (–)-**16b** preferentially associates with calf thymus DNA. After vigorous stirring and phase separation, the BuOH layer afforded a CD spectrum similar to (+)-**16b**. The spectrum of the aqueous phase was similar to that of (–)-**16b** (99CC161). Thermal denaturation studies confirmed the enantioselective binding of (–)-**16b** to DNA (00BBR(273)681). The stabilization of poly(dA-dT)₂ and poly(dI-dC)₂ [which contains inosine residues instead of guanosines because of the very high stability of poly(dG-dC)₂] by the (–)-isomer during thermal denaturation studies was significantly greater than that by the (+)-isomer or the racemic (±)-**16b** mixture. Although acridine derivatives are known as strong DNA intercalators, electronic linear dichroism (ELD) indicated that the acridine rings of **16b** are not intercalated into DNA. In addition, unlike conventional intercalators, the ligand had almost no effect on the relaxation of DNA induced by topoisomerases. The lack of interference with the methylation of N7-guanidine residues of DNA suggested that the ligand interacts within the minor groove of the double helix.

Sequence selectivity was investigated by DNase I footprinting. The (+)-isomer of **16b** failed to inhibit DNase I cleavage, even at high concentrations. However, the (–)-isomer strongly protected certain sequences against cleavage by this nuclease

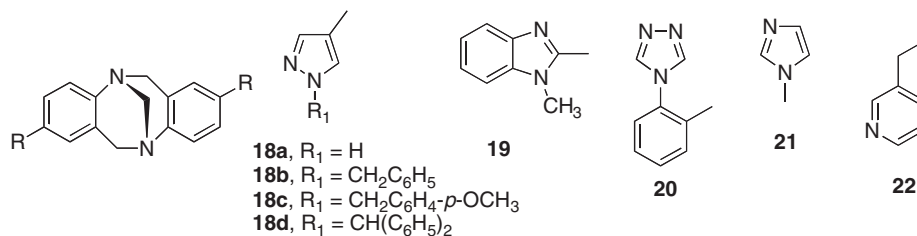


Figure 5. TB derivatives bearing aromatic heterocycles as substituents (**18–22**)

(00BBR(273)681). Compound (–)-**16b** recognized preferentially sequences containing both AT and GC base pairs, such as the motifs 5'-GTTAAC, 5'-ATGATCAT and 5'-GACGTTGTACAACGTC. The symmetric structure of **16b** complicated the analysis of the DNA binding data and mechanism. On the other hand, the DNA cleavage properties observed for the copper(I) complex of **14** (91CL1017) prompted the synthesis of an asymmetric acridine-phenanthroline TB analog **17b** (02EJM315). The spectroscopic data from the CD and ELD experiments were compatible with a bimodal binding process, implicating intercalation of an acridine ring coupled with groove binding of the phenanthroline moiety. The DNase/footprinting detected with the ligand **17b** was closer to that of phenanthroline analog **14** than to the parent acridine **16b**. The triplet sequences 5'-GTC-5'-GAC were deduced as providing an optimal binding site for compound **17b** (02EJM315).

The affinity for DNA observed for the phenanthroline TB derivative **14** (Figure 4) inspired some of us (93AQ141, 93JCS(CC)1713, 96MRC318) to develop heterocyclic TB analogs containing azole rings as substituents on the aromatic moiety (**18–21**) (Figure 5), or analogs bearing heterocyclic aromatics (see the following section).

The pyridine-extended TB derivative **22** developed by Johnson et al. (93JMC3202) exhibits very interesting results in the inhibition of the enzyme thromboxane A2 synthase (TxA2). The ED_{50} value (30 ng mL^{-1}) reported for this compound was comparable to ED_{50} values for TxA2 synthase inhibitors (sodium Furegrelate, Dazoxiben and OKY-1581) that had been extensively studied before.

3. With Heterocycles Instead of Benzene Rings

Different from the case of heterocycles as substituents (see preceding section), we will now discuss the case of heterocycles replacing the benzene rings of TBs, such as the compounds depicted in Figure 6 (**23–25**, **26a,b**) (67AG(IE)967, 93JCS(CC)1713, 96MRC318, 97T2233). All of the π -excessive amino heterocycles studied, including the amino derivatives of carbazole, pyrazoles, indazoles and benzothiazole, afforded the corresponding TB derivatives (**23–25**, **26a,b**), as would be expected from the reaction mechanism. The cyclization was always regioselective and occurred towards the *ortho* position contiguous to the heterocyclic ring; presumably, this represents the most reactive site towards electrophilic reagents (97T2233).

Quiroga et al. have described the synthesis of pyrazole **26c–g** and pyrimidine **27a,b** TB derivatives and suggested the mechanism of their formation from isolated intermediates (02TL5617, 02JCS(P1)1588). In this case, *C*-alkylation served to initiate

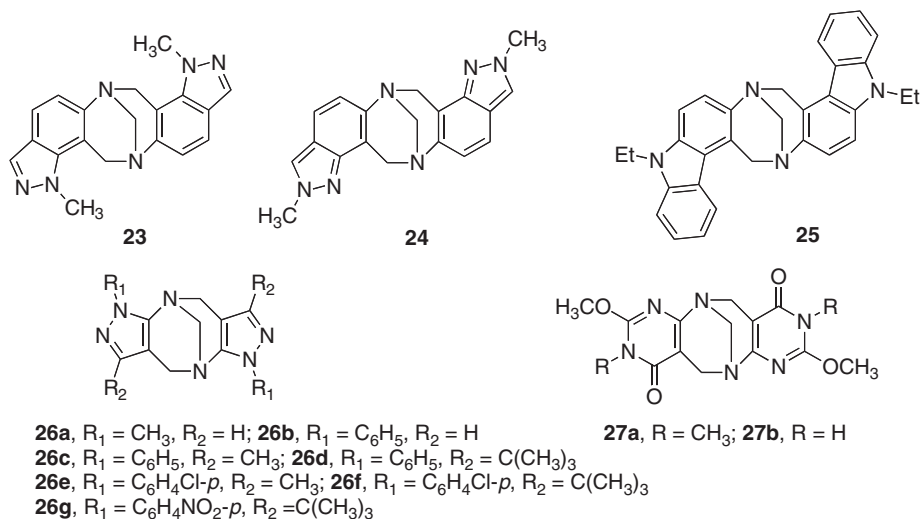


Figure 6. TB derivatives of indazole (**23**, **24**), carbazole (**25**), pyrazole (**26**) and pyrimidine (**27**)

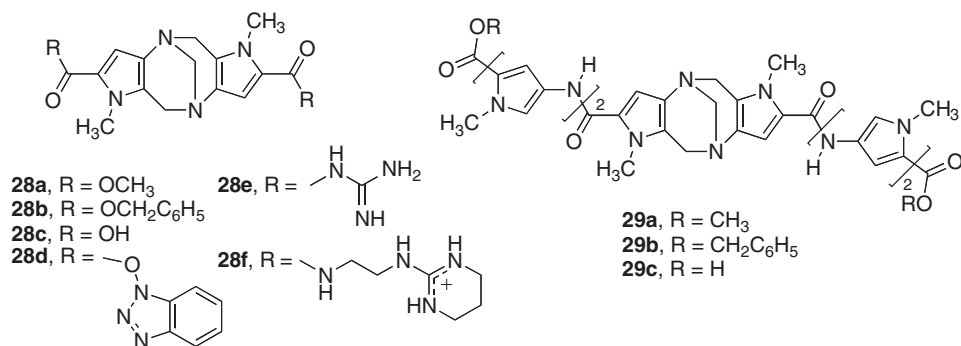


Figure 7. TB analogs of amino-*N*-methylpyrroles (**28**) and oligo *N*-methylamidopyrroles (**29**)

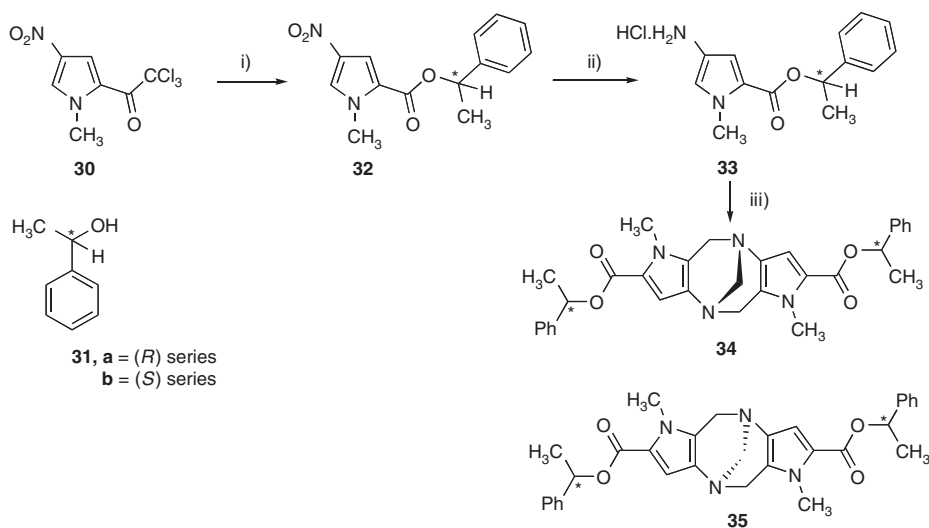
the reaction instead of Schiff base formation as proposed by Wagner (35JA1296) (Scheme 3).

The TB analogs **28a–f** (Figure 7) bearing a heterocyclic ring with functional groups, allowed for the construction of more advanced and selective systems (03TL2083). Along these lines, amino-*N*-methylpyrroles were chosen as starting materials. This choice was made because the species constitute building blocks of the natural antibiotics, e.g. distamycin and netropsin. These latter compounds bind in the minor groove of DNA with high affinity and specificity. The incorporation of the methanodiazocine scaffold into oligo *N*-methylamidopyrrole derivatives resulted in TB analogs of natural antibiotics **29a–c** that were obtained from dicarboxylic acid **28c** through an amide protocol. Preliminary experiments showed that the bisguanidine derivative **28e** and also bisacylguanidinium **28f**, exhibit affinity for DNA.

A subsequent paper (05TA1969) reported the preparation of four pyrrolo fused TBs, **34a**, **34b**, **35a** and **35b** from **33a,b** (no chiral induction was observed) (see reaction of **30**, **31a,b** and **32**). The absolute configuration of **34a**, $[\alpha]_D^{20} = -193$, was determined by X-ray crystallography. A CIAT experiment (crystallization-induced asymmetric transformation) allows the transformation of the crude mixture of **34b** and **35b** into pure **35b** (Scheme 7). The thiophene derivative **WADPIB** (03AX(E)o745) (see VI.A) also belongs to this section.

4. Porphyrin Derivatives

Crossley et al. (95JCS(CC)1077) covalently linked two tetraarylporphyrins through the methanodiazocine bridge of TB to prepare well-defined chiral cleft-containing molecules **36** and **37a,b** (Figure 8), whose molecular recognition properties could be



Scheme 7. Preparation of dipyrrolo[3,2-*b*:3',2'-*f*][1,5]diazozines. Reaction conditions: (i) NaH, THF, **31a** gave 88% **32a**, and **31b** gave 82% **32b**; (ii) Ni₂B, aq. conc. HCl, methanol, 99% **33a**, 97% **33b**; (iii) aq. CH₂O, rt, 20 h

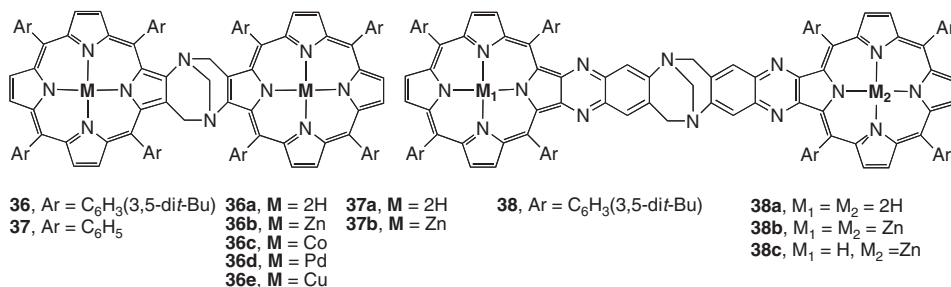


Figure 8. Porphyrin TB analogs and their metal complexes

monitored by electronic changes in the porphyrin system. Condensation of 2-amino-5,10,15,20-tetraarylporphyrin with CH_2O afforded bisporphyrin TB **36a**. Subsequent metalation of the porphyrin moieties of **36a** afforded zinc, palladium (95JCS(CC)1077), cobalt and copper (97TA1161) complexes (**36b–e**) with M–M distances of 8.4–9.0 Å, as extrapolated from the X-ray structure analysis of **37b**. The binding properties of **36b** to compounds that can exploit the two metal binding sites, such as α,ω -diaminoalkanes (95JCS(CC)1077) and histidine and lysine esters (95JCS(CC)1925), were studied by $^1\text{H-NMR}$ and UV–visible spectroscopy. 1,2-Diaminoethane displayed the greatest affinity ($K_a = 1.9 \times 10^8 \text{ M}^{-1}$) of the α,ω -diaminoalkanes tested. The affinities were found to be reduced upon extension of the alkyl chain. In the case of histidine and lysine benzyl esters, the L-form of the guests preferred the (+)-enantiomer of the host **36b** by factors of 9.2 and 2.8, respectively. L-lysine benzyl ester was bound less tightly to (+)-**36b** and (–)-**36b** than the benzyl and methyl esters of L-histidine (95JCS(CC)1925). The enantioselective recognition studies were later used for the resolution of racemic **36b** by chromatography on an L-histidine benzyl ester presaturated silica gel column. Surprisingly, the enantiomer (+)-**36b**, which has a stronger binding interaction with L-histidine benzyl ester, eluted from the column before (–)-**36b**. Moreover, the eluting fractions of the separated enantiomers (+)-**36b** and (–)-**36b** had different colors than the injected racemic material **36b**. The significant color change for (+)-**36b** indicated that (+)-**36b** was eluting as the (+)-**36b**·histidine complex, whereas the (–)-**36b** consisted mainly of the free compound. This suggestion is also in agreement with the rate of elution of (+)-**36b** and (–)-**36b** from the column, as the (+)-**36b**·histidine complex has a weaker interaction with the solid phase than free (–)-**36b**. This resolution technique was highly specific only for **36b** and the attempts to resolve **36c–e** by this column proved unsuccessful (97TA1161).

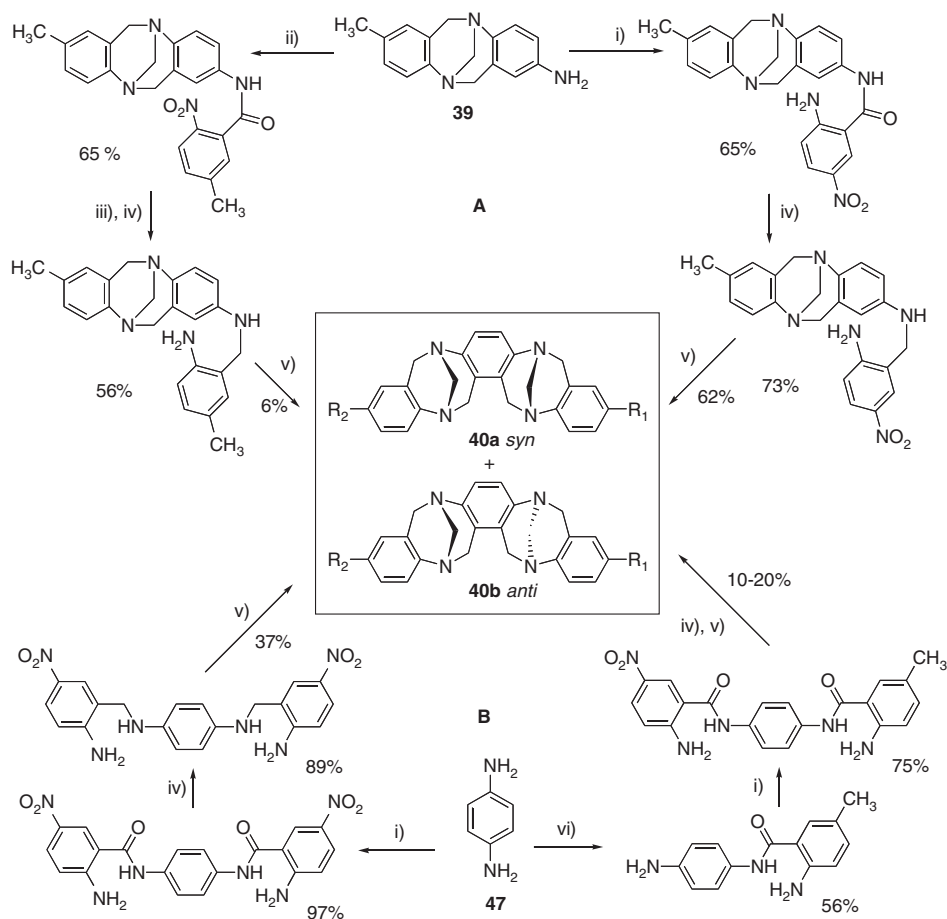
The configuration of **36b** makes it a suitable model for primary donor–primary acceptor (D–A) pairs of a bacterial photosynthetic reaction centre (PRC). However, the center-to-center distance of **36** is less than 9.0 Å, instead of the required 16.5 Å. To mimic the geometry of the D–A pair of PRC more closely, the porphyrin rings were separated by a quinoxaline-expanded bridge. The proper cavity size was achieved by the quinoxaline extension of the porphyrin rings to give quinoxalino-porphyrin TB derivative **38**. The center-to-center distance and also an intermolecular edge-to-edge shortest distance in the zinc(II) complex **38b** were determined by molecular modeling and conformed to distances found in the PRC by X-ray structural analysis (96TL6807). The photophysical characterization, intermolecular electronic energy transfers between the rigidly linked free-base porphyrins of **38a** and from the zinc (II) porphyrin to the free-base porphyrin of **38c** were investigated by steady-state absorption and emission spectroscopy, time-resolved fluorescence spectroscopy and semi-empirical calculations (00PCCP4281).

Like **36b**, compound **38b** was also found to bind ditopic α,ω -diaminoalkanes strongly. However, 1,7-diaminoheptane was the smallest guest that interacted with the receptor in a ditopic manner, exhibiting a 1:1 complex. The binding strength of larger guests was significantly higher. The affinity of **38b** to long ditopic ligands suggested the use of the quatropic ligand, *N,N,N',N'*-tetrakis-(3-aminopropyl)-butane-1,4-diamine, for the preparation of a molecular capsule with a tetraamine guest inside

the spherical dimer of **38b**. UV–visible monitoring of the titration of **38b** with the tetraamine, as well as $^1\text{H-NMR}$ studies, confirmed the initial formation of the expected 2:1 complex, which dissociated to two 1:1 complexes (two Zn-amine bonds and two free amine groups per complex) at higher ligand concentrations (98CC11).

B. MULTIPLE TB SYSTEMS

Compounds containing two (01JOC1607, 02CCC609, 04EJO1097, 04ARK(iv)86) and three (02CCC609, 04MC235, 05HCA1199, 05MI1) TB units have been reported recently. These bis- and tris-TB derivatives were prepared by a synthetic pathway similar to the Wilcox procedure for the synthesis of unsymmetrically substituted TB



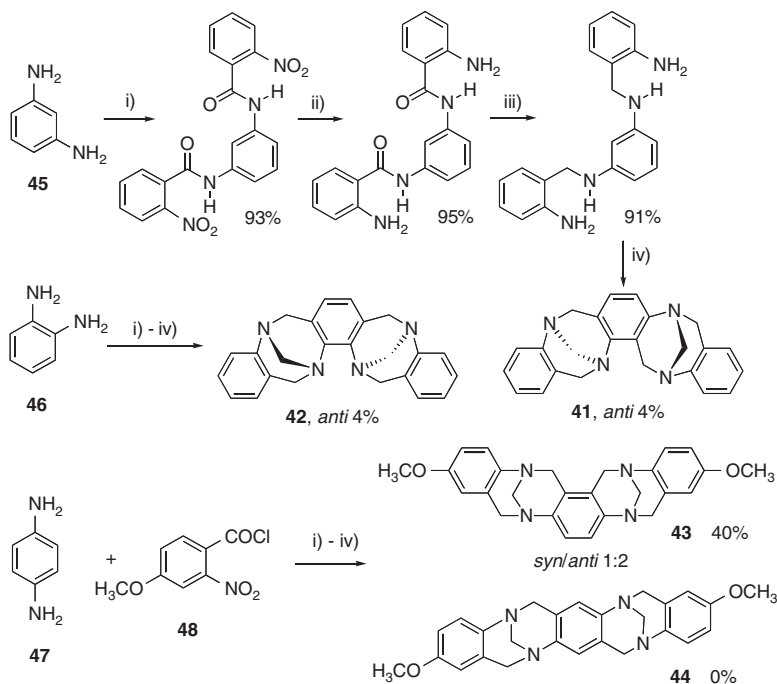
Scheme 8. Step-by-step and simultaneous preparation of bis-TB derivatives. Reaction conditions: (i) 6-nitroisatoic anhydride, THF; (ii) 5-methyl-2-nitrobenzoic acid, DCC, DMF; (iii) Pd/C, H_2 , $\text{CHCl}_3/\text{EtOH}$; (iv) $\text{BH}_3\text{-THF}$, reflux; (v) CH_2O , HCl, EtOH; (vi) 5-methyl-2-aminobenzamide, DCC, DMF

analogs (90JOC363). An original approach to bis-TBs introduced by some of us was based on the extension of amino TB derivative **39** with an additional TB unit, in a so-called TB-by-TB methodology (01JOC1607) (Scheme 8, pathway A).

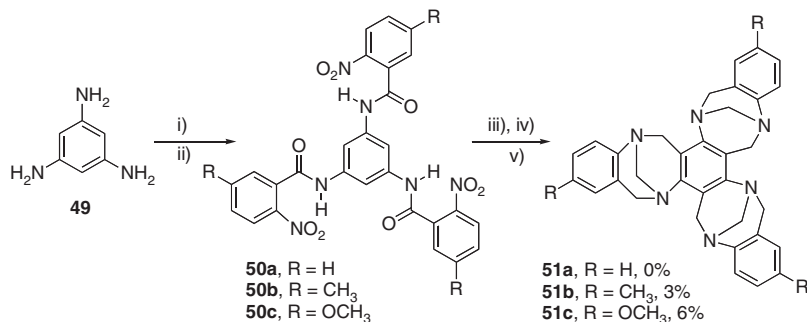
The synthesis of **39** requires five steps, the entire process involving eight or nine steps. The total optimized yield was 14% (for **40**, $R_1 = \text{CH}_3$, $R_2 = \text{NO}_2$).

An alternative shorter four-step procedure to prepare bis-TBs **41**, **42**, **43** and **44** has been reported (Scheme 9), and also tris-TB **51** from diaminobenzenes **45**, **46** and **47** and from 1,3,5-triaminobenzene **49** (02CCC609, 05MI1) (Scheme 10). Moreover, the simultaneous formation of the TB units on a central core may also be used for the preparation of multi-TB systems. It may seem that this methodology is limited only to the preparation of symmetrical oligo-TB derivatives. However, another report demonstrated that the simultaneous approach is also applicable to unsymmetrical bis-TB (04EJO1097) (see Scheme 8, pathway B). The overall yield in the preparation of **40** ($R_1 = \text{CH}_3$, $R_2 = \text{NO}_2$) was lower than that of the original step-wise method.

The racemization of bis-TB under different conditions has been studied as well as the first example of a *syn*-bis-TB, the tweezers-like isomer (05MI1). Concerning tris-TBs, the equilibrium between **51a-c** (the *syn,anti* isomer) and **52** (the *syn,syn* isomer) has been studied (05MI1). Compound **52** has a calixarene-type structure (Figure 9). The one-pot preparation of tris-TB **51c** by mixed "trogerization", similar to the



Scheme 9. Simultaneous formation of bis- and tris-TB derivatives. Reaction conditions: (i) 5-substituted-2-nitrobenzoyl chloride (**48**), pyridine, DMF; (ii) Pd/C, H_2 , MeOH, DMF; (iii) LiAlH_4 , dioxane, reflux; (iv) CH_2O , HCl, MeOH



Scheme 10. (i) 5-substituted-2-nitrobenzoyl chloride; (ii) pyridine, DMF, 12 h, rt; (iii) H₂, Pd/C; (iv) LiAlH₄; (v) CH₂O, HCl

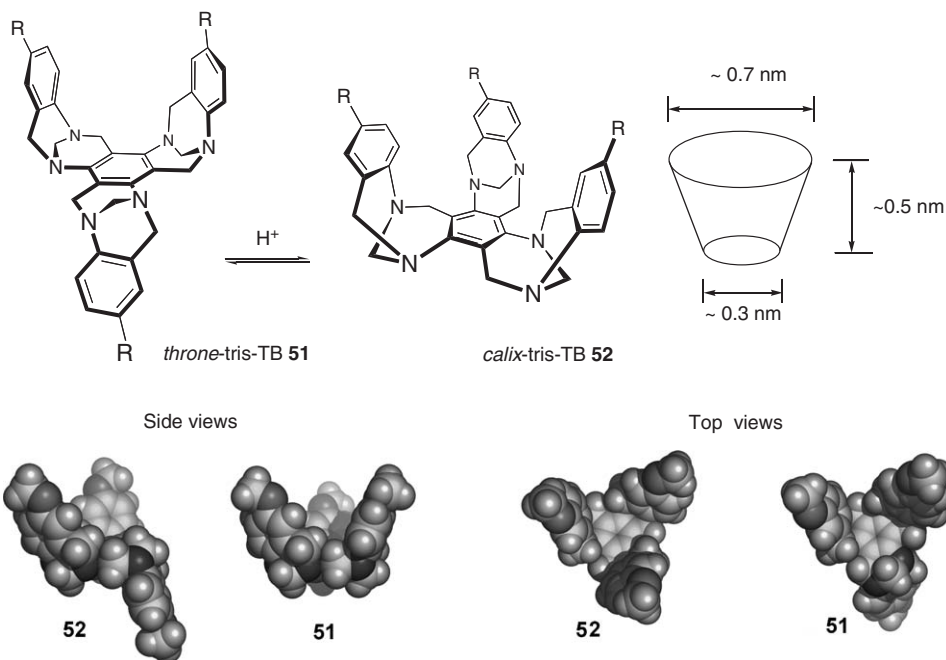


Figure 9. Conformation of tris-TBs **51** and **52**

preparation of oligo-TBs (**05OL67**) has been attempted (HMTA was used as a source of formaldehyde). The expected tris-TB **51c** was obtained in a 3% preparative yield (87% per formed bond) as the *throne* isomer. The *calix*-tris-TB was obtained by isomerization of the *throne*-tris-TB in 3% yield (**05M11**) (see structures **50a–c**).

The cyclization to form benzene-bridged bis-TBs is regio- and stereoselective. Out of the two possible regioisomers, only one isomer, whose central benzene ring is substituted in positions 1, 2, 3 and 4, was obtained (**Scheme 9**) (**01JOC1607**, **02CCC609**, **04EJO1097**, **04ARK(iv)86**). In the bis-TB systems, the *syn* configuration

("boat-like") is more attractive than the *anti* ("chair-like"), allowing for the construction of molecular tweezers. Moreover, some isomers of oligo-TB systems can provide "dish-like" configurations (e.g. *syn, syn* equivalent of **43**) resembling calixarenes. The reaction afforded unsubstituted (**41**, **42**) or methyl-substituted (**40b**, $R_1 = R_2 = \text{CH}_3$), bis- and tris-TB (**51**) derivatives only as *anti* diastereoisomers, whereas the nitro bis-TB derivatives **40** ($R_1 = \text{NO}_2$, $R_2 = \text{CH}_3$ or NO_2) were also obtained in the highly interesting reverse *syn* configuration **40a**.

The relative proportions of the separated diastereoisomers **40a** and **40b** ($R_1 = \text{NO}_2$, $R_2 = \text{CH}_3$), the only bis-TB derivatives prepared via both synthetic pathways (Scheme 8), were not identical in each of the methods. The "step-by-step" synthetic approach (01JOC1607) afforded a 4:1 mixture of isomers **40a** and **40b**. However, in the case of the simultaneous strategy (04EJO1097), a 1:1 mixture of isomers **40a** and **40b** was formed under reaction conditions nearly identical to those of the cyclization method. Only the *anti* diastereoisomer **40b** was isolated when the reaction temperature was reduced from 90 to 50°C. This difference in stereoselectivity during the formation of **40** ($R_1 = \text{NO}_2$, $R_2 = \text{CH}_3$) via similar reactions can only be explained by stereinduction of by-products, because in the reaction mixture the diastereoisomers **40a** and **40b** are in thermodynamic equilibrium due to the ready interconversion (racemization) of the methanodiazocine bridges in acidic media.

Another example of the all-TB-at-once protocol that gives excellent yields when the *para* position is occupied is summarized in Scheme 9 (05MI1). Starting from *p*-phenylenediamine **47** and the acid chloride **48**, bis-TB **43** (40% *syn:anti* 1:2) was obtained in a 35% overall yield. Moreover, it was shown that the *syn- to anti-bis-TB* ratio strongly depends on medium, e.g. the solvent used, and can be significantly driven by a template (05MI1).

In addition, the preparation of bis-TB by mixed condensation of anisidine and 1,4-phenylene-diamine with HMTA in TFA, [*i.e.*, via the oligomerization reaction recently published (05OL67)] was attempted. Under these conditions, only the expected common dimethoxy TB derivative was isolated (19%) and also both isomers of expected bis-TB (7%) in a 2:1 ratio.

Following the TB-by-TB methodology indicated in Scheme 8 (pathway A) and starting from bis-TBs **40a** and **40b** ($R_1 = \text{CH}_3$, $R_2 = \text{NO}_2$) four new tris-TBs **53**, **54**, **55** and **56** (Figure 10) were synthesized and unequivocally identified (04MC235, 05HCA1199). Compounds **53**, **54** and **55** were the first tris-TBs described and **53** (*syn, syn*) is the first example of a heterocyclic chiral molecular clip planned to be used in host-guest chemistry.

Wärnmark et al. have prepared two new tris-TBs **57** and **58** (both racemic, Figure 11) starting from the 2,6-dibromo derivative **2** ($R = \text{Br}$) (05OL2019, 06CEJ2692). The *anti, anti* diastereomer **58** is the first example of a characterized fused tris-TB with this configuration.

The preference of the *syn* or the *anti* configuration in the case of bis-TBs is a complex problem because it depends on the nature and position of the substituent on external aromatic rings. In general, both isomers are obtained, and that is the reason why the complexity of the mixtures in the case of tris-, tetra- and, obviously, longer poly-TBs should be considered (see Figure 12).

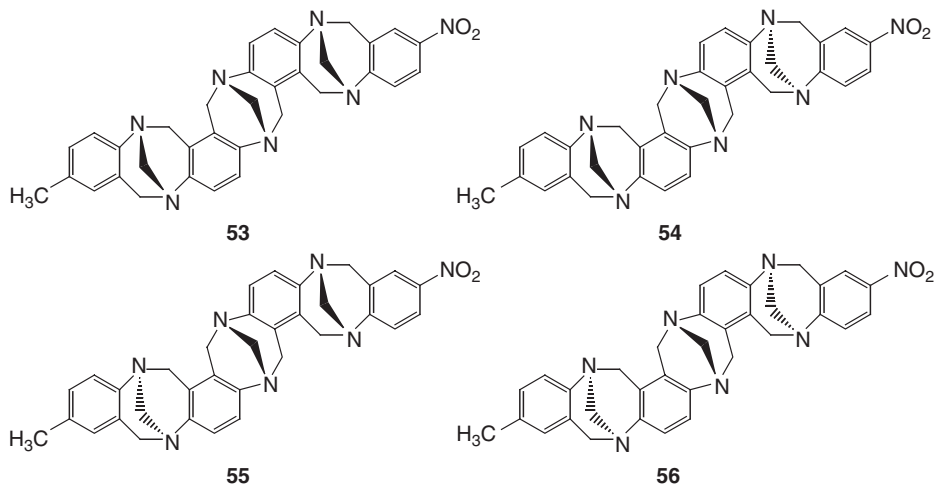


Figure 10. New tris-Tröger's bases

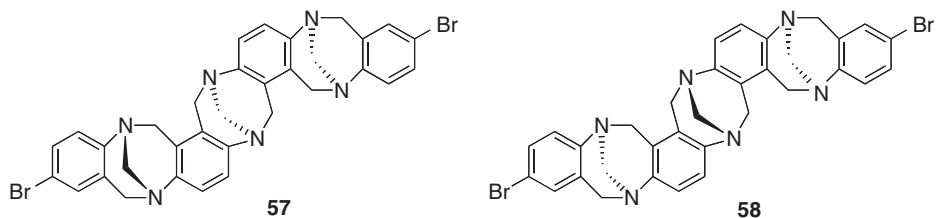


Figure 11. Tris-Tröger's bases

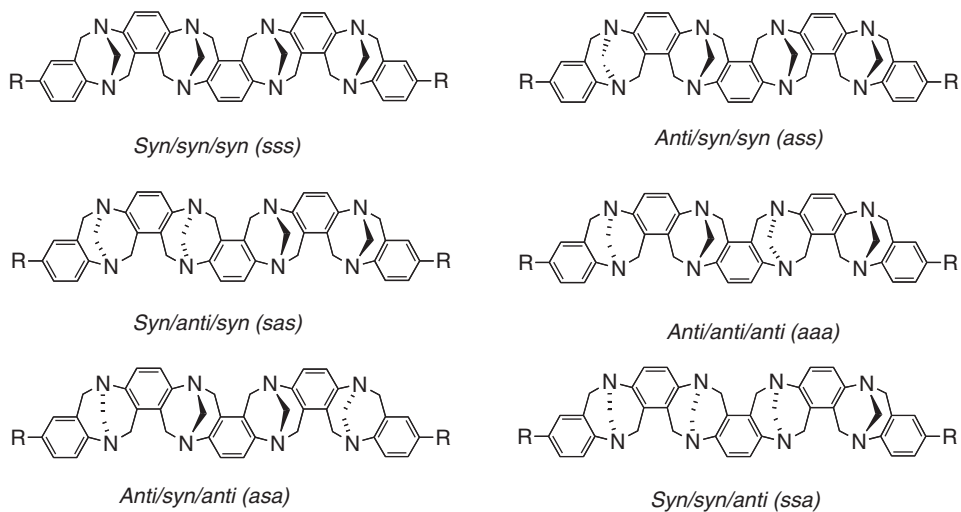
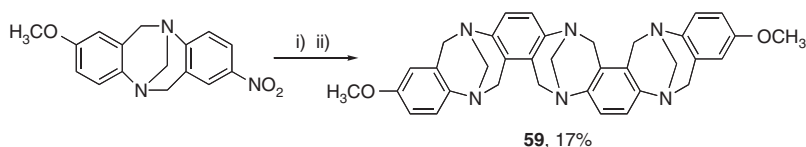
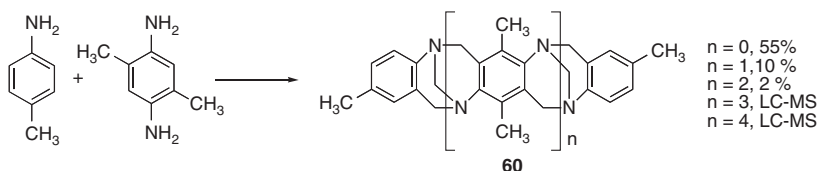


Figure 12. The six possible isomers of a symmetric (R identical) tetra-TB



Scheme 11. Stepwise preparation of linear tris-TB. (i) H_2 , Pd/C; (ii) HMT, TFA, $60^\circ C$



Scheme 12. One-pot preparation of oligo-TB. Reaction conditions: (i) HMT, TFA, $80^\circ C$

Very recently, some of us reported novel linear oligo-TB derivatives that exhibit interesting structural features (05OL67). These compounds possess cavitand-shaped binding sites. Effective new stepwise methodology for linear tris-TB **59** was reported (Scheme 11). All three possible diastereoisomers (*aa*; *sa*; *ss*) were described; two of them were isolated and the third was detected after racemization.

The regioselectivity during formation of these compounds is in agreement with the regioselectivity in the preparation of bis-TB. Importantly, for the first time an efficient one-pot reaction was used to prepare the oligo-TB **60** (see Scheme 12). The synthetic protocol allowed easy access to tetrameric (**60**, $n = 3$) and even higher order (**60**, $n > 3$) oligo-TB derivatives. This new finding should promote the design and study of novel chiral materials, with a wide variety of anticipated applications in materials science, organic and bioorganic chemistry.

In conclusion, there are several methodologies to prepare oligo-TB derivatives in a variety of yields. However, new synthetic strategies have to be discovered.

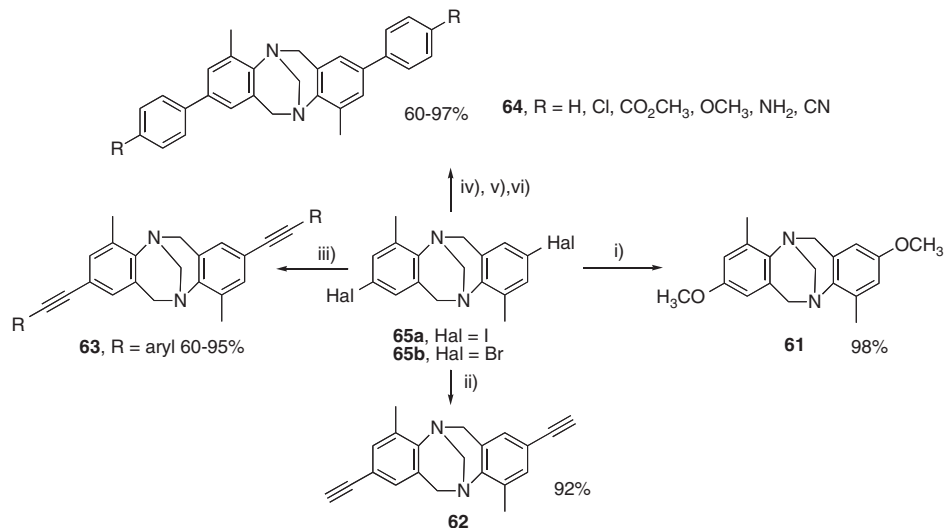
V. Reactivity of Tröger's Bases

The reactivity of TBs will be divided in three sections: classical, chiral resolution and organometallic complexes.

A. CLASSICAL REACTIVITY

The reactions of TB derivatives can be divided into the chemistry of the aromatic moiety and that of the methanodiazocine bridge. The former is based on the general reactivity of functional groups. Using cross-coupling conditions (Scheme 13), such as the Ullmann (04S1687) (pathway i for **61**), Corriu-Kumada (01S1873) (pathway ii for **62**), Sonogashira (02S2761) (pathway iii for **63**) or Suzuki (04S1687) (pathway iv or v, vi for **64**) reactions allowed the transformation of the 2,8-diiodo and

A. CLASSICAL REACTIVITY

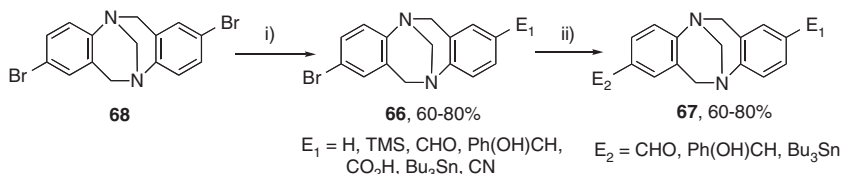


Scheme 13. Cross-coupling reaction on halogen TB derivatives. Reactions conditions: (i) NaOCH₃, CuCl; (ii) ethynylmagnesium bromide, Pd(PPh₃)₄; (iii) Pd(PhCN)₂Cl₂, P(*t*-Bu)₃, CuI; (iv) Pd[P(*t*-Bu)₃]₂, CsF, 4-substituted phenylboronic acid; (v) *n*-BuLi, THF, -78°C, then B(OCH₃)₃; (vi) Pd[P(*t*-Bu)₃]₂, CsF, 4-substituted iodobenzene

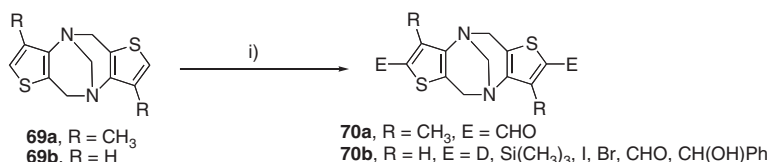
2,8-dibromo substituted TB derivatives **65**. The asymmetric mono- and difunctionalized TB derivatives **66** and **67** were prepared by electrophilic substitution of the lithium salt generated from the starting dibromo and monofunctionalized bromo **68** and **66**, respectively (02JOC6008) (Scheme 14). Diederich et al. reported the preparation of symmetrically and unsymmetrically substituted TB derivatives starting from dihalo compounds and metal-catalyzed cross-coupling reactions (05HCA2333).

An electrophilic substitution (02JCS(P1)1963) of the lithium salt of **69** has been used to prepare the thiophene difunctionalized TB analogs **70** (Scheme 15).

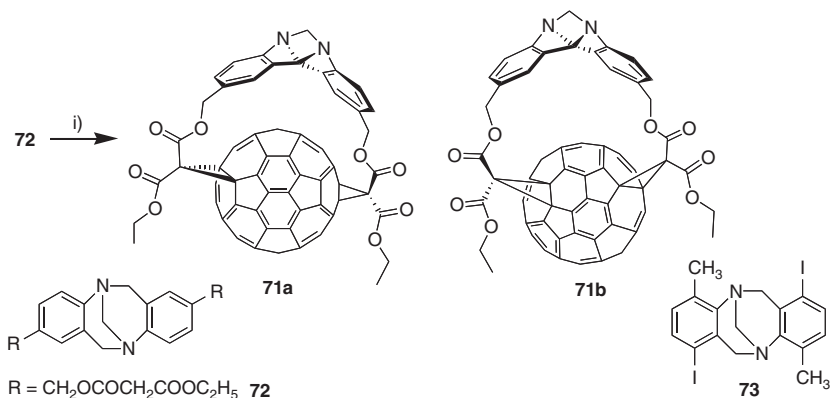
Sergeyev and Diederich (04AG(E)1738) reported a Bingel-type bicyclopropanation in the regioselective preparation of fullerene C₆₀ TB cyclic adducts **71** (Scheme 16). The synthesis of the bismalonate **72** from the corresponding diiodo-TB involves a series of classical aromatic reactions: 2,8-di-I → 2,8-di-CHO → 2,8-di-CH₂OH → **72** (05CEJ2284). The same sequence was carried out starting from the 1,7-diodo-4,10-dimethyl derivative **73**. The reaction with enantiomerically pure starting TB bismalonate **72**, diastereoselectively afforded adduct **71a**. Additionally, other bismalonate TB derivatives exhibited regio- and diastereoselectivity in the Bingel reaction with the fullerene C₆₀ (05TL109). Echegoyen, Diederich et al. (05CEJ2284) have reported several mixed TB and fullerene structures, including **71a** whose X-ray structure was determined. Wong and Diederich (06CEJ3463) extended these studies to the regio- and diastereoselective synthesis of bis- and tetrakisadducts of C₇₀ by directed remote functionalization using Tröger base tethers.



Scheme 14. Bromine–lithium exchange followed by electrophilic substitution. Reaction conditions: (i) *n*-BuLi, -78°C , electrophile (E₁); (ii) *n*-BuLi, -78°C , electrophile (E₂)



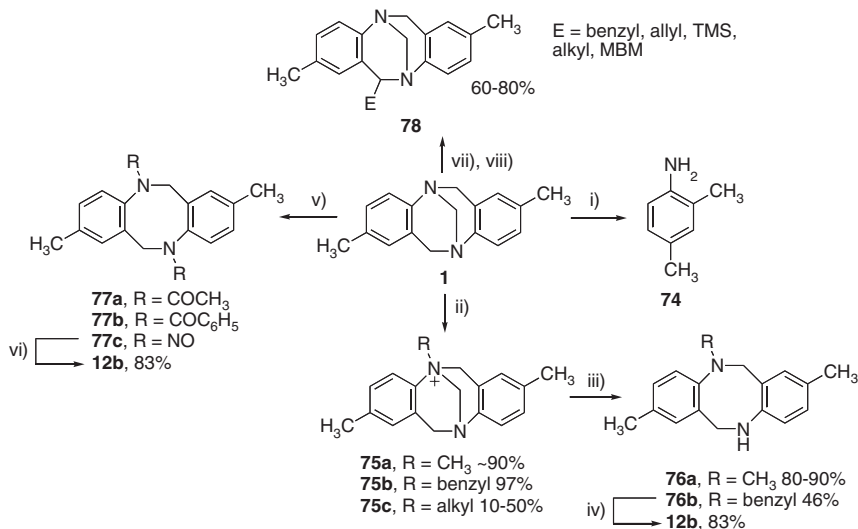
Scheme 15. Hydrogen–lithium exchange followed by electrophilic substitution. Reaction conditions: (i) *n*-BuLi, rt, electrophile



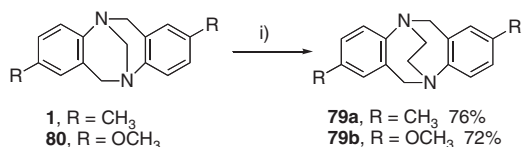
Scheme 16. Bingel reaction of bismalonate TB derivative **72** with fullerene C₆₀. Reaction conditions: (i) C₆₀, I₂, DBU, 0°C

Further reactions of the TB aromatic moiety include nucleophilic substitution (86TL5563); ester hydrolysis followed by ester (94JA4497) or amide (00JOC1907, 01JOC1607, 02H515) protocols; amidolysis (03TL2083); and reduction of the nitro (01JOC1607, 05HCA1199), amide (01JOC1607, 02H515, 04EJO1097, 05HCA1199) and benzyl ester (03TL2083) groups.

The methanodiazocine bridge of **1** is unaffected by sodium and boiling ethanol, and for the most part by Sn/HCl (35JA583). It is not oxidized by mercury oxide in Et₂O or by silver nitrate/ammonia. Degradation with HI/red-P at high temperature afforded 2,4-dimethylaniline **74** as a single isolable product (Scheme 17). An improved yield of the reduced product was achieved when **1** was first refluxed with HI and then reduced with Sn/HCl (35JA583).



Scheme 17. Reactivity of methanodiazocine part of TB **1**. Reaction conditions: (i) HI, red-P, 200°C; (ii) RX; (iii) OH⁻; (iv) Pd, H₂; (v) CH₃CO₂COCH₃ (for **77a**), C₆H₅COCl (for **77b**), HNO₂, HCl (for **77c**); (vi) CuCl/HCl; (vii) BF₃·Et₂O, *n*-BuLi, -78°C; (viii) electrophile



Scheme 18. Preparation of ethano-TB derivatives. Reaction conditions: (i) BrCH₂CH₂Br, Li₂CO₃, 105°C

Only a few reactions involving modification of the methanodiazocine bridge of TB have been described to date (see [Scheme 17](#) and [18](#)). The pK_a of the TB **1** mono-protonated salt has been determined to be 3.2 in 50% aqueous alcohol ([53RTC661](#)). Alkylation of **1** afforded only monoquaternary product **75** even in the presence of an excess of alkylating agent [[57JCS2888](#), [85JCS\(CC\)1578](#), [63HCA2970](#), [91JCS\(P2\)47](#)] (e.g. iodomethane, dimethyl sulfate, allyl and benzyl halides, etc.). Alkali treatment of **75** resulted in the fission of the endomethylene bridge and yielded the alkylamines **76** ([57JCS2888](#), [63HCA2970](#)). The catalytic hydrogenation of benzylamine **76b** gave the bis-secondary amine **12b** ([63HCA2970](#)). One example of enantioselective hydrogenation of ethyl pyruvate to ethyl lactate, over alumina supported Pt-metal catalysts in the presence of **1** has been reported ([95MI143](#)).

The acetylation, benzylation and nitrosilation of **1** were performed by Spielman in his original determination of the structure of TB **1** ([35JA583](#)). Reaction with acetic anhydride or benzoyl chloride yielded the diacetyl **77a** and dibenzoyl **77b** derivatives, respectively. Note that these reactions involved the loss of one carbon atom as

CH₂O. The dinitroso derivative **77c** was converted into the amine **12b** in high yield upon treatment with CuCl/HCl (57JCS2888). Metallation of **1** with *n*-BuLi in the presence of boron trifluoride etherate afforded an organolithium TB functionalized at a benzylic methylene position. Subsequent reaction with electrophiles furnished alkylation products **78** without loss of stereochemical integrity (96TL6267, 00TA2875).

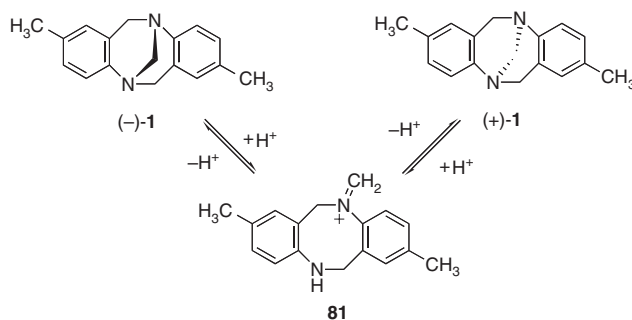
Hamada and Mukai synthesized the ethano-TB analog **79** via the reaction of **1** and its methoxy derivative **80** with 1,2-dibromomethane (Scheme 18). The endomethylene bridge was converted into endoethylene in greater than 70% yield (96TA2671).

B. CHIRAL RESOLUTION AND OPTICAL PROPERTIES OF TRÖGER'S BASES

1. Introductory Remarks

In general, the enantiomers of asymmetrically substituted compounds containing trivalent nitrogen cannot be resolved due to rapid pyramidal inversion at room temperature. Prelog and Wieland (44HCA1127) postulated that the inversion of **1** through the nitrogen atoms could be sterically discriminated by imposing ring strain. The effective resolution of (\pm)-**1** by liquid chromatography using a D-lactose column was one of the first examples of a chiral substance resolved chromatographically, and the first example of the resolution of an amine, wherein the chirality is solely due to stereogenic N-atom(s) with a very high inversion barrier. Although the resolution of (\pm)-**1** resulted only in a 5.5% isolation of both enantiomers from the racemate, optically active **1** was made available for study. The enantiomers (+)-**1** and (-)-**1** were found to be stable to the extent that they could be sublimed without any observable racemization.

However, racemization of TB is acid-catalyzed. The mechanism of TB racemization was suggested by Prelog and Wieland (44HCA1127) to proceed through the intermediacy of iminium ion **81** (see Scheme 19). The Gibbs free energy ΔG^\ddagger of acid racemization was estimated to be in the range 79.1–94.6 kJ mol⁻¹ (84JOC1127). This result is in accord with the inversion barrier (73JCS(P1)205) of diacyl **77a** and dibenzoyl **77b** (Scheme 17), reasonable models for the iminium intermediate **81** (Scheme 19).



Scheme 19. Proposed acid-catalyzed racemization of TB

Greenberg et al. (84JOC1127) examined the mechanism of acid-promoted racemization by NMR and UV spectroscopy at room temperature. However, only protonated forms of **1**, instead of the expected iminium ion **81**, were detected in acidic solutions of **1**. The fact that the NMR spectrum of monoprotonated **1** reflects C_2 symmetry indicates rapid proton exchange between the two bridgehead nitrogen atoms on the NMR time scale. On the other hand, the 13,13-dimethyl derivative of **1**, which easily loses acetone in dilute acid, was found to form an iminium ion in concentrated acid. The authors attributed this observation to the fact that the iminium ion **81** might be present in undetectable amounts during the acid racemization process involving **1**.

An enantioselective dynamic electrokinetic chromatography technique was used by Trapp et al. for determination of rate constants, enantiomerization barriers (ΔG^\ddagger (298 K) = 100.9 ± 0.5 kJ mol⁻¹) and activation parameters [ΔH^\ddagger (298 K) = 89.5 ± 2.0 kJ mol⁻¹, ΔS^\ddagger (298 K) = -42 ± 10 J mol⁻¹ K⁻¹] of **1** at pH 2.2 (02CEJ3629). Introduction of a permanent positive charge in TB **1** significantly decreased the enantiomerization, which is not in conflict with the iminium-based theory.

Absolute configuration of Tröger's base 1. The absolute configuration (AC) of Tröger's base **1** was first incorrectly assigned by Mason et al. (67JCS(B)553, 67TL137) using the analysis of the circular dichroism (CD) by means of the Exciton Coupling method. The X-ray analysis of a diastereomeric salt allowed Wilen et al. (91JOC485) to prove that the original AC assignment was erroneous and that the correct AC is (+)-(5*S*,11*S*) [(-)-(5*R*,11*R*)]. Indeed, application of the exciton chirality method to Tröger's base has led to a wrong assignment because the direction of polarization of the considered transitions has not been correctly established. The specific rotation of Tröger's base **1** is $[\alpha]_D^{20} = +280$ (*c.* 0.5, hexane) (44HCA1127) and $[\alpha]_{589}^{25} = +287$ (*c.* 0.29, hexane) (91JOC485). Some of the structures reported in Scheme 21 correspond to pure enantiomers, like **AXAGEL** [1-(+)-5*S*,11*S*] (04HCA279) and **DEFQAG** (98TA4151). The specific rotations of some dipyrrolo derivatives **34** and **35** of known absolute configuration have been reported (05TA1969) (Scheme 7).

In a series of remarkable papers, Stephens, Devlin et al. established that Wilen assignment is the correct one by calculating the VCD (Vibrational CD) and OR (Optical Rotation) of **1** (Figure 1) by means of the DFT/GIAO approximation (99CC361, 00CHI172, 01JOC3671, 01JPC(A)5356). It is important to understand that there are two OR values: the $[\alpha]_D(0)$ at zero frequency (static) and the $[\alpha]_D$ (dynamic) (01JPC(A)5356, 05CPL163). The second one is the value that has to be compared with the experimental result, but it is usually computationally prohibitive (03JOC5186). Wong and Diederich (06CEJ3463) made an extensive use of CD in their paper on fullerene-TB mixed compounds.

The calculated $[\alpha]_D$ for **1** (5*R*,11*R*) is -341.5 (aug-cc-pVDZ) and -319.8 (6-311++G(2s,2p) [the calculated $[\alpha]_D(0)$ are -242.3 and -224.0 , respectively]. The last value is in excellent agreement with the experimental result (91JOC485). Italian authors (03JOC5186) have tried unsuccessfully to use small basis sets with **1** only to have a moderate success with an acridine derivative similar to **NIHMEW** (Scheme 21): experimental $[\alpha]_D = 4800$ (04HCA279), calculated (6-31G*) $[\alpha]_D = 2384$ (03JOC5186).

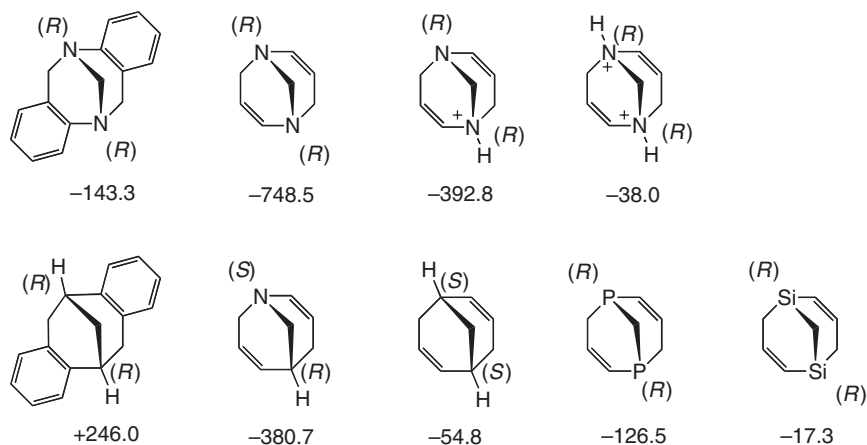


Figure 13. Calculated optical rotation values

Using the computational level recommended [B3LYP/6-311++G(2s,2p)] we have first calculated the $[\alpha]_{\text{D}}(0)$ value for compound **1** [-220.2, lit.: -224.2, (01JPC(A)5356)] (06TA191) as well as those of a series of related molecules (Figure 13).

Note, in some cases, the changes in the *R/S* notation although all the molecules of Scheme 18 have similar structures and the inversion of sign of $[\alpha]_{\text{D}}$, when compound **2-R,R** (-143.3) is compared with the corresponding carbocycle (+246.0). Although it has been postulated that the high $[\alpha]_{\text{D}}$ values of TBs are related to both the skeleton rigidity and the presence of aromatic rings (03JOC5186), it is clear that the aromatic rings are not necessary (compare the values, -143.3 with -748.5, for the first and second structure of Figure 13).

2. Chiral Resolution of Tröger's Base

TB **1** is one of the classic compounds used for studying the separation properties of chiral sorbents (for a review see 01CHI403). As mentioned earlier, enantiomers of **1** were first separated by liquid chromatography on an α -D-lactose stationary phase in 1944 (44HCA1127). Very good resolution of (\pm)-**1** was achieved on a cellulose triacetate (CTA) system (73MI277, 80JCH(193)308, 93JCH(637)37, 98JCH(813A)1, 00JCH(888A)73, 03MI239). The thermodynamics of the adsorption (93JCH(637)37) and mass transfer kinetics (98JCH(813A)1) of **1** on this phase with EtOH as the solvent were investigated by Guiochon and coworkers using frontal analysis (02JCH(944A)3). For both enantiomers, the adsorption enthalpies and entropies decrease with increasing temperature in the interval of 30–40 °C. The opposite trend holds true for Gibbs free energies (93JCH(637)37). Recently, the separation of (+)-**1** and (-)-**1** on CTA was applied by Morbidelli et al. as a model system for simulated moving bed (SMB) chromatography (00JCH(888A)73, 00MI1530, 02MI69, 99MI3735, 99MI381). Chromatographic enantioseparation of TB **1** has been performed on (3,5-dimethylphenyl)carbamate and 4-methylbenzoate derivatives of

polymer, consisting of only 2,5-anhydro-D-glucitol units, i.e., (1-6)-2,5-anhydro-D-glucitol as a chiral stationary phase for HPLC (98JPS(A)901). Similar studies based on α -D-glucopyran and α -D-mannopyran have been reported (01MI27, 02CHI498). The optically active polymer derived from 1-(3-pyridyl)dibenzosuberyl methacrylate exhibited chiral recognition ability toward **1** (98MI635). An improved apparatus for solid-liquid multi-stage counter-current extraction was developed. Using (\pm)-TB as a racemic model compound, it was demonstrated that the present technique is a powerful tool for continuous enantioseparation (03JCH(1017A)63). To elucidate chiral recognition difference between pairs of enantiomers of (\pm)-**1**, Oguni et al. (96CHI372) determined the ^{13}C nuclear spin-spin relaxation times in the presence of Chiralcel OJ (see Section VI.D). Optically active (*R*)(+)-4-(1-(1-naphthyl)ethyl-carbamoyloxy)phenylacetylene was shown high chiral recognition with regard to racemic **1** (96MI139).

Methods leading to the enantioseparation of (\pm)-**1** were also developed by using (+)-poly-(triphenylmethylmethacrylate) (81CL835, 99MI2772), *trans*- and *cis*-tris(4-phenylazophenyl-carbamate) (86CL983) and a steroidal glycoside (96JCH(724A)285) as chiral selectors in high-performance liquid chromatography (HPLC) or capillary electrochromatography (CEC), respectively. Other results dealing with TBs and capillary chromatography can be found in references (02MI462, 03MI2508). The application of supercritical fluid chromatography (SFC) and gas chromatography (GC) techniques to modified cyclodextrins (Chirasil- β -Dex) (91AG(E)987, 00JA1424) and the simulated moving bed (SMB) separation of (+)-**1** and (-)-**1** on amylose carbamate derivatives (Chiralpak-AS) (01JCH(908A)185) have also been reported. High levels of resolution (enantioselective factor $a = 4.8 \pm 0.2$) of **1** were achieved by molecular imprinting of (+)-**1** and (-)-**1** to methacrylic acid-ethylene glycol dimethylacrylate copolymers. The polymers prepared in the presence of (+)-**1** or (-)-**1** demonstrated a distinct preference for (+)-**1** or (-)-**1**, respectively. In the case of the reference polymer, involving copolymeration with (\pm)-**1** as a template, no enantioselectivity was observed (99MI363). TBs have been used to test new chiral stationary phases for HPLC resolution of enantiomers (86CL515) as well as for testing optical rotation detectors (01JCH(939A)41). The enantioselective adsorption of **1** was investigated on cellulose tris(3,5-dimethylphenylcarbamate) membrane supported on a teflon membrane filter (92CL1959). Molecularly imprinted polymers (MIPs) selective for TB have been designed and synthesized, and used for their HPLC; baseline separation of racemic TB was readily achieved, and enantioseparation factors (a) of up to $4.8^\circ \pm 0.2$ were obtained (01ACA(435)115).

For many years it was asserted that the resolution of enantiomers of **1** by diastereomeric salt formation with chiral acids was not feasible because of the ready racemization of the partially resolved salts in acidic media. The first success in resolving (\pm)-**1** with an acid resolving agent was described by Wilen et al. (91JOC485). Reaction of (\pm)-**1** with (-)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate **82** in EtOH yielded the diastereomeric salt (+)-**1**·(-)-**82** in a surprising 93% yield; 186% based on the amount of (+)-**1** in the racemate. The authors interpreted this finding as involving conversion of the (-)-**1** to (+)-**1** during formation of the precipitated diastereomeric salt (+)-**1**·(-)-**82**, which is in accord with the facile

racemization of TB derivatives in acid medium (44HCA1127). In other words, the resolution was supported by a crystallization-induced asymmetric transformation (CIAT) of the diastereomeric salt. The CIAT of diastereoisomers with covalently bound resolving groups (2-phenylethyl, Scheme 7) was recently achieved via crystallization from HCl/H₂O/CH₃OH system (05TA1969).

3. Chiral Resolution and Chiral Induction of TB Analogs

In 1966, Metlecsics and coworkers (66JOC3356) observed a diastereoselective formation of phenyl- substituted TBs. Although TB analogs are chiral and their formation is not enantioselective, there have been relatively few reports of their resolution. Hamada and Mukai enantioseparated (\pm)-ethano-TB **79a** via diastereomeric salt formation using optically active di-*p*-toluoyl-tartaric acid in acetone. The attempted resolution of its methoxy derivative **79b** failed under the same as well as modified conditions (96TA2671). Application of this procedure to resolve the naphthyl TB derivative proved successful only under anhydrous conditions (98TA4151). The resolution of a proflavine TB analog was achieved by crystallization with dibenzoyl tartaric acid. The enantiomeric excess (*ee*) of the separation was *c* 80% (determined by NMR) (99CC161). Crossley and coworkers resolved the dizinc(II) bisporphyrin TB analog by chromatography over preabsorbed L-histidine benzyl ester on silica gel (97TA1161). Kostyanovsky et al. (03MC111) have described a case of spontaneous resolution of a TB and later Lenev, Kostyanovsky et al. described the absolute configuration of TBs using X-ray diffraction and CD (06TL319).

An elegant synthesis to form optically pure TB analogs via diastereoselective cyclization of a chiral precursor was described by Webb et al. (91JA8554). Maitra et al. reported chiral induction of a 7-deoxycholic acid template in the preparation of diastereoisomers **83** and **84** (Figure 14) (95JCS(P1)2049, 92JOC6979). As the two diastereoisomers have different orientations in space, the authors expected that the spacer lengths linking the two aniline fragments to the steroid would influence the stereoselectivity during the preparation of **83** and **84**. Systematic alteration of the

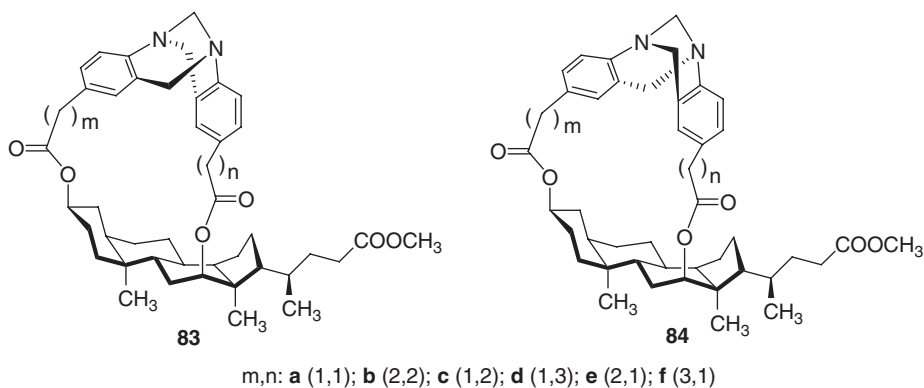


Figure 14. Diastereoisomers of steroid TB derivative

spacer lengths provided the most affected isomer, (*S,S*)-**83c**, in 75% yield with 70% diastereoselectivity (95JCS(P1)2049). However, it was impossible to separate the diastereoisomeric mixture by chromatography, even using a C₁₈ HPLC column. Only slow crystallization of the mixture from EtOH afforded a small amount of the pure diastereoisomer **84a** (92JOC6979).

An excellent example of the use of the TB moiety as a chiral auxiliary in asymmetric synthesis is the preparation of the above-mentioned fullerene TB derivative **71a**. The high asymmetric induction in the addition of **72** to fullerene C₆₀ was attributed to the relatively large distance between the two reacting fullerene bonds spanned by the TB tether (04AG(E)1738). Sicker et al. used **1** for discrimination of enantiomeric cyclic hemiacetals and methylacetals finding a weakly discriminating effect (94MRC727).

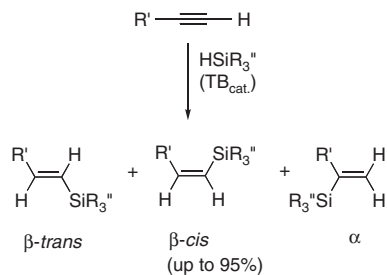
C. ORGANOMETALLIC COMPLEXES

Despite its chirality, little has been done to exploit TB as a chiral ligand. Xu et al. (98TA1651) tried to use (-)-**1** as a chiral ligand in 1,4-addition of aryllithium reagents to α,ω -unsaturated *tert*-butyl esters. Harmata and Kahraman reported the asymmetric induction of (+)-**1** in the addition of diethylzinc to aromatic aldehydes. However, the enantioselectivity was poor (*ee* 7–22%). The higher *ee* of the product (up to 86%) was achieved by the modified TB chiral ligand (+)-**78** (E = CH₂OCH₂CPh₂OH) (00TA2875). Cadmium(II) complexes of TBs have been reported (87MI503).

The nitrogen atom of TB is able to form a donor–acceptor bond with heavy metals such as rhodium, iridium (95TL369) and mercury (00RCB1241) via the nonbonding *sp*³ orbital. Goldberg and Alper (95TL369) reported that addition of an ethanolic solution of **1** to a solution of rhodium(III) or iridium(III) chloride in EtOH at room temperature, resulted in the formation of a pink solid and dark-violet powder, respectively. ¹H-NMR spectra and elemental analysis showed that both nitrogen atoms are coordinated to metal atoms, resulting in the formation of complexes of the general formula **1**·2MCl₃. Both complexes were air stable and nonhygroscopic. Their catalytic activity was tested on the hydrosilylation of terminal alkynes. This reaction can afford the normal *syn*-addition product (β -*trans*-alkenylsilane) and the thermodynamically less stable *anti*-addition product (β -*cis*-alkenylsilane), as well as the α -isomer (Scheme 20). The rhodium(III) complex readily catalyzed the addition of various silanes to terminal alkynes. The *anti*-addition product was formed in some cases with selectivities up to 95% (95TL369).

The TB (+)-**1** adduct of methyltrioxorhenium [(+)-ReO₃CH₃], characterized by its crystal structural and spectroscopic data, was reported by Herrmann et al. The catalytic properties of this complex were tested in the epoxidation of olefins and the oxidation of sulfides. However, no enantioselective reactions of the pro-chiral olefins and sulfides were observed (97JOM(538)203).

Elimination of the endomethylene bridge in **1** leads to the eight-membered cyclic diamine **12b** with the vibrational freedom of the two methylene carbons restricted by their being a part of the aromatic rings. Although the axial positions in the



Scheme 20. Hydrosilylation of terminal alkynes catalyzed by **1**·2MCl₃ complex

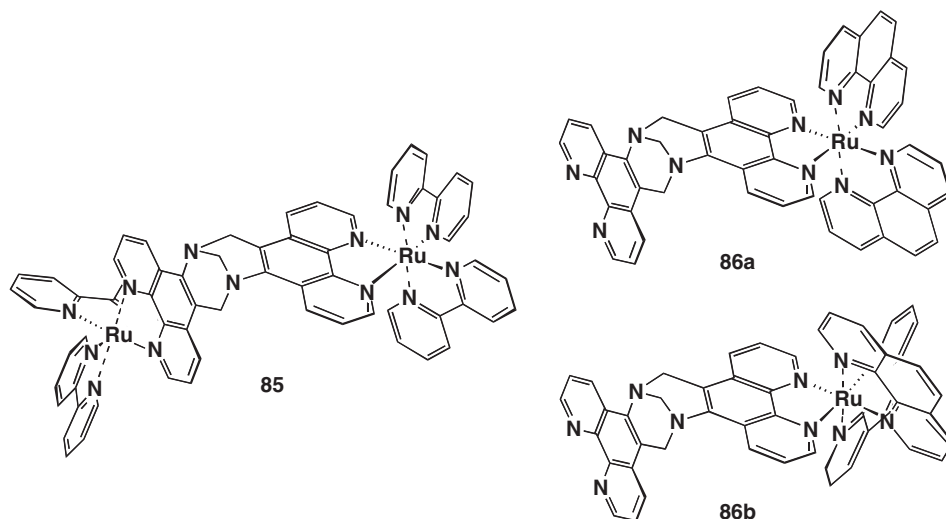


Figure 15. Ruthenium(II)-bipyridyl-TB phenanthroline complexes

bis-complex of this diamine are open for five and six coordination, only four-coordinated complexes with copper(II), palladium(II), nickel(II), platinum(IV) and zinc(II) were prepared (78ZN(B)67, 82ICA231, 82JCS(D)2545).

Another method of TB complex formation involves using the TB periphery as a binding site. Towards this end, the bismetal complexes of porphyrin TB conjugates **36a** and **38a** were used as diamine receptors (95JCS(CC)1077, 98CC11). The phenanthroline TB analog **14** has been employed as a bridging ligand for the preparation of a bimetallic ruthenium(II) complex **85** (Figure 15). Because of the chirality of the ruthenium(II) precursors, Ru(Bpy)₂Cl₂, and also of the TB unit, this complex (**85**) was obtained as a mixture of diastereomers (97TL1567). The diastereomer formation was evident from the complexity of the NMR spectra. It was found that stereoisomer formation could be reduced by the use of a mononuclear species that forms only two diastereoisomers. Recently, the mononuclear ruthenium(II) complex of phenanthroline TB **14** was synthesized and both its diastereomeric forms **86a** and **86b** were separated and subsequently characterized by 1D and 2D NMR techniques (04TL2863). The identical emission properties of **86a** and **86b** indicated an absence

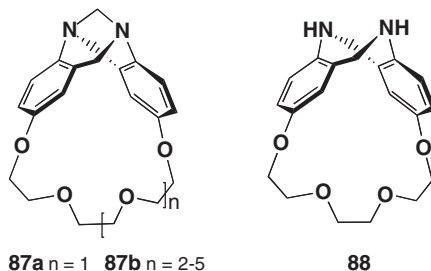


Figure 16. TB macrocycles with crown ether framework

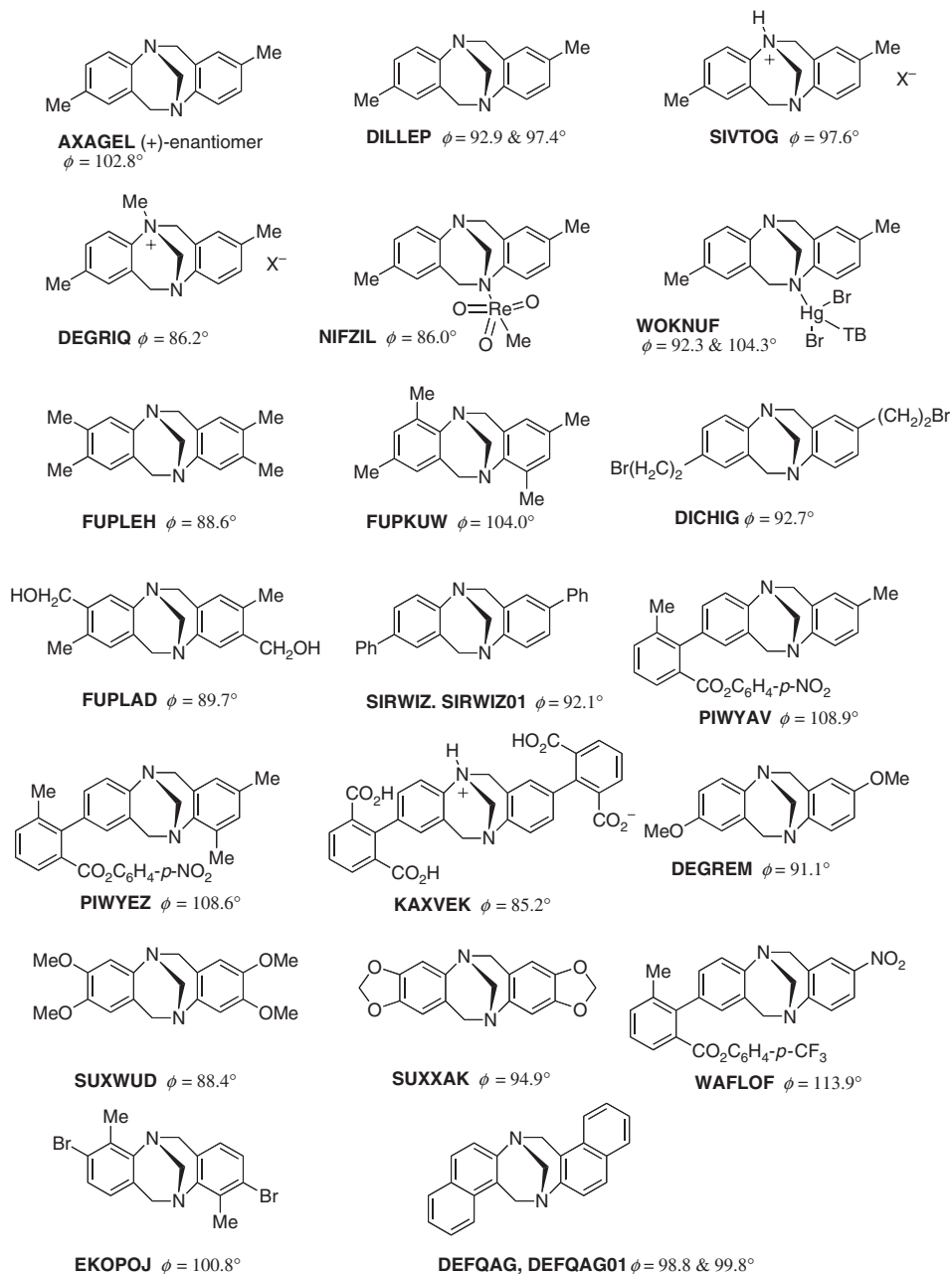
of the influence of stereoisomerism on the photophysical properties of **86**. As mentioned above, the copper(I) complex of **14** was used to effect the cleavage of DNA (91CL1017).

Indian (97T11859) and Japanese (98JHC209) authors simultaneously described TB macrocycles **87** (Figure 16), products that contain a crown ether framework for cation binding. The ability of these systems to complex alkali metal cations was investigated using Cram's picrate extraction method. The data showed that the macrocycles have good extraction capabilities and display high binding affinities ($K_a \approx 10^5 \text{ M}^{-1}$) for all the cations studied. However, they show hardly any selectivity (97T11859). Subsequently, Miyahara et al. (99TL1705) prepared the dibenzodiazocine **88** by removing the endomethylene bridge in **87a**. Generally, the enantiomers of dibenzodiazocine derivatives **12** cannot be resolved because of rapid interconversion of the enantiomers. However, the polyether tether present in **88** was short enough to prevent such inversion processes. Its optical resolution was achieved by HPLC separation using a cellulose-based Chiralcel OJ column. Preliminary complexation studies showed that diamine **88** is a good ligand for metal salts in a manner that is reminiscent of the corresponding open chain **12b** (82ICA231). For example, $(\mathbf{88})_2 \cdot \text{NiCl}_2$ complex was readily obtained as orange crystals (99TL1705).

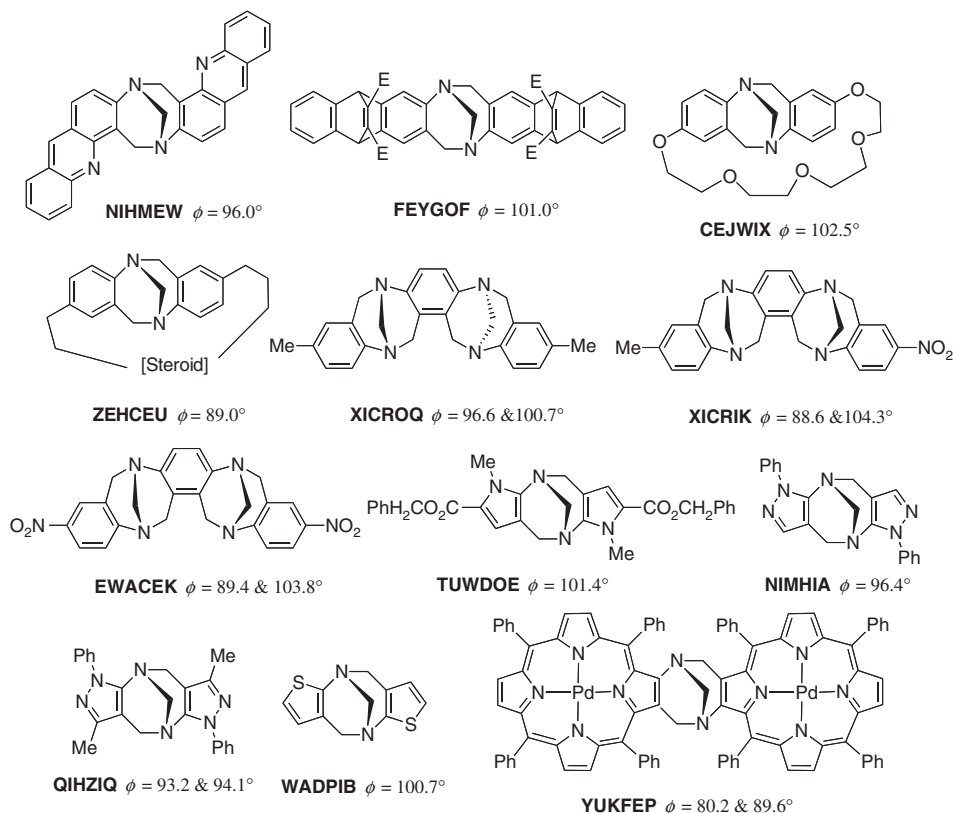
VI. Physicochemical Properties

A. MOLECULAR AND CRYSTAL STRUCTURE

Scheme 21 reported the X-ray structures of TBs found in Cambridge Structural Database (CSD) together with their refcodes: AXAGEL (04HCA279), DILLEP (85TL5749, 86AX(C)224), SIVTOG (91JOC485), DEGRIQ (85JCS(CC)1578), NIFZIL (97JOM(538)203), WOKNUF (00RCB1241), FUPLEH (88JOC98), FUPKUW (88JOC98), DICHIG (86AX(C)253), FUPLAD (88JOC98), SIRWIZ (91JCS(P2)47), SIRWIZ01 (97AX(B)317), PIWYAV (94JA4497), PIWYEZ (94JA4497), KAXVEK (89JA8055), DEGREM (85JCS(CC)1578), SUXXAK (01JCR(S)243), SUXXAK (01JCR(S)243), WAFLOF (04AG(E)5056), EKOPOJ (03EJO3179), DEFQAG (98TA4151), DEFQAG01 (03MC111), NIHMEW (97BSF495), FEYGOF (87JA1865), CEJWIX (98JHC209), ZEHCEU (95JCS(P1)2049), XICROQ



Scheme 21. Structures reported in the CSD



Scheme 21. Continued

(01JOC1607), XICRIK (01JOC1607), EWACEK (04EJO1097), TUWDOE (03TL2083), NIMHIA (97T2233), QIHZIQ (01AX(C)281), WADPIB (03AX(E)0745) and YUKFEP (95JCS(CC)1077). The X-ray structure of the dipyrrolo derivative **34a** has been reported recently (05TA1969) and included in the CSD database (CCDC-269349).

The rigid V-shape of the TB skeleton, formed by methanodiazocine bridging of the aromatic rings of the molecule, has played a considerable role in supramolecular chemistry. The X-ray structure of racemic **1** was reported by Wilcox in 1985 (85TL5749). The aromatic rings of TB analogs are oriented roughly at right angles to each other. The dihedral angle between the aromatic rings depends on the substitution pattern of the aromatic rings. In the compounds examined to date, the dihedral angle ranges from 81° to 104° (88JOC98, 95JCS(CC)1077, 95JCS(P1)2049). The (*R,R*)/(*S,S*) absolute configuration assigned to (-)/(+)-**1** by a combination of vibrational-CD (VCD) spectroscopy and *ab initio* density functional theory (DFT) (99CC361) was in accord with results obtained from X-ray crystallography of monoprotonated TB salts containing chiral anions (91JOC485). The opposite absolute configuration of **1**, deduced from CD measurements, was reported earlier by Mason (67TL137, 67JCS(B)553). The structure, VCD and IR spectra predicted,

using *ab initio* DFT, were in excellent agreement with the X-ray structure and the experimental spectra recorded in CCl_4 and CS_2 solutions of **1** (00JA2346).

We have summarized in **Scheme 21**, the relevant crystallographic information concerning TBs as reported in the CSD version 5.26 (updated August 2005, CSD refcodes given in bold) (**02AX(B)380**). The angle ϕ is the angle formed by the planes containing the two aromatic rings. For most compounds, only one value of ϕ is given in **Scheme 21**, but there are several molecules for which two values are reported (two different determinations, usually two temperatures, were reported for **SIRWIZ** and **DEFQAG** but the angles are identical or very similar). Two cases should be distinguished:

(i) Double molecules, like **WOKNUF** (two identical TBs linked by a mercury atom), **XICROQ**, **XICRIK** and **EWACEK** (these three being bis-TBs). For these molecules, two angles are expected, but most of these molecules having an element of symmetry, the angles should be similar, which is not the case: $92.3/104.3^\circ$ (12.0°), $96.6/100.7^\circ$ (4.1°) and $89.4/103.8^\circ$ (14.4°). In the case of the “asymmetric” **XICRIK**, the difference is 15.7° ($88.6/104.3^\circ$).

(ii) Tröger's bases with two independent molecules in the unit cell: **DILLEP** $92.9/97.4^\circ$ (4.5°) [note that the (+)-enantiomer has $\phi = 102.8^\circ$], **QIHZIQ** $93.2/94.1^\circ$ (0.9°) and **YUKFEP** $80.2/89.6^\circ$ (9.4°) (these are the angles we measured on **YUKFEP**, in the original article the angles are reported as 81.0 and 89.7°).

The straightforward conclusion is that crystal-packing effects are important and can cause deformations of $\pm 6^\circ$. The second one is that TBs should be relatively flexible molecules.

Examination of **Figure 17** and **Scheme 21** shows that there are four “abnormal” compounds (framed in **Figure 17**). One, with a very low ϕ angle [**YUKFEP**, 80.2° (81.0)]

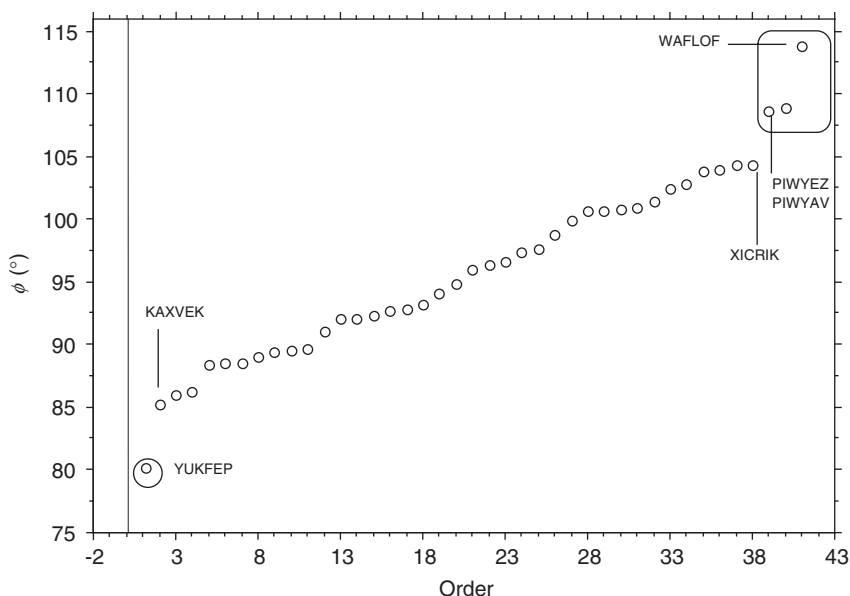


Figure 17. Variation of the ϕ angle ($^\circ$) in an order of increasing ϕ values

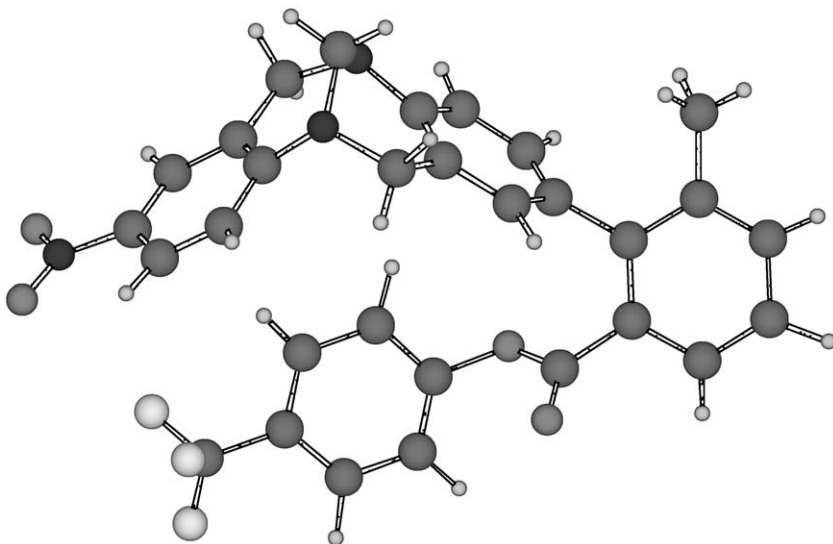


Figure 18. Molecular structure of **WAFLOF** showing the interaction responsible for the increase in ϕ

(95JCS(CC)1077), the other independent molecule has a “normal” value of 89.6° . The pyrrole rings, used to define the aromatic planes, are very distorted in this porphyrin derivative, which may be related to the small angle; the authors limited themselves to point out that the value is somewhat smaller than the average angle in other TB analogs (95JCS(CC)1077). The three other compounds (**WAFLOF**, **PIWYAV** and **PIWYEZ**) have abnormally high ϕ angles. For the remaining ones there is a smooth variation of the ϕ angle. These three last compounds correspond to Wilcox–Diederich’s molecular torsion balances that have been designed to present interactions between the lateral branch and one of the phenyl rings of the TB resulting in high ϕ values (see Figure 18) (94JA4497, 98JA11192, 04AG(E)1738, 02JOC7057).

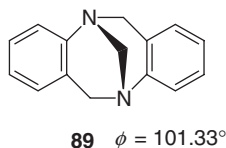
Excluding these four compounds, 37 ϕ values remain, the mean being 95.3° , the minimum value 85.2° (**KAXVEK**) and the maximum 104.3° (**WOKNUF** and **XICRIK**) (see Figure 17). Wilcox et al. (88JOC98), from a series of seven ϕ values, reported a range of 88° – 104° . There are no significant differences between benzenes (31 compounds, 95.1°) and five-membered heterocycles (6 compounds, 95.9°), but between neutral (31 compounds, 96.5°) and cations or metal complexes (6 compounds, H^+ , R^+ , metals, 91.9°), there seems to be a significant decrease of ϕ angle (4.6°).

Since the crystal structures are not suitable for studying the influence of the substituents on the geometry of TBs, we decided to carry out DFT calculations to avoid phase effects. We have calculated four TBs differing only in the position of the methyl group, including the original TB, 2,8-dimethyl-6*H*-12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (06TA191). The following ϕ angles were calculated: 1,7-dimethyl 103.8° , 2,8-dimethyl 101.4° , 3,9-dimethyl 101.5° and 4,10-dimethyl 105.4° . The 2,8-dimethyl derivative should be compared with **AXAGEL** (102.8°) and **DILLEP** (92.9 and 97.4°), so the calculated value 101.4° , is much closer to the

(+)-enantiomer (Scheme 21). From the fact that the calculated geometry of an isolated molecule is more similar to that of the enantiomer than to that of the racemic, no consequence can be drawn: the differences in geometry in the crystals are due to packing effects that actually are quite different in **AXAGEL** and **DILLEP**.

The presence of methyl groups close to the diazocine ring increases the ϕ angle 2.4° in 1,7 and 4.0° in 4,10 with regard to the 2,8 or 3,9-derivatives. There are two compounds with methyl groups in 4,10: **FUPKUW** 104.0° and **EKOPOJ** 100.8° , but the effects, as expected, are blurred by the packing.

We have then examined the flexibility of the skeleton, *i.e.*, the effect of ϕ on the energy by carrying out B3LYP/6-31G* calculations on model **89**. For the minimum energy conformation the angle ϕ amounts to 101.33° .



The variations of the energy with the ϕ angle are reported in Table 1 and Figure 19.

The results of Table 1 confirm the flexibility of TBs and the flat nature of their potential curves (Figure 19).

We have carried out calculations on some charged species (compounds **90–93**, Figure 20) to check the observation, previously reported, that cations and metal complexes have lower ϕ values (4.6°) than neutral TBs. The results show that quaternary ammonium salts have ϕ angles about 5° lower than protonated cations (that duplicates in double salts). Mono-protonation alone is not sufficient to modify ϕ (compare **89** and **90**); actually if one compares the neutral **DILLEP** (92.9 and 97.4°) with the mono-protonated derivative **SIVTOG** (97.6°) and the mono-quaternary salt **DEGRIQ** (86.2°), the quaternary salt has a ϕ value 11.4° lower than the protonated cation which is similar to the neutral molecule.

B. QUANTUM MECHANICAL CALCULATIONS

Tröger's bases including **1** have been the subject of several theoretical studies at the *ab initio* or DFT levels. Some of these papers have already been commented in

Table 1. Conformational analysis of compound **89** calculated at the B3LYP/6-31G* level

Angle ϕ	Energy (hartree)	Relative energy (kJ mol ⁻¹)
85.00	-689.515450	5.09
90.00	-689.516508	2.31
95.00	-689.517120	0.70
100.00	-689.517381	0.02
101.33	-689.517388	0.00 (minimum)
105.00	-689.517282	0.28
110.00	-689.516844	1.43

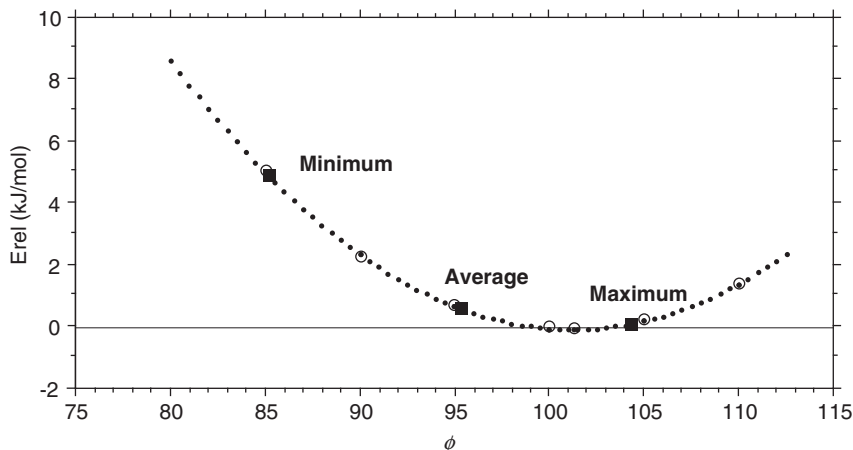


Figure 19. Variation of the relative energy with the angle ϕ : white circles correspond to Table 1 values; black squares to the experimental minimum (**KAXVEK**), mean ($\phi = 95.3^\circ$) and maximum values (**WOKNUF** and **XICRIK**). The curve corresponds to the equation $E_{\text{rel}} = 197.71 - 3.908 \phi + 0.0193 \phi^2$

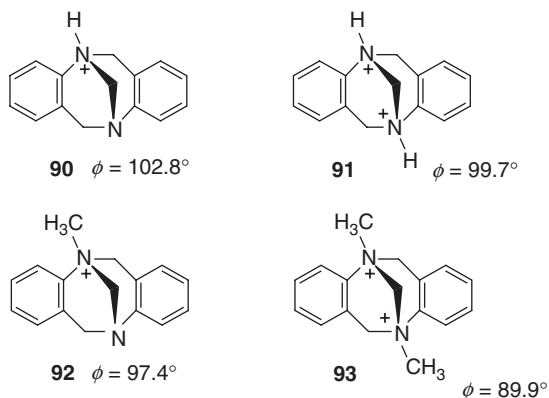


Figure 20. Calculated ϕ angles (B3LYP/6-31G* level) for models of mono and dications

connection with X-ray molecular geometries (VI.A) (**06TA191**) and with optical rotation studies (V.B) (**00JA2346**, **01JPC(A)5356**, **03JOC5186**, **06TA191**). TBs are excellent substrates for theoretical calculations owing to their rigid geometry and moderate size.

Galasso and coworkers (**03CP(288)33**) have carried out MP2 and B3LYP calculations on compounds **DILLEP 1**, **SUXWUD** and **SUXXAK** (Scheme 21) and, at the same time, determined the ^{13}C NMR and the photoelectron spectra. The theoretical results satisfactorily reproduced the experimental data including the X-ray geometries (VI.A). An important paper reports a theoretical study of alkyl- π and aryl- π interactions (**02JOC7057**). The authors extended their calculations to Wilcox's

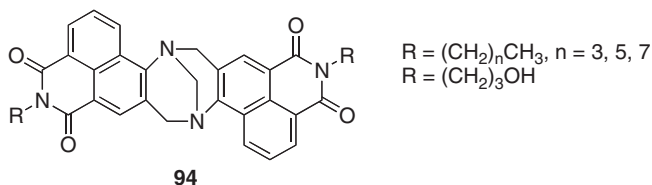
structures (VI.E) with considerable success. In Section V.B several papers were commented about theoretical calculations of optical rotation, for instance 01JPC(A)5356, 06TA191).

C. UV AND IR SPECTRA

The IR spectra of TBs are not very significant and are usually relegated to the experimental part. On the other hand, detailed comparison of IR and Raman spectra have been used to distinguish between *syn* and *anti* isomers of symmetric bis-TB derivatives (05MI1).

In addition, the UV spectra have been explored more thoroughly. In two papers, Tatibouët and Demeunynck reported the study of acridine derivatives. First they noted that the UV-visible absorption of the acridine chromophore in **16a** (NIH-MEW, Scheme 21) exhibits large variations as compared to the parent acridine (97BSF495). As was commented in Section IV.A.2, these authors recorded the UV-visible spectrum of (\pm)-**16b** in the presence of increasing concentrations of calf thymus DNA, experiments used to demonstrate that **16b** interacts with DNA (99CC161). As reported in Section IV.A.4, the UV-visible titration of **38b** with tetraamines confirmed the formation of 2:1 and 1:1 complexes (98CC11).

The fluorescent characteristics of TB **1** have been investigated experimentally. A one-photon-induced fluorescent spectrum was observed and the peak wavelength was at 337 nm with a full-width at half-maximum of ~ 85 nm. The violet radiation of the **1** crystal could result from the $\pi^* \rightarrow \pi$ transition of the benzenoid π bond (99MI1793).



Brown, Lewis and their coworkers synthesized naphthalimide-containing TBs **94** in order to study their fluorescence properties (05TL2149). The effect of several co-solvents on the fluorescence emission is modest and under further investigation. Unlike their fluorescence spectra, the electronic absorption spectra of TBs **94** are relatively insensitive to solvent.

D. NUCLEAR MAGNETIC RESONANCE SPECTRA

The geometry of TB derivatives was also studied by nuclear magnetic resonance (NMR). The ¹H-NMR spectrum exhibits, in addition to the aromatic peaks, an AA'BB'CC' spin system for the methanodiazocine unit (see Figure 21). The assignment of the *exo* (H_AH_{A'}) and *endo* (H_BH_{B'}) protons is mostly carried out via selective NOE irradiation of the bridging methylene protons (H_CH_{C'}). This resulted in enhancing the intensity of the *exo* protons. In the aromatic and most heteroaromatic TB derivatives, the lower field doublet was assigned to the *exo* and the higher field

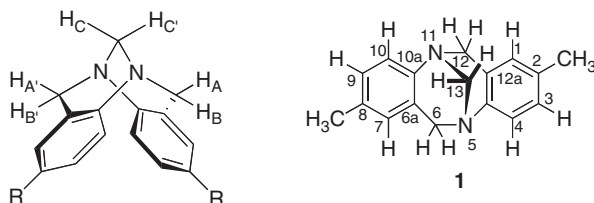


Figure 21. Detail structure of TB and NMR numbering

Table 2. Experimental chemical shifts and calculated absolute shieldings (both in ppm) of Tröger's base **1**

Atom	Chemical shift (experimental) (02MRC743)	Absolute shielding (calculated)	Atom	Chemical shift (experimental) (02MRC743)	Absolute shielding (calculated)
H-1	6.721	25.2346	C-1	127.26	50.9887
CH ₃	2.231	29.6255	C-2	133.42	43.1795
H-3	6.792	24.7341	CH ₃	20.81	160.8032
H-4	7.045	24.7374	C-3	128.11	50.0740
H-6 <i>endo</i>	4.121	27.7728	C-4	124.77	51.8651
H-6 <i>exo</i>	4.666	27.2060	C-4a	145.37	27.8086
CH ₂ -13	4.320	27.6822	C-6	58.66	118.9786
N	-340.4		C-6a	127.48	46.8785
			C-13	67.05	112.8295

doublet to the *endo* protons, whose signal is always broader than the signal of the *exo* protons because of the *W* long range coupling between the *endo* protons and the corresponding *anti* proton of the methylene bridge (H_B with H_C and H_B' with H_C') (86TL5563, 91CL1017, 93JCS(CC)1713, 96MRC318, 96MRC708, 97T2233, 99MRC73). The chemical shift of the *endo/exo* protons are strongly influenced both by the nature and the geometry of the constituent rings. This effect was most pronounced for the *endo* protons (99MRC73).

To briefly summarize the situation, in general (including compound **1**) the *endo* protons appear more shielded than the *exo* ones, but in some acridine derivative the opposite happens (99MRC73). The GIAO approximation was used to calculate the absolute shieldings (06TA191). In Table 2 we have summarized the experimental chemical shifts from one of our previous works (02MRC743), together with the absolute shieldings (GIAO/B3LYP/6-311 + +G(d,p)//B3LYP/6-31G*). Using the TB **1** labeled on one of the nitrogen atoms, $\Delta^{13}\text{C}(^{15}\text{N})$ isotope shifts have been measured on C-6 and C-4a.

Taking into account that TMS has $\sigma = 32.075$ ppm (^1H) and 183.15 ppm (^{13}C) the following equations are obtained:

$$\delta(^1\text{H}) = (30.7 \pm 0.6) - (0.96 \pm 0.02) \sigma(^1\text{H}), \quad n = 8, \quad r^2 = 0.997 \quad (1)$$

$$\delta(^{13}\text{C}) = (173.8 \pm 0.9) - (0.951 \pm 0.009) \sigma(^{13}\text{C}), \quad n = 10, \quad r^2 = 0.999 \quad (2)$$

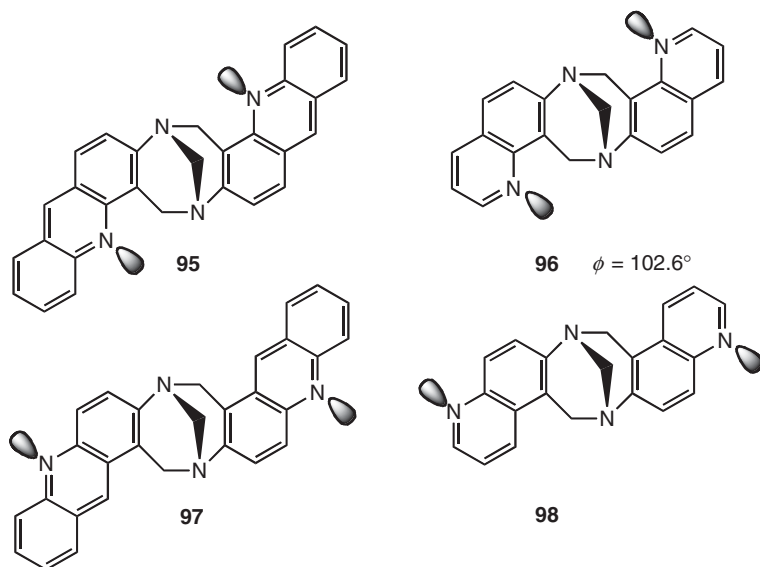


Figure 22. Lone-pair effects of TBs **95–98** on methylene chemical shifts

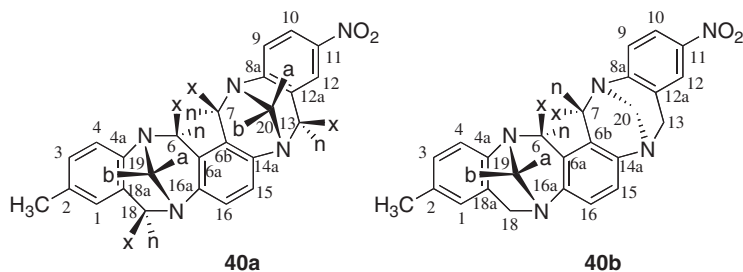


Figure 23. The numbering of atoms in bis-TBs **40a** and **40b**

The most important result is that the *endo* and *exo* protons of the methylene group at position 6 are exactly predicted as experimentally found. Then we have calculated a model of acridine TB **95** where the terminal benzene rings have been deleted (the quinoline derivative **96**, see Figure 22).

For **96**, the *exo* proton of the position 6 is calculated at $\sigma = 26.6680$ while the *endo* one is calculated at $\sigma = 26.7161$. Using equation [1], the following chemical shifts are predicted, 5.17 (*exo*) and 5.13 ppm (*endo*), the experimental values for **95** being 5.11 (*exo*) and 5.12 ppm (*endo*) (99MRC73), thus the calculations are able to explain why a clear difference of 0.55 ppm for **1** becomes almost null for acridines. Note that compounds **97** (03ARK(i)1) and **98** (96MRC318) that have the lone pair removed from the N-CH₂-Ph methylene bridge at position 6 (see **1**) present *endo/exo* signals like **1**.

The relative configuration of the stereogenic units in bis- and tris-TBs has been unequivocally determined on the basis of homoallylic couplings and NOE experiments (Figure 23). For instance, homoallylic couplings between H-6n and H-7x,

H-6x and H-7n ($\theta_{\text{Hn-Hx}} = 112\text{--}113^\circ$, measured on calculated geometries) are observed in the *syn*-bis-base **40a** (Scheme 8, $\text{R}_1 = \text{CH}_3$, $\text{R}_2 = \text{NO}_2$), the stereochemistry of which has been previously established by X-ray crystallography, and also between H-6n and H-7n, H-6x and H-7x ($\theta_{\text{Hn-Hn}} = 105^\circ$ and $\theta_{\text{Hx-Hx}} = 120^\circ$) in the *anti*-bis-base **40b**. Dipolar interactions were also found, from a series of NOE experiments, between H-6x and H-7x, H-6n and H-7n in the above *syn*-bis-base **40a** and between H-6x and H-7n, H-6n and H-7x in the *anti*-bis-base **40b** (05MRC665). All of these observations allow the determination of the relative configuration of the two stereogenic units and have been used for the unequivocal assignment of the stereochemistry of tris-bases (04ARK(iv)86, 05HCA1199, 05MRC665, 05OL2019).

Detailed ^{13}C NMR studies also have been carried out in TB and oligo-TB derivatives (96MRC318, 96MRC708, 00JPR(342)269, 02JCS(P1)1588, 05MRC665). Long-range couplings detected from 2D ^1H - ^{13}C and also ^1H - ^1H correlation spectra have been extensively used. Useful correlations, important for correct assignments, are observed between the methylene protons of the diazocine ring and the quaternary aromatic carbon atom fused to it, and also between the aromatic carbon atom bonded to one of the diazocine nitrogen atom and the *exo* proton of the methylene group linked to the same nitrogen atom. These correlations allow the assignment of the corresponding protons and quaternary carbon atoms in oligo-TB.

^{13}C NMR relaxation times.

^{13}C nuclear spin-spin relaxation times (T_{2c} s) have been used to elucidate chiral recognition differences between the pairs of enantiomers of the TB when they interact with a cellulose stationary phase of chiral discrimination HPLC (96CHI372). T_{2c} , determined in the presence of the chiral packing material, decreases monotonically as the mobility decreases just as the peak width, inversely proportional to T_{2c} , becomes larger. (T_{2c} s) for the enantiomer, which eluted first on the Chiralcel OJ column (cellulose tris-4-methylbenzoate coated on silicagel), were longer than those of the second-eluted enantiomer, and the (T_{2c} s) difference observed was found to reflect the retention order of enantiomers on the chiral HPLC column.

E. OTHER PROPERTIES

The methanodiazocine bridge of TB has been incorporated into receptor designs to afford chirality and a rigid V-shaped geometry. Wilcox, Crossley, Maitra, Demeunynck, Lhomme and their coworkers have utilized the properties of TB in the construction of molecular torsion balances, chiral solvating agents, water-soluble cyclophanes, hydrogen- and metal-ligand-bonding receptors as well as DNA binders.

Wilcox et al. designed molecular torsion balances **99–101** to study edge-to-face aromatic interactions (see Figure 24, 99) (94JA4497) and CH- π interactions (see Figure 24 and compounds **100** and **101**) (98JA11192), properties that play key roles in protein folding and molecular recognition. The energetic barrier ($\sim 2\text{ kJ mol}^{-1}$ in these experiments) of two possible conformational folded-unfolded states was calculated from equilibrium constants determined by NMR spectroscopy. The experiments supported the conclusion that the electrostatic potential of the aromatic rings is not a dominant aspect of the aryl-aryl interaction. Experimental data of edge-to-face interactions were subsequently compared to the molecular mechanics calculations by

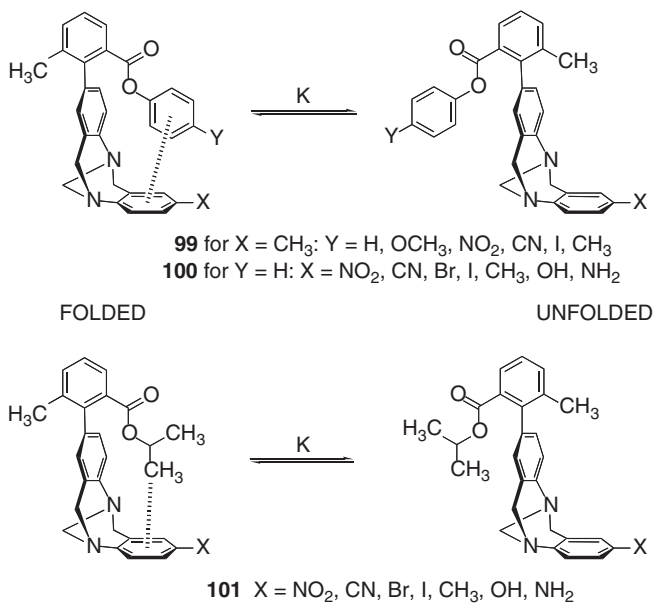


Figure 24. Conformational states (folded and unfolded) for ‘Wilcox’ molecular torsion balance

Nakamura and Houk (99OL2049). On a much more rigorous basis, the problem of the equilibria represented in Figure 24 has been studied by Ribas et al. (02JOC7057). Using quantum mechanical and quantum mechanical/molecular mechanical calculations in conjunction with continuum solvation models, the CH- π interactions have been studied. The authors warned against extrapolating conclusions derived from gas-phase studies to folding models and vice versa.

In one of the most beautiful applications of TBs, compound **2** (R = CH₂NH₂), first prepared by Wilcox (85TL5749), was resolved into the (*R,R*) and (*S,S*) enantiomers (01JA12700). One of these enantiomers was used to coordinate, using its terminal amino groups, a scissor-like heterotopic zinc(II) porphyrin. TB **2** (R = CH₂NH₂) induces the bis-porphyrin to adopt a chiral conformation (atropoisomer). A series of elegant experiments, using CD and ¹H NMR spectroscopy, allowed Kubo et al. to demonstrate both chirality transfer and memory effects.

The solubility of TB **1** in supercritical carbon dioxide over the pressure range from 8 to 19 MPa and from 308 to 328 K has been measured using a flow system. Models based on chemical association, which did not require the critical parameters of the solute, were used to correlate the experimental data (00JCED464). Addition of methanol dramatically enhances the solubility (00MI823).

VII. Uses and Applications

The TB scaffold has been used extensively for the construction of molecular receptors following the initial studies of Wilcox and coworkers (88JA6204, 86TL5563, 89JA8055, 92JA1398, 92JA10189, 02H515).

A. CHIRAL SOLVATING AGENTS

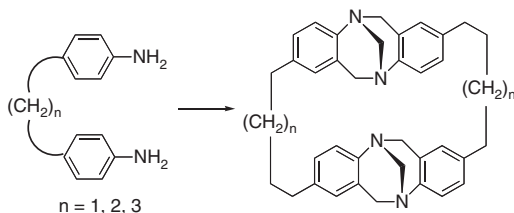
Wilen et al. (91JOC485) observed that ^1H NMR spectra of CDCl_3 solutions of racemic alcohols ($\text{Ph-CR}^1\text{R}^2\text{OH}$) showed anisochrony of at least one set of peaks in the presence of (+)-**1**. These results were best interpreted in terms of the participation of **1** as a chiral solvating agent that serves to effect discrimination between diastereomers. Enantiopure (+)-**1** generated intrinsically non-identical chemical shifts in specific nuclei of the associated diastomeric complex formed between (+)-**1** and an enantiomeric alcohol. The discrimination of enantiomeric cyclic hemiacetals and methyl acetals derived from hydroxamic acids and lactams with the 2*H*-1,4-benzoxazin-3(4*H*)-one and 2*H*-1,4-benzothiazin-3(4*H*)-one skeleton was investigated using for the first time, (5*R*,11*R*)-(+)-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, the TB enantiomer, as a chiral solvating agent (CSA) (94MRC727).

B. CYCLOPHANES AND WATER-SOLUBLE CYCLOPHANES

The unique geometry of the TB was attractive for preparing macrocycles. Introduction of a TB unit in a macrocycle was first described by Fukae and Inazu (84MI223). Racemic [2,2]cyclic TB **102b** ($n = 2$) was prepared in 45% yield (Scheme 22). Repeated fractional recrystallization achieved the separation of **102b** into the *meso* and *rac* forms. The synthetic method was also applied to [1,1] ($n = 1$, **102a**) and [3,3] ($n = 3$, **102c**) analogs successfully but with very low yields (10–13%).

The ability of water-soluble cyclophanes to form inclusion complexes with aromatic, aliphatic and alicyclic substrates inspired Wilcox and colleagues to develop macrocyclic analogs of TB as rigid chiral receptors for small, neutral organic molecules (86TL5563, 88JA6204, 91JA8554, 92JA10189, 02H515).

The first examples of the cyclophane TB family included a bis[*p*-(alkoxy)phenyl]methane system containing two secondary ammonium groups (**103**; Figure 25). Their binding properties were studied by NMR titrations carried out in DCl/KCl buffer ($\text{pD } 1.9 \pm 0.1$). The association of hosts **103** to test benzenoid substrates did not reach 350 M^{-1} and no significant selectivity was observed (see Table 3). Nevertheless, the diphenylmethane unit provided a host **103a** with consistently better guest binding properties than the comparable host **103b** derived with diphenylpropane. The authors interpreted this finding by proposing that the geminal dimethyl group in host **103b** destabilizes the occupied host more than it destabilizes the unoccupied host (88JA6204, 86TL5563).



Scheme 22. Trögerophanes **102a–102c**

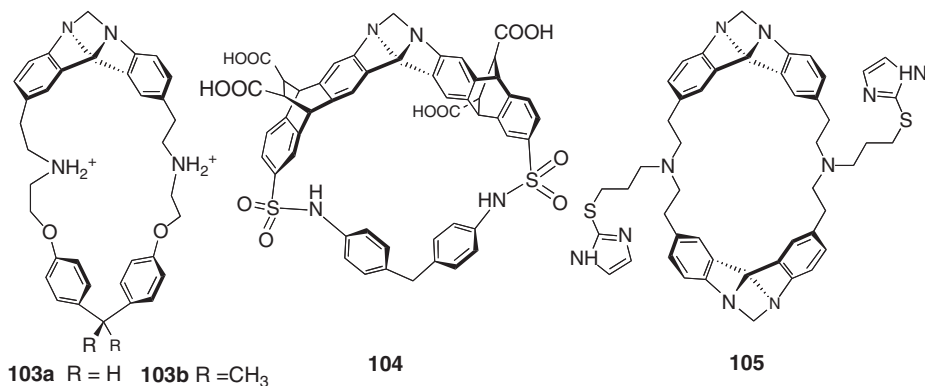


Figure 25. Water-soluble TB cyclophanes

Table 3. Association constants K_a (M^{-1}) of receptors **103** with aromatic compounds

Substrate	103a	103b
2,4,6-Trimethylphenol	100	70
4-Methoxyphenol	60	—
4-Toluenesulfonic acid	330	250
4-Methylphenol	50	40
4-Cyanophenol	170	70
4-Nitrophenyl acetate	140	—
1,3-Dihydroxynaphthalene	330	200

Optically pure, water-soluble macrocyclic TB tetraacid **104** has been examined as a receptor for terpenes. A 1H NMR study in an ND_4Cl/ND_3 buffer at pD 9.0 in D_2O showed that host **104** binds the isomeric menthols with reasonable selectivity [(-)-menthol $K_a = 2.5 \pm 0.2 \times 10^3 M^{-1}$], (+)-menthol $K_a = 2.0 \pm 0.2 \times 10^3 M^{-1}$, (+)-isomenthol $K_a = 1.0 \pm 0.2 \times 10^3 M^{-1}$] (91JA8554). This indicates that the axial groups on the cyclohexane nucleus may not fit in the host cavity. This notion is consistent with the results obtained by studying the interaction of **104** with 4-*tert*-butylcyclohexanol. In this latter case, the guest bearing an axial substituent (*cis* isomer, $K_a = 8.6 \times 10^3 M^{-1}$) was accommodated less well in this shape-selective cavity **104** than its *trans* isomer ($K_a = 4.1 \times 10^4 M^{-1}$) (92JA10189).

A recent contribution includes the synthesis and study of cyclophane bis-TB derivative **105** bearing imidazolylsulfide groups on the alkyl bridge. These receptors were designed to bind biologically relevant phosphates in their natural environment. The imidazolylsulfide groups were introduced to promote electrostatic interactions and to enhance solubility. Studies of the complexes formed from **105** and *O*-phosphorylethanolamine, 4-nitrophenyl phosphate, and 4-nitrophenol were performed using NMR spectroscopy in 0.1 M KCl/DCl buffer at pD 1.4, below the critical micelle concentration of **105**. Experiments showed that **105** interacted with 4-nitrophenyl phosphate ($K_a = 830 M^{-1}$) 10 times more readily than with its nonphosphate analog, 4-nitrophenol (02H515).

C. HYDROGEN-BONDING RECEPTORS

Wilcox et al. described carboxylic acid TB derivatives such as **106** (Figure 26) as hosts for cyclic urea and adenine derivatives (89JA8055, 92JA1398). The receptor design was based on formation of four hydrogen bond donor–acceptor pairs between two properly arranged carboxylic acids of **106a** and the targeted urea or adenine base moieties. Binding affinities for the interaction of **106a** with 9-ethyladenine, biotin methyl ester and several other guests were determined by NMR and UV/fluorescence spectroscopy techniques. Support for the suitability of **106a** to recognize adenine derivatives was provided by comparing the binding of 9-ethyladenine to **106a** ($K_a = 140 \text{ M}^{-1}$), benzoic acid ($K_a = 30 \text{ M}^{-1}$) and 2,6-diphenic acid ($K_a = 20 \text{ M}^{-1}$) in THF- d_8 , as well as by noting the relative weak binding of **106a** to 6-*N*-methyl-9-ethyladenine ($K_a = 14 \text{ M}^{-1}$), a guest that cannot form four concurrent hydrogen bonds with the host.

To increase the measured association constants, it was considered feasible to carry out analytical experiments in CHCl_3 instead of THF. However, host **106a** was poorly soluble in CHCl_3 , and therefore the more soluble hosts **106b** and **106c** were prepared. Association constants for these hosts with several guests were determined in CDCl_3 (Table 4) (89JA8055, 92JA10189).

The dicarboxylic acids **106b–d** were used for determining the effect of H_2O on hydrogen bonding in these systems. The experiments showed that small amounts of water can have a very large effect on the entropy and enthalpy changes associated with a binding event. The more tightly self-enclosed diacid **106d** was less affected by water as it is far less susceptible to hydration than the more opened hosts **106b** and **106c** (92JA1398).

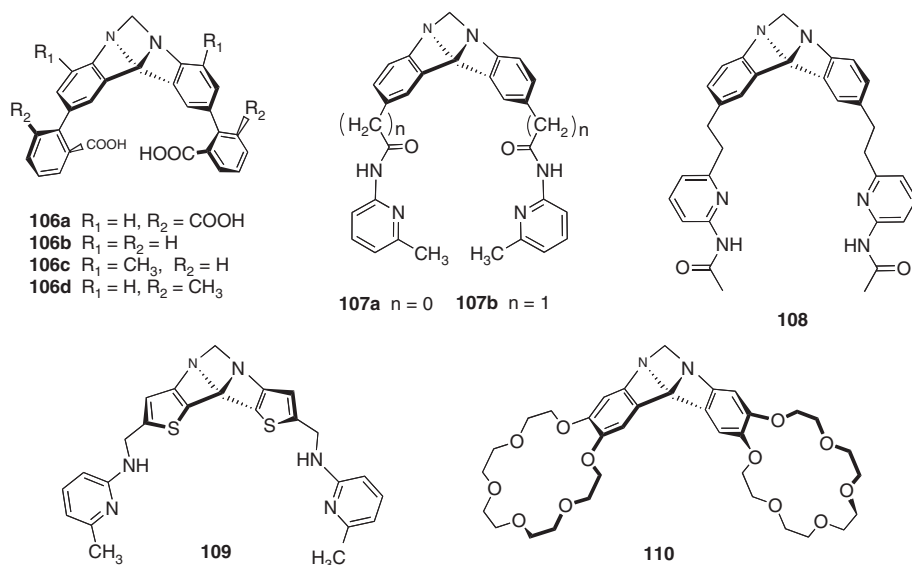


Figure 26. TB derivatives as hydrogen-bonding receptors

Table 4. Association constants K_a [M^{-1}] of **106b** and **106c** with biotin and adenine related compounds

	106b	106c
9-Ethyladenine	$(4.5 \pm 1.7) \times 10^4$	$(5.1 \pm 1.0) \times 10^5$
Biotin methyl ester	$(1.7 \pm 0.3) \times 10^4$	—
2-Imidazolidinone	$(2.1 \pm 0.4) \times 10^4$	$(4.4 \pm 0.5) \times 10^4$
2-Aminopyrimidine	$(2.6 \pm 0.5) \times 10^3$	$(9.4 \pm 0.4) \times 10^3$

Table 5. Association constants K_a [M^{-1}] of receptors **107–109** with dicarboxylic acids

Diacid	107a	107b	108	109
Glutaric	1.0×10^3	2.4×10^2	1.1×10^2	2.5×10^2
Adipic	1.7×10^3	3.5×10^2	5.3×10^2	3.6×10^2
Suberic	1.5×10^4	4.8×10^2	1.0×10^3	2.1×10^2
Sebacic	3.1×10^3	5.8×10^2	6.5×10^3	3.9×10^2

The design and synthesis of amidopyridine TB receptors **107** to recognize dicarboxylic acids with precise chain lengths were reported by Goswami and Ghosh (97TL4503). The receptors include two amidopyridine units that are angularly displayed by the TB spacer on a concave face to bind dicarboxylic acids. The complexation study, based on 1H NMR spectroscopic titrations carried out in $CDCl_3$ containing 2% DMSO- d_6 , with a series of dicarboxylic acids showed that the cavity of TB analog **107a** is selective for suberic acid (97TL4503) (see Table 5). Strong complexation of **107a** with suberic acid was also observed by fluorescence detection, which afforded a binding constant ($K_a = 2.5 \times 10^4 M^{-1}$), close to the value observed in the 1H NMR titration experiments (00JOC1907). The more flexible receptors **107b** and **108** exhibited weaker binding to the same dicarboxylic acids. A marginal increase in K_a was observed for suberic and sebacic acid. However, the stoichiometry of these complexes, determined from the breaks in the titration curve ($\Delta\delta$ vs. $C_{\text{guest}}/C_{\text{host}}$), was 1:2 (guest:host) rather than 1:1 (00JOC1907).

Studies of the binding of dicarboxylic acids to the TB analogs **107** (Figure 26) included the observation of chiral recognition, using (+)-camphoric acid as a chiral diacid guest, as it was expected to provide a close match to the cavity dimensions of **107**. The NMR spectra showed two different sets of amide protons upon titration of (\pm)-**107a** with (+)-camphoric acid. The authors explained the chemical shift variation by the different stabilities of the diastereomeric associates of the enantiomers in solution. Attempts to resolve racemic **107a** by crystallization and chromatographic separation with (+)-camphoric acid as a chiral template failed (00JOC1907).

Kobayashi and Moriwaki (04H399) recently described the thiophene TB derivative **109** bearing two pyridylamino groups, whose hydrogen-bonding mode is similar to receptors **107** reported by Goswami and Ghosh (97TL4503). The complexation

Table 6. Association constants K_a [M^{-1}] of the complexation of **110** with bisammonium salts of α,ω -diaminoalkane

Ammonium salt	n	K_a [M^{-1}]
Butane-1,4-diylbis(ammonium chloride)	4	5.0×10^5
Pentane-1,5-diylbis(ammonium chloride)	5	7.0×10^5
Hexane-1,6-diylbis(ammonium chloride)	6	2.6×10^6
Heptane-1,7-diylbis(ammonium chloride)	7	7.8×10^6
Octane-1,8-diylbis(ammonium chloride)	8	3.7×10^6

properties of **109** were studied by 1H NMR spectroscopic titration methods in $CDCl_3$ containing 0.5% DMSO- d_6 . The target guests were aliphatic and aromatic dicarboxylic acids. The stoichiometry and association constants were determined from titration curves generated by following the chemical shift of the 3'-H of the pyridine ring. All dicarboxylic acids studied, except for malonic acid and phthalic acid, were suggested to form complexes with 1:1 stoichiometry. The thiophene receptor **109** binds these dicarboxylic acids nonselectively with approximately the same binding affinity as receptor **107b** (see Table 5). On the contrary, significantly higher selectivity was determined for malonic ($K_a = 1.9 \times 10^5 M^{-1}$) and phthalic ($K_a = 7.0 \times 10^4 M^{-1}$) acids, which bind to receptor **109** with a 1:2 (guest:host) stoichiometry (04H399).

Hansson et al. (98TL4565) also investigated the use of the TB scaffold in the design of hydrogen-bonding receptors. Their TB analogs were based on the methanodiazocine linking of two benzo-18-crown-6 ethers, entities that are widely considered as being strong primary ammonium ion complexation partners. Condensation of 4-aminobenzo-18-crown-6 with formalin afforded only the linear symmetric derivative **110**, of the three possible geometrical bis(18-crown-6) isomeric TB analogs that could potentially have been produced. Its complexation properties were tested with bisammonium salts of α,ω -diaminoalkane by NMR spectroscopy in a 1:1 mixture of CD_3OD and $CDCl_3$ (see Table 6). The experiments revealed that bisammonium salts with $n = 6-8$ bind with an affinity almost equal to host **110**. However, a slight preference for heptane-1,7-diylbis(ammonium chloride) was observed. The enantiomeric discrimination of receptor **110** for chiral bisammonium salts was examined using racemic **110** and L-cystine methyl ester dihydrochloride. The 1H NMR spectrum at a 1:1 ratio revealed that the aromatic protons as well as the protons of the methylene bridge were doubled compared to free **110**. This is consistent with the formation of two diastereomeric complexes, L-(-)-**110** and L-(+)-**110**. The diastereoselectivity calculated from the 1H NMR spectrum was found to be 62:38. Related experiments with L-lysine methyl ester dihydrochloride did not reveal any enantiomeric discrimination (98TL4565).

The thermodynamic and hydrogen-bond basicity of **1** have been reported by the group of Berthelot, Laurence and coworkers (04CJC1413). TB **1**, TB **110** and another mixed crown ether TB have been reported in a communication dealing with a novel chiral stationary phase for HPLC (94JCS(CC)1811).

VIII. Pseudo-Tröger's Bases (Compounds Related to TBs)

Although it is not the purpose of this review, we want to point out a number of structures that have skeletons related to TBs (Figure 27). Often the driving force that led the authors to prepare them has been the analogy with **1**.

Compound **89** was the model for the dibenzobicyclo[3.3.1]nonane **111** (98TL9809, 00JOC3042, 02NJC720, 03MC106, 05SUP369), **112** (96BMC743), **113** (90TL1825, 99TL4133), **114** (86AX(C)1630), **115** (99CJC113), **116** (95TL6619, 99CJC113), **117** (88DAN(303)646, 98T997, 98TL7239) (also with thiophene instead of benzene rings (98JCS(P1)3557) and the still unknown ring system **118**.

IX. Conclusions

Studies involving TB derivatives are ongoing, with many potentially important properties remaining to be discovered and explored (Figure 28). For example, dicarboxylic TB derivatives **119** (96TL5791) that are more flexible than the described receptors **106** (89JA8055, 92JA10189) have been synthesized (Figure 26). Dithia **120** and mercapto **121**, and derivatives prepared by Bag and Kiedrowski could prove useful in organic and bioorganic chemistry for studying biologically important thiol and disulfide groups (99AG(E)3713, 99TL1289). The TB derivatives **122**, **123** (85TL5749) could also play an important role in chiral molecular recognition. Considerable effort is currently focused on exploiting TB derivatives as novel materials, as well as analyzing their use in analytical methods development. TB analogs are also promoting investigations of second harmonic reflections from chiral surfaces (05JPC(B)5261). Meanwhile, novel sulfone derivatives have been shown to serve as novel aromatic chelates (03MI1401). New analogs of TB that are fluorescent via excited state intramolecular proton transfer and exhibit large Stokes shifts have recently been described (04TL5601). These systems could be used as optical sensors.

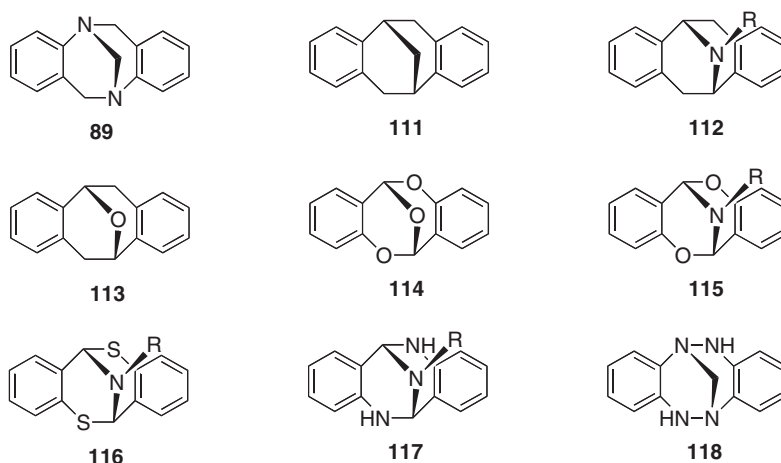


Figure 27. Some pseudo-Tröger's bases

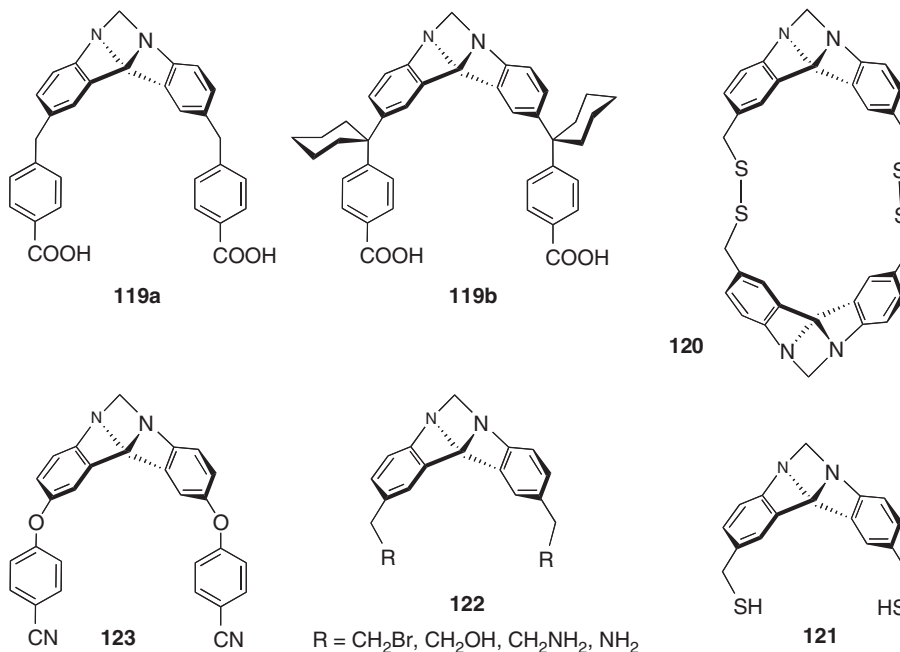


Figure 28. TB derivatives reported

In conclusion, TB derivatives are highly useful synthetic building blocks. They embody chiral tectons (05ACR313) exhibiting a wide range of applications. These properties include biomimetic molecular recognition processes as well as complex interactions with important biomolecules. Emerging directions offer exciting new possibilities for the synthesis and applications of novel oligo-TB systems.

Acknowledgements

Grant from the Ministry of Education of the Czech Republic MSM 6046137307, LC06077 and grants 203/05/0786, 203/06/1038 and 301/04/1315 from Grant Agency of the Czech Republic (GACR), and EU grant QLRT-2000-02360 and CIDNA to V. K., 203/03/D049 from GACR to B. D. and in part the National Institutes of Health via grant R01EB002044 to R. S. supported this work. The Spanish group (J. E. & C. P.) acknowledges successive grants from the Ministry of Science and Education of Spain.

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Nucleophilic Aromatic Substitution of Hydrogen as a Tool for Heterocyclic Ring Annulation

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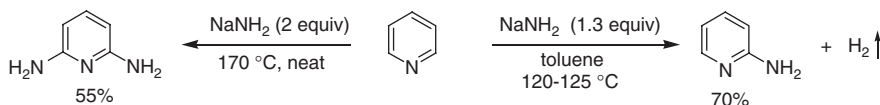
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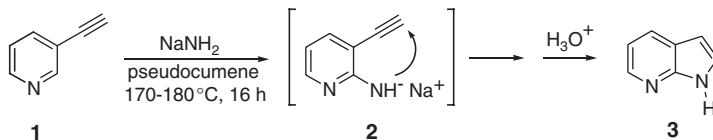
I. Introduction

The history of nucleophilic substitution of hydrogen in aromatic compounds apparently started in 1882 when Hepp obtained picric acid by reacting potassium ferrocyanide with 1,3,5-trinitrobenzene (1882LAC344). In 1906, Sachs reported on the amination of naphthalene with sodium amide, but yields of 1- and 2-aminonaphthalene were rather poor (1906B3006). Both works essentially did not influence the development of organic chemistry. However, later Chichibabin and Zeide demonstrated that heating pyridine with NaNH₂ powder in toluene produced 2-aminopyridine in good yield (14ZRO1216). In the absence of a solvent and at higher temperature, 2,6-diaminopyridine can be obtained (40MI173) (Scheme 1). The Chichibabin amination was applied to benzo analogs of pyridine and 5-membered heterocycles, most successfully to benzimidazoles (51ZOK884) and other condensed imidazole systems (for reviews see (78RCR1042, 88AHC(44)1)).

Since the 1960s, the study of the Chichibabin reaction stimulated a great interest in the problem of nucleophilic substitution of hydrogen. As a result new types of related transformations were found, their mechanisms were detailed and experimental



Scheme 1



Scheme 2

protocols were strongly improved. Finally, for all such reactions a convenient symbol $S_{\text{N}}\text{H}$ had been proposed (76RCR454) to underline their non-similarity with substitution of other functional groups (S_{N} *ipso*).

At the present time, $S_{\text{N}}\text{H}$ methodology finds an ever-increasing use in organic synthesis described in a monograph (94MI1) and a whole series of reviews (87KGS1011, 88AHC(43)301, 88T1, 02RCR707, 04AHC(86)1, 04CRV2631). A major advantage of this methodology is that it eliminates the necessity of first introducing a good leaving group into an aromatic substrate. Moreover, in classical S_{N} *ipso* reactions an acid such as HHal , H_2SO_4 or HNO_2 is normally liberated that has to be scavenged. Unlike this, in $S_{\text{N}}\text{H}$ processes a water molecule is typically formed and this can contribute to “green chemistry” (02RCR707).

For many decades nucleophilic replacement of hydrogen was mainly used for simple functionalization of a heterocyclic nucleus (04CRV2631). But gradually its synthetic potential was expanded. One of the most significant steps in this direction was the discovery of $S_{\text{N}}\text{H}$ reactions leading to heterocyclic ring closure. The synthesis of 7-azaindole **3** by aminating 3-ethynylpyridine **1** without isolation of its intermediate 2-amino-3-ethynylpyridine **2** represents one of the first examples of such conversions (Scheme 2) (64CB2717).

The number of similar cyclizations, including tandem and cascade sequences where an $S_{\text{N}}\text{H}$ reaction is a key step, has been considerably increased. As a rule, they are easily performed allowing at times the synthesis of complex polynuclear heterocycles in one step. The present paper, which summarizes about 130 articles on this topic, shows $S_{\text{N}}\text{H}$ cyclizations to be a very promising strategy for heterocyclic ring annulations.

II. General Survey of $S_{\text{N}}\text{H}$ Substitution

A. SUBSTRATES

There are three groups of substrates for which $S_{\text{N}}\text{H}$ reactions are especially characteristic: (i) neutral azines and azoles; (ii) azinium and azolium salts and (iii) nitroarenes. Their electron-deficiency and, thus, their ability to react with nucleophiles strongly differ from each other. Azinium salts are the more electrophilic and are able to add even neutral nucleophiles very easily. Triazines, *s*-tetrazines and polynitroarenes also possess high electrophilicity. At the same time substrates such as pyridine (82JHC1285, 72JA682) and cinnoline (03CHE87), at a low temperature (e.g. in liquid ammonia as a solvent), do not react even with sodium amide. It should also be

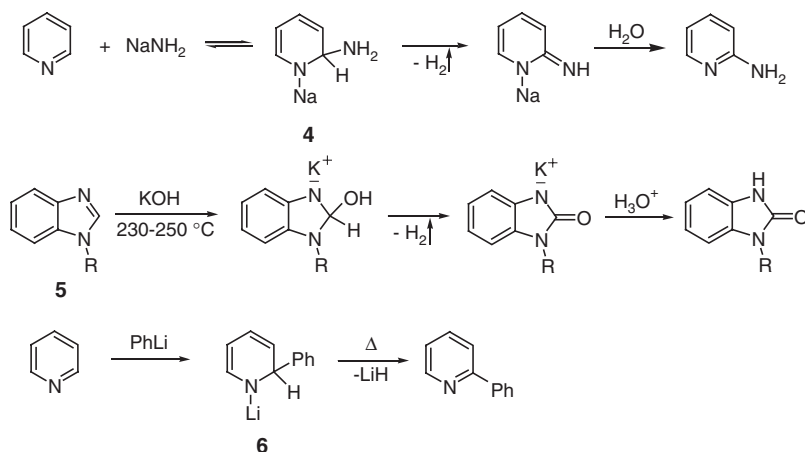
kept in mind that the electrophilicity of azaaromatics can be substantially increased at their conversion into *N*-oxides.

B. MECHANISMS

Commonly, nucleophilic aromatic substitution of hydrogen consists of two main steps: (i) formation of an σ^H -adduct with a nucleophile and (ii) its aromatization. As a rule, the second step is a rate-limiting step, because the hydride ion, which formally has to be lost, is a very poor leaving group. Numerous investigations have shown that spontaneous aromatization of such σ^H -complexes (conventional S_N2Ar substitution) occurs quite rarely. Usually, elimination of hydride ion is strongly facilitated by adding a special oxidant. In these cases the aromatization proceeds via a single-electron transfer mechanism (see for instance (93JA8960)). Non-conventional types of S_NH reactions, which do not require an external oxidant, also exist. In these reactions, an electron pair is removed not as hydride ion but with another group present in the σ^H -complex. Particularly, vicarious nucleophilic substitution of hydrogen as well as *cine*- and *tele*-substitution can be attributed to these transformations. All of them are briefly discussed below.

1. S_N2Ar Reactions without External Oxidant

The most striking example of these reactions is the Chichibabin amination performed in its classical variant under heterogeneous conditions. The reaction is accompanied by the evolution of hydrogen gas that is conveniently monitored. Presumably, on elimination, the hydride ion is combined with an acidic proton, likely from an amino group **4**, to form a hydrogen molecule; the reaction mechanism without details is shown in Scheme 3.



Scheme 3

Similar evolution of hydrogen gas is also observed when nitrogen-containing heterocycles, e.g. benzimidazole **5**, undergo hydroxylation with powdered anhydrous alkali. In spite of the high temperature (180–300°C depending on substrate activity), this reaction proceeds surprisingly in a smooth way and has preparative value especially in condensed imidazoles and perimidines series (71KGS124). Auto-aromatization with a loss of lithium hydride also occurs on heating the adduct of pyridine with phenyllithium **6**, producing 2-phenylpyridine (63CJC3127, 66AHC(6)229).

Thus, spontaneous elimination of hydride ion commonly demands a high temperature and is characteristic for anionic σ^{H} -complexes only.

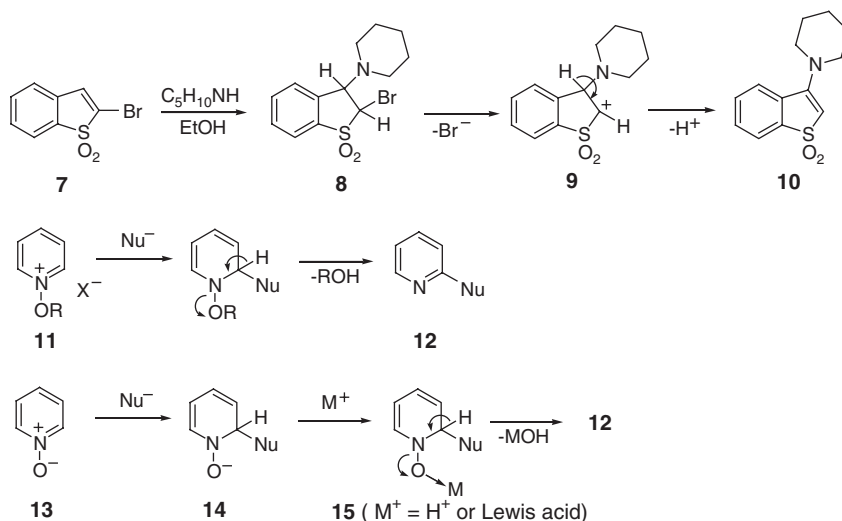
2. $S_{\text{N}}2\text{Ar}$ Reactions with External Oxidant

The higher a substrate's electron-deficiency, the more difficult is aromatization of the σ^{H} -complex and the greater is the need to use an oxidant. Thus, for a long time HNO_3 , Br_2 , I_2 , $\text{K}_3\text{Fe}(\text{CN})_6$, sulfur, quinones and other oxidants were applied to stabilize adducts of azinium and azolium salts with nucleophiles. Although anionic and dianionic adducts are aromatized easier than neutral ones, they also often need an oxidant to accelerate the process. Perhaps Bergstrom was the first to realize this and systematically used KNO_3 and other nitrates for performing the Chichibabin reaction in liquid ammonia (34JA1748). But a more significant contribution in this field was brought by H. C. van der Plas (82JHC1285). He suggested potassium permanganate (KMnO_4) as an extremely convenient oxidant allowing the amination in liquid ammonia of diazines, triazines and tetrazines that are unstable under the classical Chichibabin protocol (for review see (87KGS1011, 88AHC(43)301, 04AHC(86)1)). In the presence of KMnO_4 , highly electron-deficient substrates can be aminated or alkylaminated by liquid ammonia or alkylamines acting as nucleophiles and solvents simultaneously. For those alkylamines, in which KMnO_4 is poorly soluble, the complex $\text{AgPy}_2\text{MnO}_4$ was recommended as an alternative oxidant (88KGS1696).

Oxidation of σ^{H} -complexes with air oxygen is also possible, though for neutral adducts it demands hours and even days for completion. Alkylamination of 5-azacinnoline serves as a typical example (77KGS1554). In nitroarenes the NO_2 group itself was often found to be an acceptor of hydride ion (see Section III.D.1). Similarly, the ring $\text{C}=\text{N}$ bond on amination of azaheterocycles can also intercept hydride ion (78RCR1042).

3. *cine*- and *tele*-Substitution

The process in which a leaving group departs from a position vicinal to the addition site is named *cine*-substitution. For instance, interaction of 2-bromobenzothiophene-1,1-dioxide **7** with piperidine results in 3-piperidinobenzothiophene-1,1-dioxide **10** (65AG557). The reaction mechanism includes formation of σ^{H} -adduct **8**, elimination of bromide ion followed by stabilization of intermediate **9** via proton departure (Scheme 4). Another example is the smoothly proceeding nucleophilic substitution of hydrogen in *N*-alkoxyazinium salts, e.g. **11**, where an alcohol molecule serves as a leaving group. *cine*-Substitution reactions are also



Scheme 4

widespread among heteroaromatic *N*-oxides, e.g. **13**. However, since the less stable hydroxide anion has to be lost in this case, the second step (**14** to **15** to **12**) needs proton or Lewis acid catalyst.

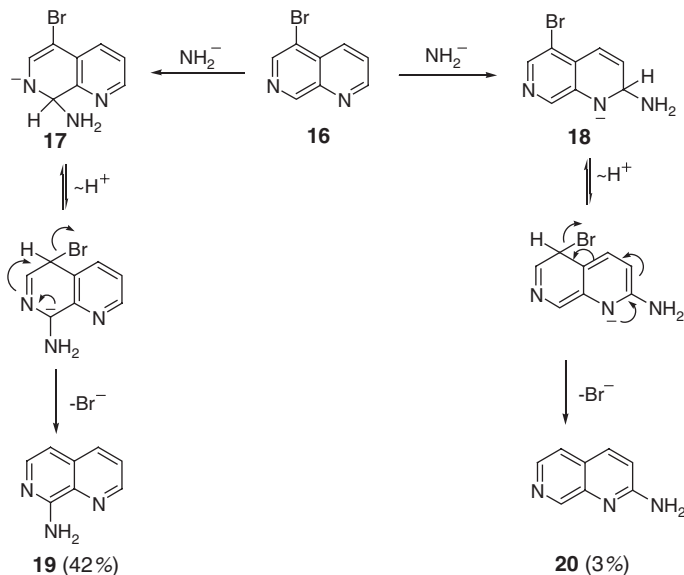
cine-Substitution often occurs via an aryne mechanism (82T427). Hydrogen loss in this case is the result of an acid–base reaction that does not strictly correspond to the topic of this review.

The $\text{S}_{\text{N}}\text{H}$ transformations in which a leaving group departs from a more remote position of the ring or even from a side chain are classified as *tele*-substitution. For example, 5-bromo-1,7-naphthyridine **16** with KNH_2 in liquid ammonia gives a mixture of 8-amino- and 2-amino-1,7-naphthyridines **19**, **20** in 42 and 3% yields correspondingly (78JHC731). Intermediate σ^{H} -adducts **17** and **18** are likely to be stabilized as shown in Scheme 5.

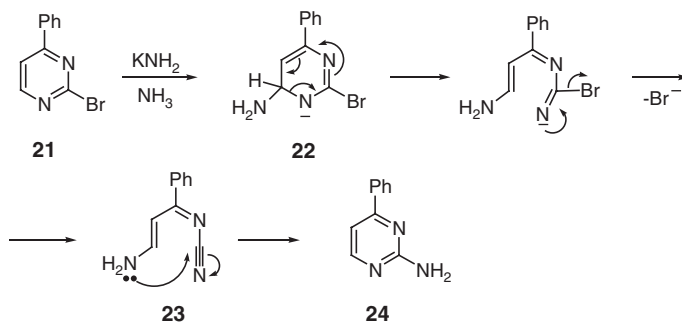
Sometimes *tele*-substitution proceeds via a multi-step pathway known as an ANRORC-mechanism (78ACR462, 85T237). Thus, 2-bromo-4-phenylpyrimidine **21** with KNH_2 in liquid ammonia affords 2-amino derivative **24** (Scheme 6) (74RTC111). Thorough investigation of this reaction has shown that it begins with the addition of a nucleophile at position 6 occupied with a hydrogen atom and not the halogen atom. The σ^{H} -adduct **22** then undergoes ring opening followed by elimination of bromide ion producing cyanamino derivative **23**. Intramolecular addition of the amino group to the $\text{C}\equiv\text{N}$ bond results in ring closure and formation of compound **24**.

4. Vicarious Nucleophilic Substitution of Hydrogen

The theory and practice of vicarious nucleophilic substitution of hydrogen (VNS) were examined in detail mostly by Mąkosza and his co-workers (87ACR282,

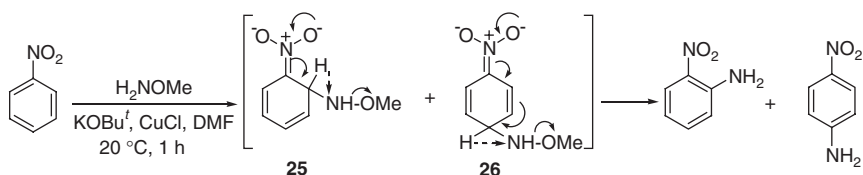


Scheme 5



Scheme 6

04CRV2631). An essential peculiarity of these reactions is that a leaving group (X) is contained in the nucleophile and transformation of the σ^{H} -adduct into the final product proceeds as base-induced elimination of HX. For instance, nitrobenzene is aminated with *O*-methylhydroxylamine in the presence of *t*-BuOK and a catalytic amount of CuCl giving a mixture of *ortho*- and *para*-nitroanilines in 93% total yield and isomeric ratio 71:29 (Scheme 7) (96JOC442, 99JCS(P1)1437). The MeONH^- anion acts as the nucleophile. Elimination of a methoxide group from σ^{H} -adducts 25 and 26 induces positive charge on the amine nitrogen atom, which is compensated by a 1,2-hydride shift. The nitro group creates electron-deficiency in the aromatic ring and stabilizes the σ -complex.



Scheme 7

III. Heterocyclizations Based on S_NH Reactions

All heterocyclizations based on S_NH reactions can be conveniently divided into following four types:

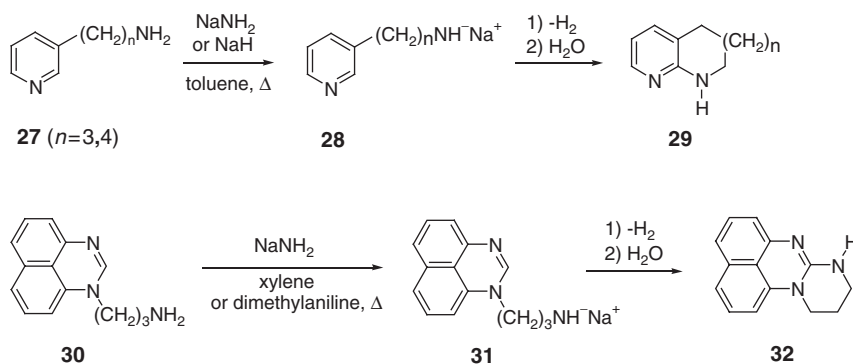
- (1) Intramolecular one-step S_NH cyclizations.
- (2) Tandem cyclizations initiated by an S_NH reaction in which subsequent heteroring closure is realized by an intramolecular addition to a multiple bond, a condensation or an $S_N ipso$ substitution.
- (3) Tandem S_NH - S_NH cyclizations when a hetero-ring annulation is a result of two consecutive S_NH reactions.
- (4) Complex multi-step cyclizations when the S_NH reaction initiates several other processes sometimes including repeated S_NH reactions, classified as cascade sequences (96CRV137).

A. INTRAMOLECULAR ONE-STEP S_NH CYCLIZATIONS

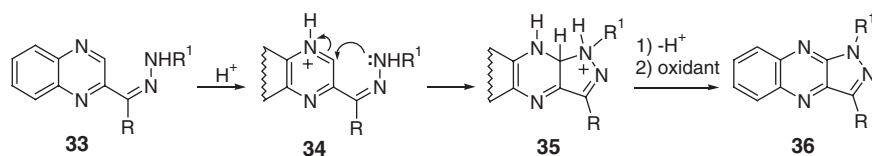
Cyclizations of this kind are, perhaps, the most numerous. They may proceed either by the conventional S_N2Ar pathway (oxidative or non-oxidative) or through one of the above-mentioned non-conventional mechanisms. The term “one-step” means of course that all possible precursors of substrate as well as non-isolable intermediates are not taken into consideration.

1. Non-oxidative S_N2Ar Reactions

Information concerning such cyclizations is very scarce. Thus, as far back as 1973 it was found that the heating 3-(ω -aminoalkyl)pyridines **27** with sodium hydride or sodium amide in toluene results in formation of bicyclic compounds **29** (73JHC39). Another example is the intramolecular amination of 1- γ -aminopropylperimidine **30** by $NaNH_2$ in xylene or *N,N*-dimethylaniline (Scheme 8). The reaction produces 1,2,3,4-tetrahydropyrimido[1,2-*a*]perimidine **32** in good yield (00UP). Notably, the sodium amide that easily aminates other pyridines and 1-*R*-perimidines (78RCR1042) in both above cyclizations acts simply as a base to generate alkylamide ions **28**



Scheme 8



Scheme 9

and **31**. These examples confirm the well-known fact that intramolecular reactions are much more favorable than intermolecular ones.

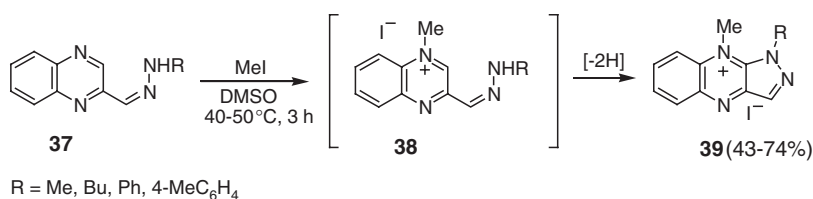
2. Oxidative S_N2Ar Reactions

Most such reactions are referred to as intramolecular hydrazination of aryl- and hetarylhydrazones resulting in pyrazole ring annulation. For example, heating 2-acylquinoxaline hydrazones **33** in a slightly acidic or neutral medium in the presence of an oxidant affords pyrazolo[4,5-*b*]quinoxalines **36** (Scheme 9) (57AG479, 66ZC329, 86IJC(B)215, 86IJC(B)901, 01JHC829, 02MC68, 03RCB2175, 03T6311). Evidently, the reaction pathway includes protonation of the substrate (acid catalysis) that favors nucleophilic attack of the terminal amino group at C(3) in cation **34**. Oxidation of σ^H -adduct **35** then gives pyrazole **36**. Oxygen, sulfur, chloroanil, nitrobenzene and azabenzene were used as oxidants. In some cases cyclization of **33** to **36** was performed with an excess of phenylhydrazine or hydroxylamine. The latter are supposed to participate in dehydrogenation of the σ^H -adduct resulting in their reduction into aniline and ammonia, respectively. In the absence of an acid the reaction needs a prolonged heating in a high-boiling solvent or just melting (Table 1).

Treatment of hydrazones **37** with methyl iodide leads to spontaneous cyclization of intermediate salts **38** into pyrazoloquinoxalium compounds **39** (Scheme 10) (02MC68, 03RCB2175). In agreement with expectation, electron-withdrawing groups

Table 1. Intramolecular hydrazination of hydrazones **33**

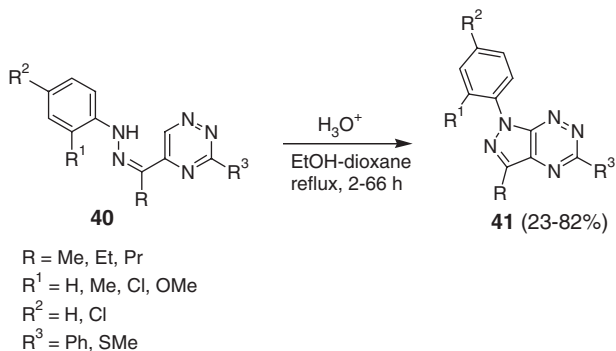
R	R ¹	Reaction conditions	Yield of 36 (%)	Ref.
H	Ph 4-MeC ₆ H ₄ 4-ClC ₆ H ₄ 4-BrC ₆ H ₄	PhNHNH ₂ , AcOH, aq. HCl, reflux, 5–10 h	^a	57AG479 66ZC329 86IJC(B)901
H	Ph 4-MeC ₆ H ₄ 4-ClC ₆ H ₄ 4-BrC ₆ H ₄	Ph-N = N-Ph	^a	86IJC(B)215
H	H Me CH ₂ Ph	O ₂ , EtOH, aq. H ₂ SO ₄ , reflux, 4 h	75–80	02MC68 03RCB2175
Me	Ph	S, 220–260 °C, 20 min PhNO ₂ , 210 °C, 5 h Chloroanil, xylene, reflux, 4 h NH ₂ OH · HCl, EtOH, aq. HCl, reflux, 30 min	42 65 65 62	03T6311
Me	4- R ¹ -5-R ² - thiazolyl-2	NH ₂ OH · HCl, EtOH, aq. HCl, 100–110 °C, 2–4 h	29–63	03T6311
Me	PhCO 2-ClC ₆ H ₄ CO 4-ClC ₆ H ₄ CO	Chloroanil, xylene, reflux, 12 h	35–48	01JHC829

^aUnknown yield.**Scheme 10**

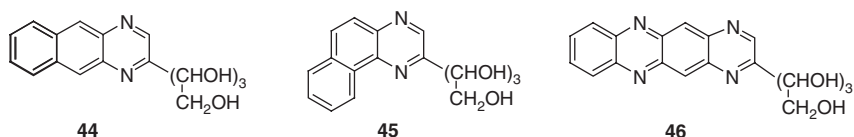
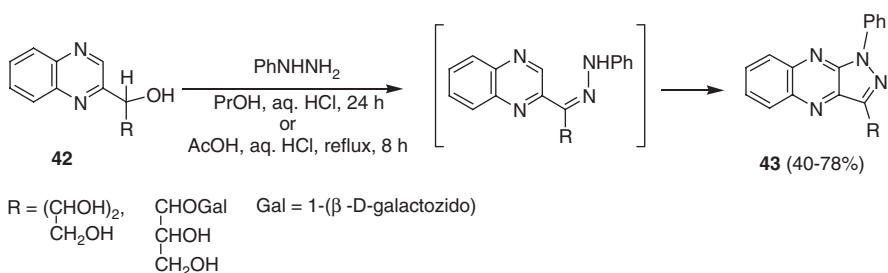
(R = 4-NO₂C₆H₄, 4-HO₂CC₆H₄ etc.) inhibit the process. Apparently, air oxygen as well as the salts **38** may serve as oxidants in this transformation.

Like **33**, 5-acyl-*as*-triazine arylhydrazones **40** are converted into pyrazolo[4,3-*e*]-*as*-triazines **41** on heating in acidic medium (Scheme 11) (00H2175).

Reactions of this type proceed quite easily even with hydrazones obtained *in situ*. Thus, interaction of 2-polyhydroxyalkylquinoxalines **42** with an excess of phenylhydrazine in the presence of HCl affords pyrazoles **43** in moderate to good yield



Scheme 11



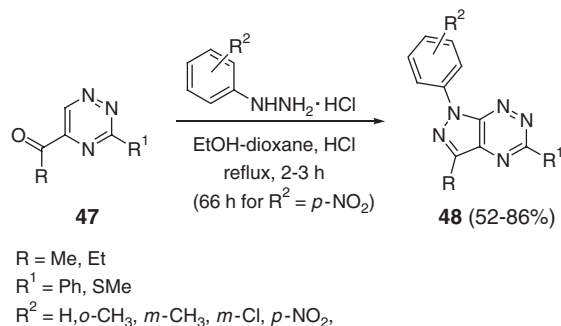
Scheme 12

(Scheme 12) (58CB113, 58CB2273). Phenylhydrazine may act here as a hydride ion acceptor. Compounds **44–46** undergo similar cyclization.

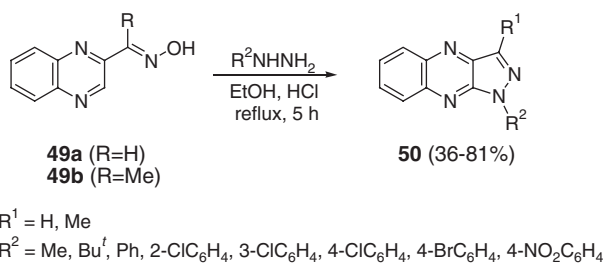
5-Acyl-*as*-triazines **47** react with arylhydrazones hydrochlorides in acidic medium to yield pyrazolotriazines **48** (Scheme 13) (00H2175). If any electron-withdrawing group is present in the hydrazine reagent, a more prolonged heating is necessary.

Since oximes are more stable to oxidation and often more available than the corresponding carbonyl compounds they also can be used as starting material for the cyclizations. For instance, quinoxaline-2-aldehyde oxime **49a** as well as ketoxime **49b** are converted by hydrazine in acidic medium into flavazoles **50** (Scheme 14) (01JHC829). Hydroxylamine, which is liberated in the first step, may act as a hydride ion acceptor. This minimizes using a large excess of arylhydrazine or any another oxidant.

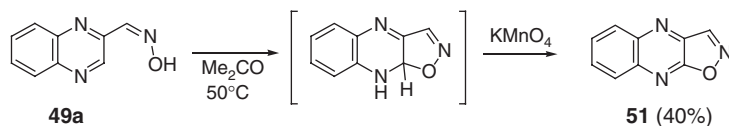
Oximes themselves as *O*-nucleophiles can be subjected to intramolecular oxidative S_NH cyclizations. Thus, oxime **49a** is transformed into isoxazoloquinoxaline **51** on heating with KMnO₄ in acetone (Scheme 15) (03RCB2175).



Scheme 13



Scheme 14

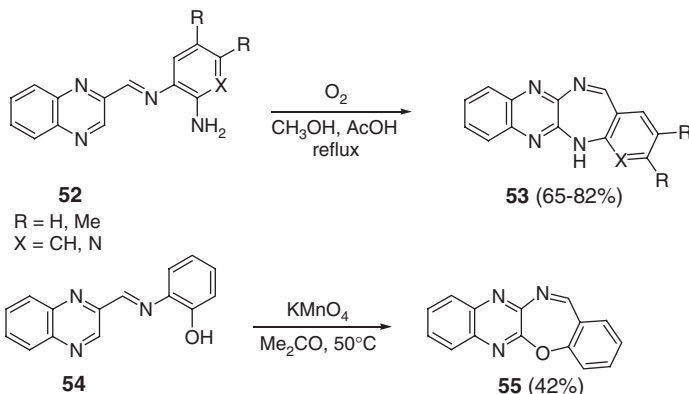


Scheme 15

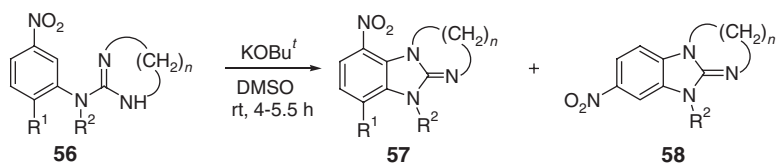
Similar cyclizations with participation of a less nucleophilic arylamino group or phenolic hydroxyl group are also possible. For example, azomethines **52** and **54** are converted into diazepines **53** and oxazepines **55** on heating under oxidative conditions (Scheme 16) (03RCB2175).

Despite the high nucleophilicity of the guanidine functionality, S_NH cyclization often demands ionization of an NH -group. Thus, treatment of N -(3-nitrophenyl) guanidines **56** with t -BuOK in DMSO leads to imidazole ring closure by nucleophilic substitution of hydrogen *ortho* or *para* to the nitro group, depending on the nature of substituent R^1 and on methylene chain length (Scheme 17) (92S596).

Somewhat structurally different guanidines **59** undergo similar cyclization furnishing benzimidazoles **60** and **61** (Scheme 18) (92S596). Increasing the N -substituent volume in the guanidine moiety, evidently, favors *para*-substitution. The starting nitroarene probably serves as an oxidant causing yields less than 60%.



Scheme 16

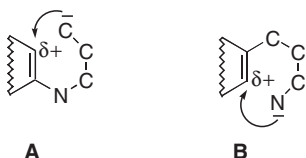


n	R ¹	R ²	Yield, %	
			57	58
2	H	Me	14	-
3	H	Me	22	-
3	H	CH ₂ Ph	44	-
3	Cl	Me	7	58
4	H	Me	-	38

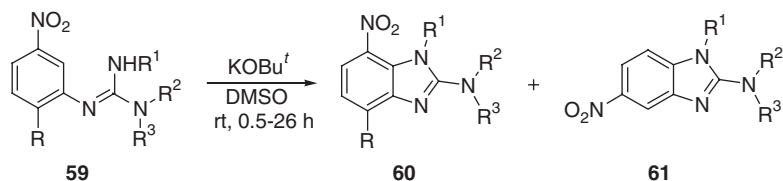
Scheme 17

Interestingly, compound **56** (R¹ = H, R² = CH₂Ph, n = 3) on prolonged heating in acetonitrile in the presence of MnO₂ is also able to cyclize as a neutral form. However, in this case, unlike the *t*-BuOK/DMSO system, only *para*-substitution occurs providing **58** in 56% yield. In the authors' opinion, the main reason for this difference is due to MnO₂ that initiates the radical mechanism. However, it may be that the new conditions are favorable for producing the more stable *para*-isomer **58**.

There are several examples of pyridine ring closure by an intramolecular oxidative S_NH reaction in accordance with cyclization Schemes **A** and **B**:

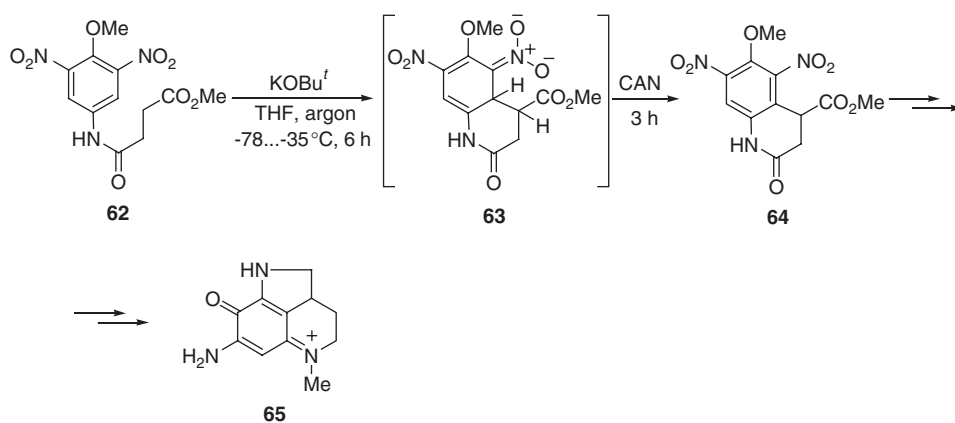


Scheme **A** was employed in the multi-step synthesis of the marine sponge alkaloid makaluvamine **65** that displays cytotoxic activity (98JOC9846, 98SL845).



R	R ¹	R ²	R ³	Total yield, %	Ratio 60 : 61
H	-(CH ₂) ₄ -	H	H	58	28 : 1
H	-(CH ₂) ₄ -	Me	H	58	19 : 1
Cl	-(CH ₂) ₃ -	H	H	34	1 : 0
Cl	-(CH ₂) ₃ -	Me	H	55	1 : 0
H	-(CH ₂) ₃ -	CH ₂ Ph	H	44	1 : 0
H	Pr ^{<i>i</i>}	Pr ^{<i>i</i>}	H	50	1 : 0
H	Ph	Pr ^{<i>i</i>}	H	44	0 : 1

Scheme 18

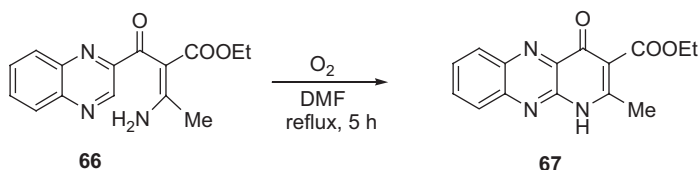


Scheme 19

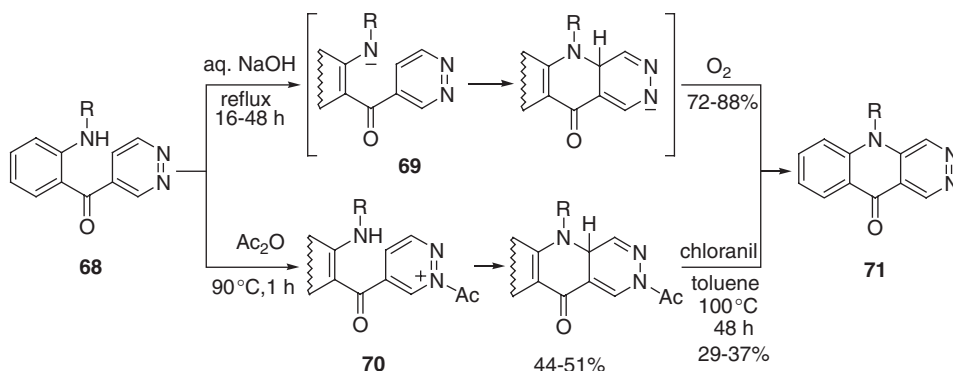
In particular, *N*-arylsuccinimide **62** (obtained from anizidine in three steps) with *t*-BuOK in THF produces the corresponding carbanion, which instantly cyclizes into σ^H -adduct **63**. The latter, on oxidation with cerium ammonium nitrate (CAN) gives lactame **64** in 53% yield (Scheme 19).

The alternative Scheme **B** is based on *N*-nucleophilic attack. Thus, bubbling air through a boiling solution of ethyl 3-amino-2-(quinoxaline-2-carbonyl)crotonoate **66** in DMF furnishes pyrido[2,3-*b*]quinoxaline **67** (Scheme 20) (04RCB1267). The latter has a structural similarity to derivatives of 4-quinolone-3-carboxylic acid, well known because of their high antibacterial activity.

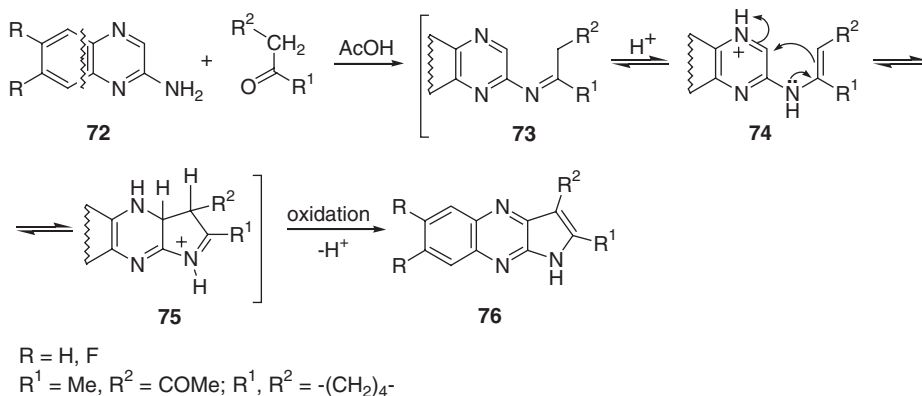
Heterocyclization of 4-(2-alkylaminobenzoyl)pyridazines **68** into diazaacridones **71** can be promoted either by ionization of their *NH*-group into more nucleophilic anions **69** or by converting them into *N*-acylpyridinium salts **70** possessing higher electrophilicity (Scheme 21) (89LAC481). The reactions are performed in the



Scheme 20



Scheme 21



Scheme 22

presence of an external oxidant, in particular, air oxygen or chloroanil. In both cases nucleophilic attack occurs exclusively on the pyridazine C(5) atom that is commonly more reactive than C(3) (01CHC1461).

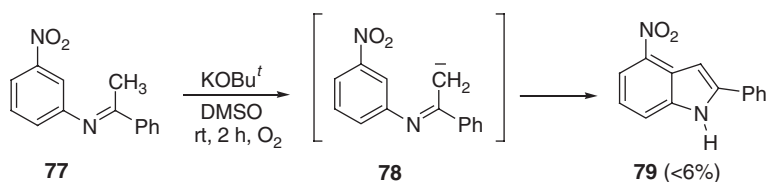
Imines **73**, generated *in situ* from 2-aminoquinoxalines **72** and ketones in acetic acid, are transformed spontaneously into pyrrolo[2,3-*b*]quinoxalines **76** (Scheme 22) (02RCR707). The S_NH cyclization seems to proceed by equilibrium amounts of enamine **74**. Adducts **75** are oxidized, apparently, with air oxygen or cation $72H^+$.

Noteworthy, imine **77** is slightly cyclized into 2-phenyl-5-nitroindole **79** in the presence of a base (Scheme 23) (04T247). This is probably due to the reduced electrophilicity of the benzene ring in intermediate anion **78**. No cyclization of **78** at the position *para* to the nitro group has been observed.

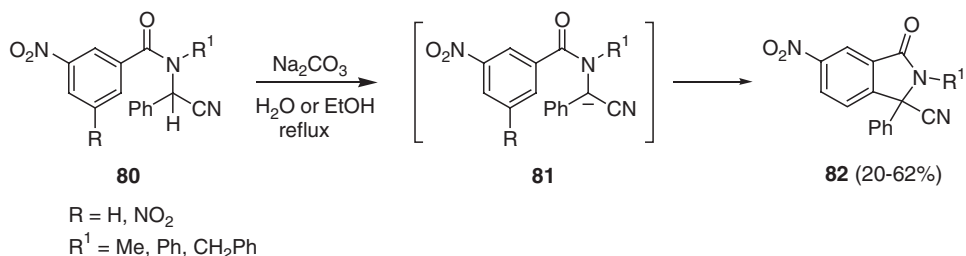
m-Nitrobenzoic acid amides **80** display essentially greater activity to cyclization in basic medium. Heated with Na_2CO_3 in aqueous or alcoholic solution, they are converted into isoindolinones **82** in moderate yield (Scheme 24) (72CC849). The reaction most likely proceeds by intermediate carbanion **81**. The substrate itself, as well as the reaction product, may accept a hydride ion from the σ^{H} -adduct. However, the use of an external oxidant, for example benzoquinone, provides a higher yield of **82**.

A tendency of nitroarenes to nucleophilic substitution of hydrogen *ortho* to the nitro group remains unchanged in methanesulfonamides **83**, which are easily converted into 2,1-benzothiadiazoline 2,2-dioxides **84** in *t*-BuOK/DMF (Scheme 25) (92PJC1121). Only traces of isomeric product of *para*-substitution were observed.

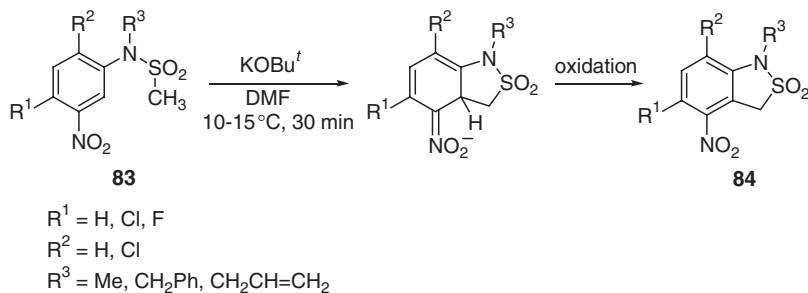
Owing to the absence of any activating groups, a surprising exception from the above reactions represents the double $\text{S}_{\text{N}}\text{H}$ cyclization of bis-amidrazone **85a** in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (Scheme 26) (98JA2989). This leads to the formation of the remarkably stable antiaromatic 16π -electron mesoionic compound **87a**. Regrettably, the cited article does not provide any experimental details as well as possible reaction mechanism. However, one can assume that the step-wise cyclization proceeds either through two mono-*N*-anions or, that is less probably, via dianion **86a** (the latter is depicted here for simplicity) followed by oxidation of the σ^{H} -adduct with air oxygen. Recently, a similar cyclization has been conducted for pyridine bis-amidrazone **85b** but the yield of **87b** did not exceed 10% (05AG(E)5255).



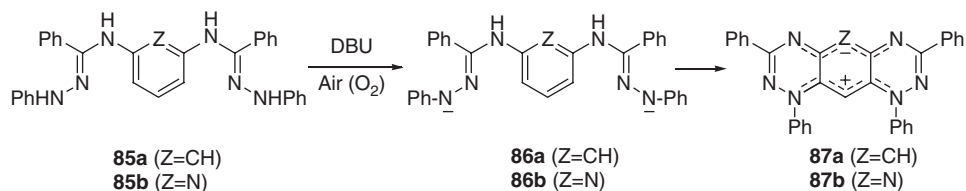
Scheme 23



Scheme 24



Scheme 25



Scheme 26

3. *tele*-Substitution Reactions

Only a few reactions of this type are known. For example, treating 2-(1,2-dibromoalkenyl)quinoxalines **88** with sodium trithiocarbonate in aqueous methanol results in thiophene ring closure to thieno[2,3-*b*]quinoxalines **89** (Scheme 27) (01JCS(P1)154).

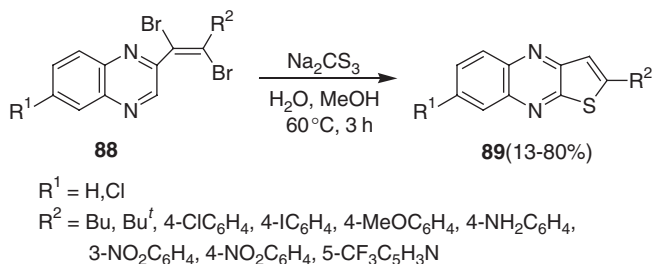
The reaction, evidently, starts with addition of trithiocarbonate ion across the exocyclic C=C bond followed by elimination of a CS₂ molecule from intermediate **90**. Intramolecular *S*-nucleophilic attack and subsequent departure of two bromide ions from σ^{H} -adduct **91** furnishes condensed thiophene **89** (Scheme 28).

Substrate π -deficiency is, apparently, a critical factor. Thus, dibromovinyl derivatives of monocyclic azines, e.g. pyrimidine **92**, pyrazine **93** and quinoline **94** are not subjected to this reaction (01H2139). On the contrary, lumazines **95** and pyrimidopyridazines **97** form the corresponding thiophenes **96** and **98** (Scheme 29) (03RCB1403, 05JHC413).

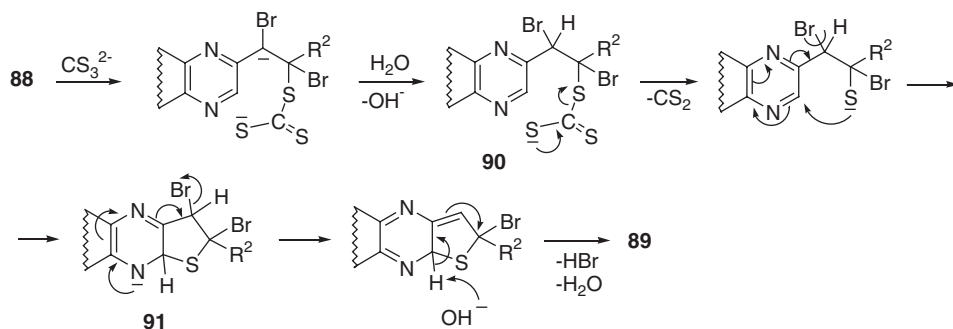
5-(Dibromovinyl)phthalazine **99** reacts with Na₂CS₃ similarly to produce *peri*-condensed thiirane **100** in 50% yield (Scheme 30) (01H2139).

4. VNS Reactions

Historically, the first example of such a cyclization was the high-yield synthesis of 2-substituted benzimidazoles **104**, on treatment of *N'*-aryl-*N*-hydroxyamidines **101** with benzenesulfonyl chloride in the presence of a base (usually Et₃N or pyridine) under anhydrous conditions (58JCS2086). The reaction most likely proceeds through



Scheme 27



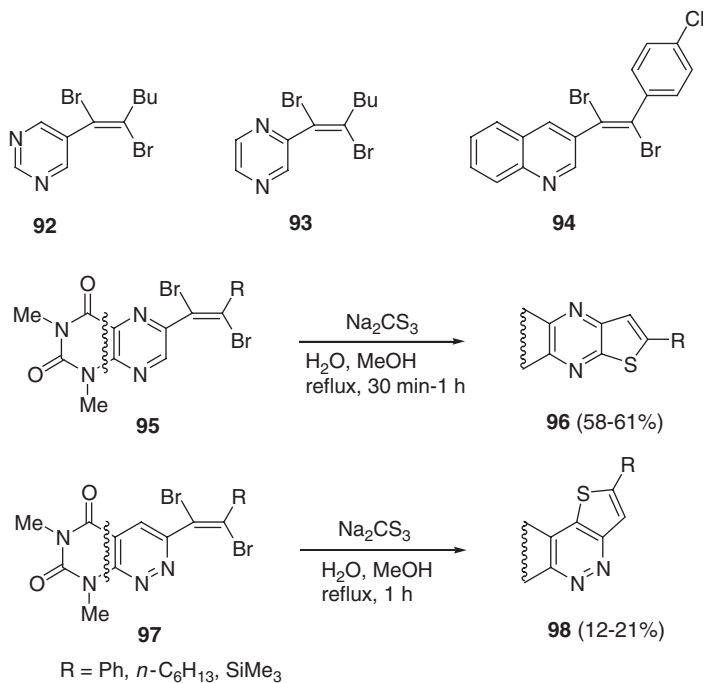
Scheme 28

benzenesulfonyl derivative **102** and its anion **103** although the authors expressed an opinion that this might be a kind of Beckmann rearrangement (Scheme 31).

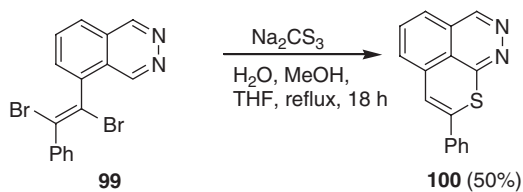
This approach has been extended in several other works. *N*-Arylamidine hydrochloride **105** with one equivalent of sodium hypochlorite and a base can be converted into benzimidazoles **107a–c**, including the famous fungicide thiabendazole **107b**, in excellent yield (65JOC259). The *N*-chloroamidine **106** might be isolated, if desired, prior to addition of base (Scheme 32).

In another study *m*-nitroguanidines **108** treated with *t*-BuOK in DMSO or DMF produced 2-amino-4-nitrobenzimidazoles **109** in 4–65% yield (Scheme 33) (99JCS (P1)1153). Two other products were 5(6)-nitro- **110** (1–24%) and 5(6)-alkoxybenzimidazoles **111** (4.7–13%). Predominant nucleophilic attack on the position *ortho* to the nitro group can be explained by the higher positive π -charge that it carries at atom C(2). In Małosza's opinion, it may also be assisted by coordination of a potassium ion (serving as a counterion at the nucleophilic center) to an oxygen atom of the NO_2 group (87ACR282). Noteworthy, as the size of vicarious OR groups is increased, the yield of *para*-cyclization products also grows, possibly due to steric hindrance to *ortho*-substitution.

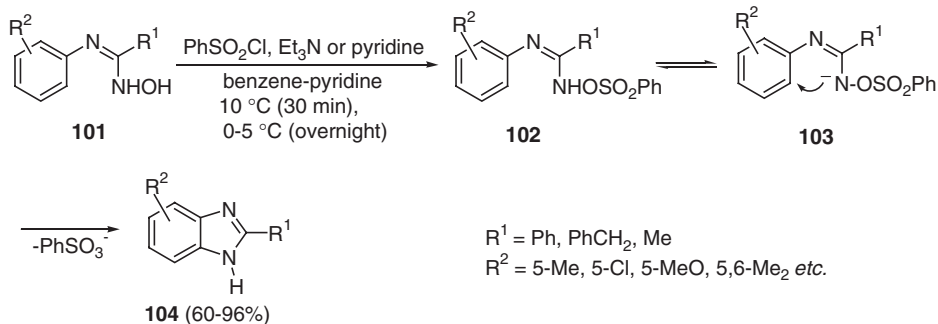
In several instances similar transformations were conducted under base-free conditions. Thus, heating *N,N'*-diphenylbenzamidine **112** with hydrogen peroxide at 80 °C leads to the formation of 1,2-diphenylbenzimidazole **114** in 67% yield (Scheme 34) (99IZV626). Though the mechanism of this conversion remains unclear,



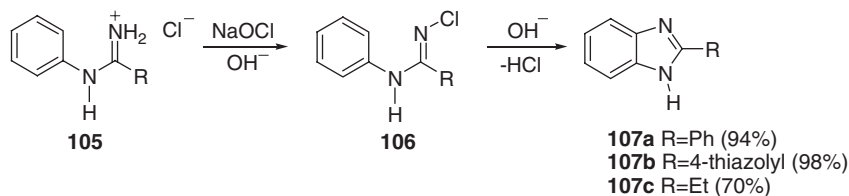
Scheme 29



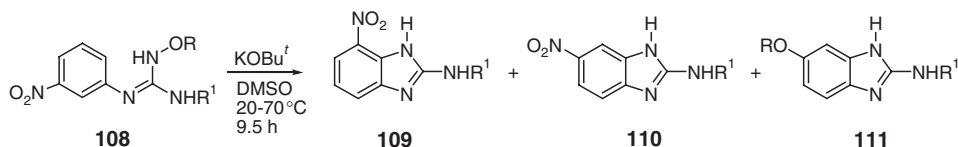
Scheme 30



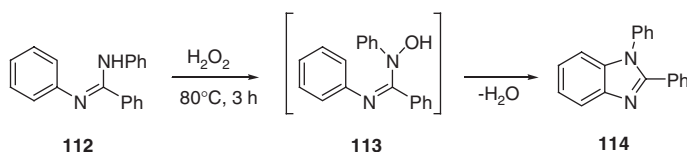
Scheme 31



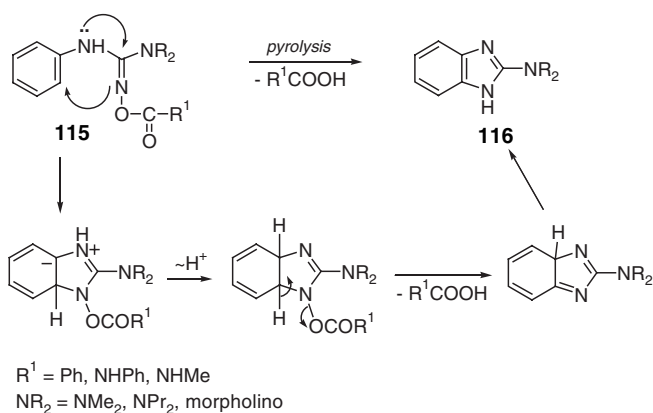
Scheme 32



Scheme 33



Scheme 34



Scheme 35

one can propose that *N*-hydroxyamidine **113** is formed as an intermediate then undergoing the *VNS* cyclization.

Pyrolysis of guanidines **115** affords 2-dialkylaminobenzimidazoles **116** in 13–27% yield (73ZC292). A plausible mechanism is shown in Scheme 35. Acyloxy functionality serves as a vicarious leaving group.

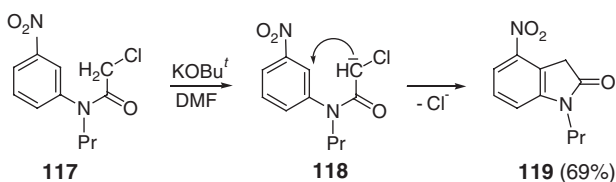
3-Nitro- α -chloroacetanilide derivative **117** in *t*-BuOK/DMF is rapidly cyclized into indole **119** via intermediate α -chlorocarbanion **118** (Scheme 36) (94H1701).

The VNS reaction of *N*-alkyl-*N*-(3-nitrophenyl)chloromethylsulfanilides **120** with NaOH in DMSO provides benzo- γ -sultams **121** and **122** (Scheme 37) (84TL4791, 87ACR282, 92S571). As in many above examples, the *ortho*-cyclization product prevails even in the presence of a chlorine atom in the position *para* to the nitro group. When R¹ = F the contribution of *ipso* substitution increases but still remains less than that of S_NH cyclization.

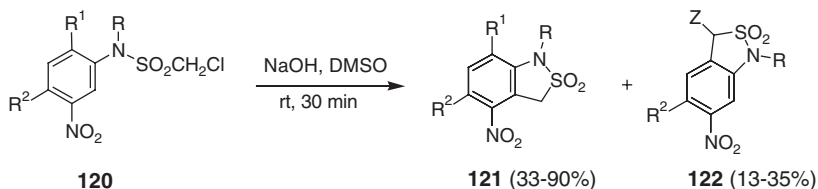
Under similar conditions compounds **123** give benzo- δ -sultams **124** and **125** (Scheme 38) (84TL4791, 92S571).

The conversion of sulfamides **126** and **128** into *peri*-condensed sultams **127** and **129** underlines the generality of this method (Scheme 39) (92S571).

Unlike chloromethylsulfamides **120**, their pyridine and quinoline analogues bearing a chloromethylsulfonylamido substituent in position 3 do not undergo this cyclization, possibly due to their insufficient electron deficiency. Indeed, more electrophilic



Scheme 36



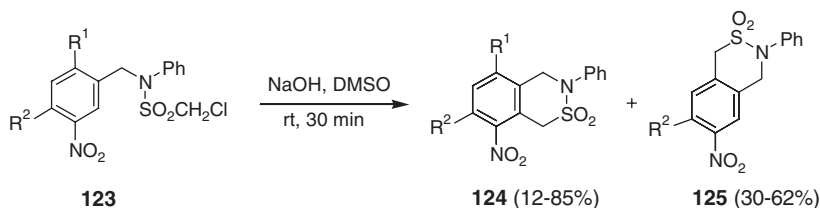
R = Me, C_8H_{17} , PhCH_2 , MeOCH_2

R^1 = H, Me, Cl, F

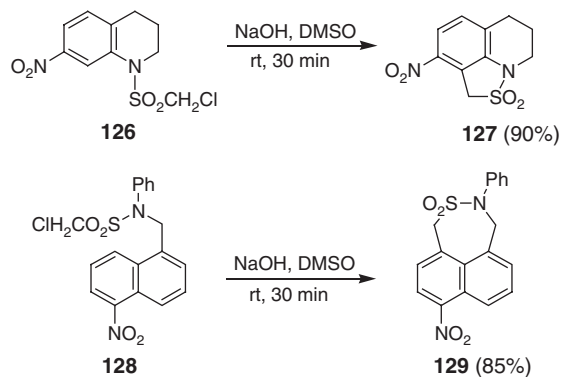
R^2 = H, Me, Cl, OMe

Z = H, Cl

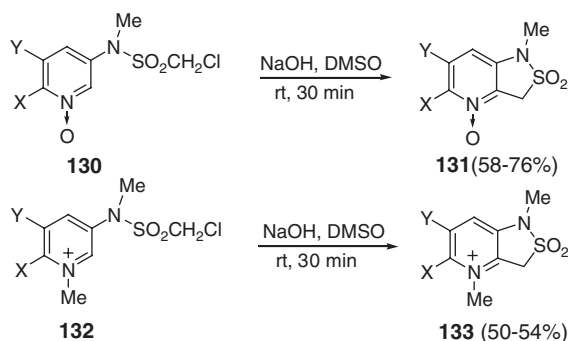
Scheme 37



Scheme 38



Scheme 39



Scheme 40

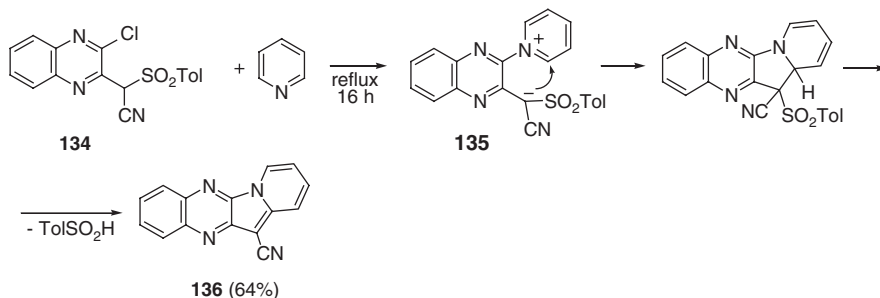
N-oxides **130** as well as pyridinium or quinolinium salts **132** afford sultams **131** and **133** in good yields (Scheme 40) (01T5009).

Interestingly the tandem-like *VNS* cyclization of quinoxaline derivative **134** into indolizino[2,3-*b*]quinoxaline **136** takes place on refluxing of the former in pyridine. Evidently, the reaction proceeds with participation of betaine **135** that spontaneously cyclizes (Scheme 41) (92KGS107).

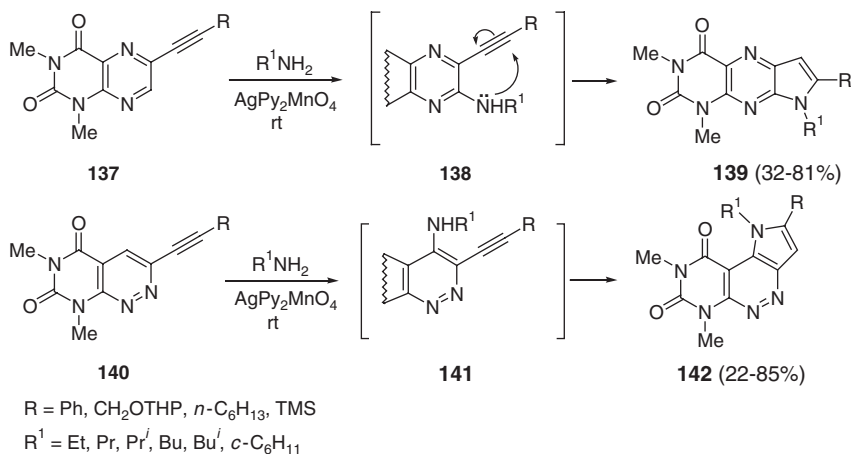
B. TANDEM CYCLIZATIONS INITIATED BY AN S_NH REACTIONS

1. Tandem S_NH Reactions and Addition to Multiple Bonds

This type of cyclization has been already illustrated by the formation of 7-azaindole on Chichibabin amination of 3-ethynylpyridine (Scheme 2). Similarly, 6-alkynyl-1,3-dimethylumazines **137** (03RCB1403, 05JHC413) and 3-alkynyl-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones **140** (05JHC413, 03RCB441)



Scheme 41

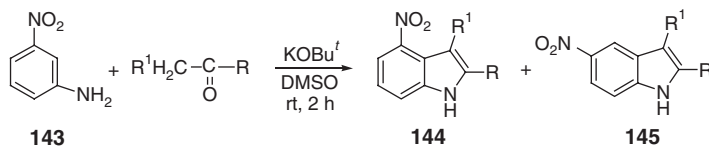


Scheme 42

react with primary alkylamines in the presence of AgPy₂MnO₄ to afford pyrroles **139** and **142** (Scheme 42). Obviously, the first formed amines **138** and **141** are quickly cyclized by nucleophilic addition of the amino group across the carbon–carbon triple bond. On using bulky *tert*-butylamine, the latter stage proceeds slowly due to steric hindrance. As a consequence, *N*-*tert*-butylpyrroles **139** (**142**) as well as *N*-*tert*-butylamino derivatives **138** (**141**) are isolated in comparable amounts.

m-Nitroaniline **143** reacts with methylene active ketones in *t*-BuOK/DMSO leading to a mixture of isomeric indoles **144** and **145** in moderate total yield (Scheme 43) (99TL5395, 04T247). When R¹ = H the cyclization proceeds predominantly in the position *ortho* to the nitro group. In all other cases the yield of *para*-substitution product **145** essentially increases and becomes similar to that of **144**.

The first step of the reaction seems to be a nucleophilic attack of the enolate anion on position 2 or 6 of *m*-nitroaniline. In the second stage, the cyclocondensation of anionic σ^H-complex (**146** to **147** to **148** to **144**) or previously oxidized adduct (**149** to **144**) occurs (Scheme 44). The participation of air oxygen and, apparently, substrate

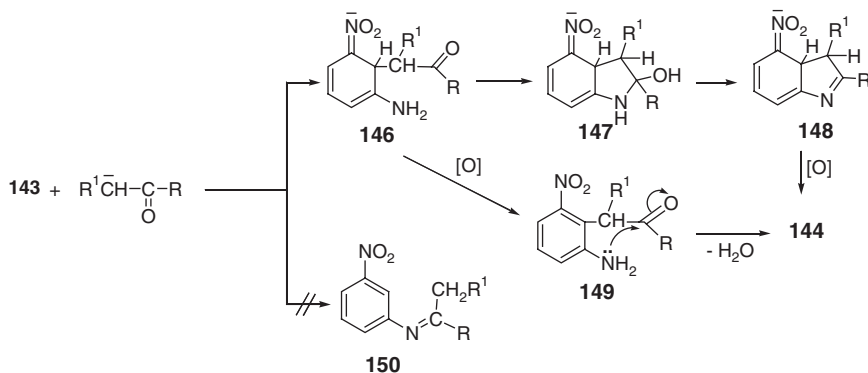


R = Me, Et, *c*-C₃H₅, Bu^t, Ph, 2-Py, 2-furyl, 2-thienyl, 2-(*N*-methylpyrrolyl)

R¹ = H, Me

R, R¹ = -(CH₂)_{*n*}, *n* = 3-5; *o*-xylenyl

Scheme 43

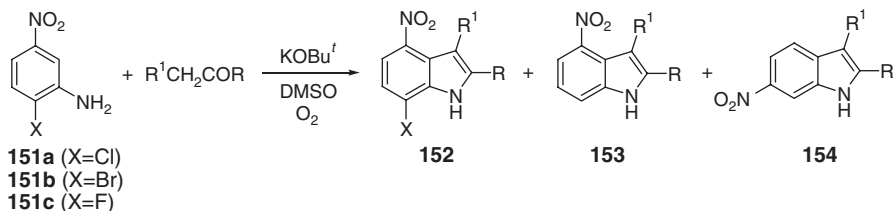


Scheme 44

in oxidation of the σ^{H} -adduct has been proved experimentally. Reaction of **143** with acetophenone carried out under an argon atmosphere results in decreasing yields of indoles **144** and **145** to 28 and 4% respectively. But bubbling oxygen through the mixture provides 66% of **144** and 4% of **145**. Another possible mechanism, including formation of azomethine **150** followed by S_NH cyclization, is less probable since authentic Schiff's base **150** prepared from *m*-nitroaniline and acetophenone when treated with *t*-BuOK in DMSO gives less than 6% of 2-phenyl-5-nitroindole.

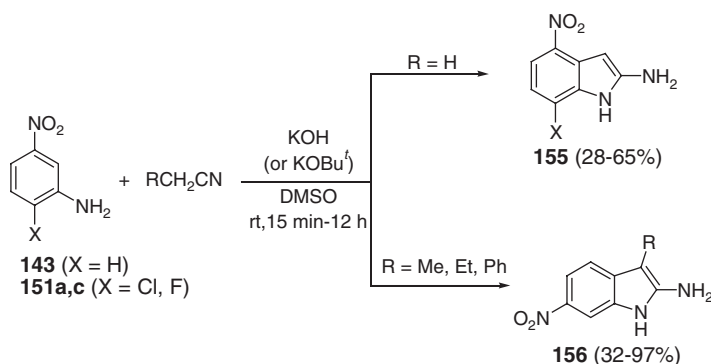
The preference of an oxidative S_NH process over substitution of halogen is observed in similar reactions of *m*-nitroanilines **151** bearing a halogen *para* to the nitro group (Scheme 45) (04T247). In cases of chloride **151a** and bromide **151b**, apart from *ortho*-cyclization product **152**, a substantial amount of indole **153** is also formed. The mechanistic aspects of dehalogenation were not discussed in the original paper, except an opinion that it likely proceeds at one of the intermediate steps leading to indole **153** and not via direct dehalogenation of **152**. For 6-fluoro-3-nitroaniline **151c** the main transformation **151** to **152** is accompanied by tandem *ipso*-substitution, a condensation process leading to 6-nitroindoles **154**.

m-Nitroaniline **143** and its 6-halogeno derivatives **151a,c** react with alkyl cyanides in basic medium to yield **155** or **156** (Scheme 46) (00H533). Similar to the above heterocyclizations, the first step of this conversion is nucleophilic attack of alkyl cyanide carbanion on a position *ortho* or *para* to the NO₂ group. The exact



X	Yield, %		
	152	153	154
Cl	21-36	5-16	-
Br	37	33	-
F	33-50	-	3-15

Scheme 45



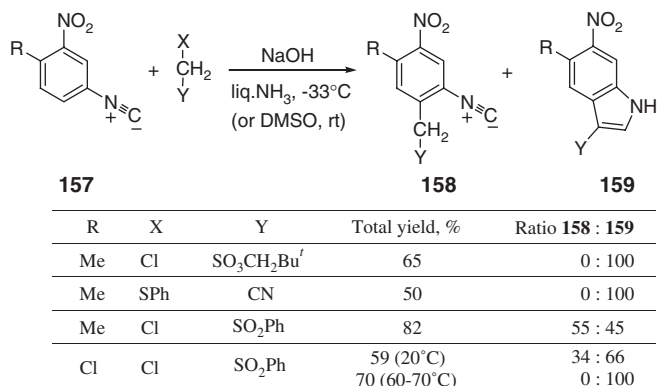
Scheme 46

orientation is sterically dependent. The carbanion generated from acetonitrile attacks an *ortho* position whereas secondary carbanions add to a C(6) atom.

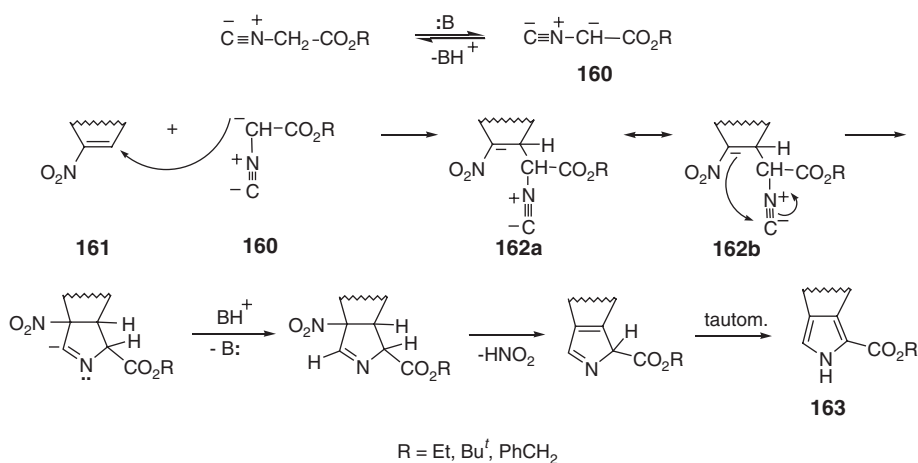
The VNS reaction of *m*-nitrophenylisocyanides **157** with carbanions of methylene active compounds containing a leaving group X at an α -position gives products **158**, which are able then to cyclize into indoles **159** (Scheme 47) (84TL4793). Substrate **157** behaves as a bifunctional electrophile with one electrophilic center at the ring carbon atom and the second one at the terminus of the isonitrile group. Correspondingly, reagent XCH_2Y twice displays its nucleophilic character, the second time being included in **158**.

2. The Barton–Zard Condensation

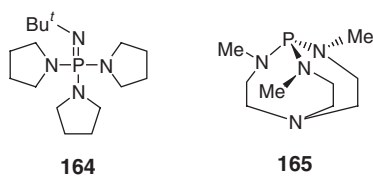
The Barton–Zard condensation is one more important and marvelous $\text{S}_{\text{N}}\text{H}$ heterocyclization leading to pyrrole ring annulation to nitroalkenes, nitroarenes or nitrohetarenes on being treated with alkyl isocynoacetates in the presence of a base (85CC1098, 90T7587). The reaction starts with nucleophilic attack of alkyl isocynoacetate carbanion **160** *ortho* to the NO_2 group of substrate **161**. The



Scheme 47



Scheme 48



Scheme 49

σ^{H} -adduct **162** is then cyclized into pyrrole **163** that is accompanied by a loss of HNO₂ (Scheme 48).

DBU is usually applied as base to generate isocyanacetate carbanions. However, stronger non-nucleophilic bases like **164** and **165** (Scheme 49) are also of importance and often increase the yield of pyrroles **163** (96TL8391, 00SL213).

To enter the Barton–Zard condensation, a substrate must have essentially nitroalkene character. This is the reason why the reaction with nitrobenzene fails and 1-nitronaphthalene also reacts slightly (94CC1019). An additional NO₂ group on the naphthalene ring substantially facilitates the transformation but the expected dipyrroles are not formed (95TL4381). Table 2 presents various substrates, the corresponding products and some other details of the Barton–Zard condensation.

3-Nitropyridine **166** in the Barton–Zard condensation behaves specifically affording tricyclic compound **167** (00SL213). Evidently, 4-azaisoindole derivative **168** formed in the first step reacts further with another molecule of nucleophile that results in imidazole ring closure (Scheme 50). Under the same conditions 4-nitropyridine remains unchanged.

In the case of quinoxalines **169a,b**, benzothiadiazole **172a** and benzoselenodiazole **172b** the reaction exhibits a remarkable dependence on the base. Whereas in the presence of DBU all these substrates react with ethyl isocyanoacetate to yield pyrimidine *N*-oxides **170** and **173** only, the use of phosphorane **164** provides pyrroles **171** and **174** predominantly (Scheme 51) (96TL8391).

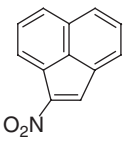
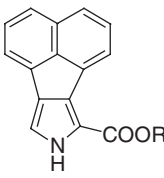
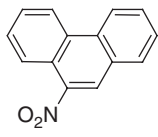
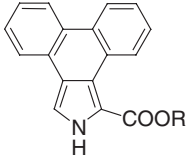
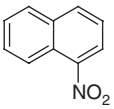
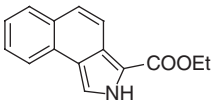
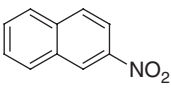
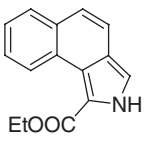
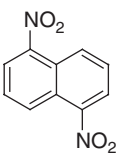
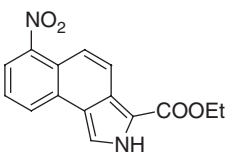
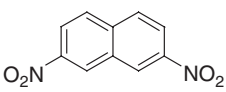
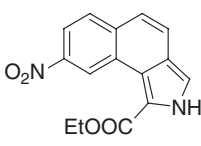
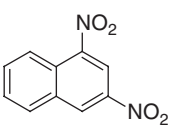
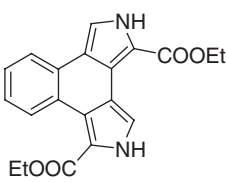
The change of reaction course was attributed by the authors to acoplanarity of the NO₂ group and the benzene ring in σ^{H} -adduct **175** on using phosphorane base. In their opinion the acoplanarity might be caused by the bulkyness of counterion **164H**⁺ that ultimately causes cyclization into pyrroles **171** and **174** (path “*b*”) (Scheme 52). One can see, however, that such rotation should equally favor pyrimidine ring closure (path “*a*”). In this connection a more logical explanation may consist in a donor–acceptor *H*-interaction between the σ^{H} -adduct and conjugated base **H-B**⁺ as shown in structure **176**. Obviously, the more effectively the negative charge in the σ^{H} -adduct is delocalized, the more probable should be cyclization in accordance with path “*a*”. This seems to occur with **DBU·H**⁺. As to salt **176** with **164H**⁺ as counterion, the extremely high basicity of phosphorane **164** resists proton donation and can not inhibit the normal course of the Barton–Zard condensation. Further studies of the influence of bases on directionality of the reaction are needed.

Interaction of 3-nitro-1-phenylsulphonylindole **177** with ethyl isocyanoacetate in the presence of DBU also proceeds specifically to furnish pyrrolo[2,3-*b*]indole **181** (96CC1909, 97CC1873, 99S1117). In accordance with the authors’ assumption, σ^{H} -adduct **178** formed on *C*-nucleophilic attack of isocyanoacetate carbanion on atom C(2), undergoes ring opening (**178** to **179**) to produce intermediate phenylsulfonylamide **180** (Scheme 53). Intramolecular addition of its phenylsulfonylamino group across the C = N bond and subsequent elimination of HNO₂ provide **181**.

Thus, it follows from Schemes 51 and 53 that heterocyclic substrates in the Barton–Zard condensation often behave anomalously.

In conclusion, it should be noted that the Barton–Zard condensation formally might be considered as a tandem S_NH–S_N *ipso* process (see Section III.B.3). However, the corresponding σ^{H} -complex is stabilized here not via elimination of any auxiliary leaving group or oxidation but by means of an intramolecular nucleophilic attack on an isonitrile fragment. This is due to the amphoteric nature of isocyanoacetate ion acting at first as a nucleophile and then as an electrophile.

Table 2. Substrates and products of the Barton-Zard condensation

Substrate 161	Base applied	Reaction product 163	Yield (%)	Ref.
	DBU		14-47	94CC1019 96JA8767 96JCS(P1)417 96TL4873 98JOC8455
	DBU		53-87	94CC1019 94TL2493 95AG(E)683 95TL4381 95TL9441 96JCS(P1)417 98JOC3998 00SL213
	DBU		2-10 22-33 21	94TL2493 96TL8391 97TL1403 00SL213
	DBU 164		- 14	00SL213
	DBU 164		45 78	00SL213
	DBU 164		44 71	00SL213
	DBU 164		25 31	00SL213 97TL1403

(continued)

Table 2 (continued)

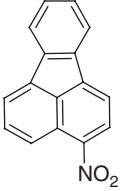
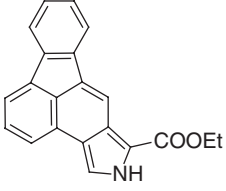
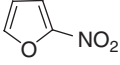
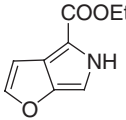
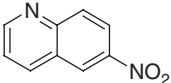
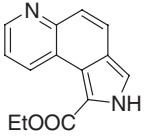
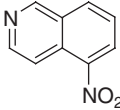
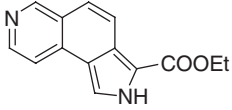
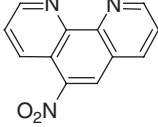
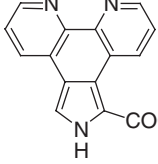
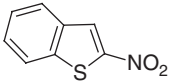
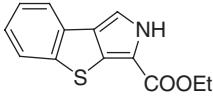
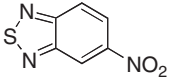
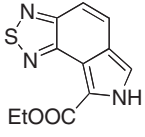
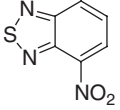
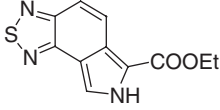
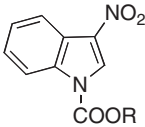
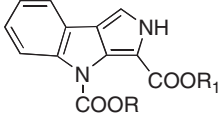
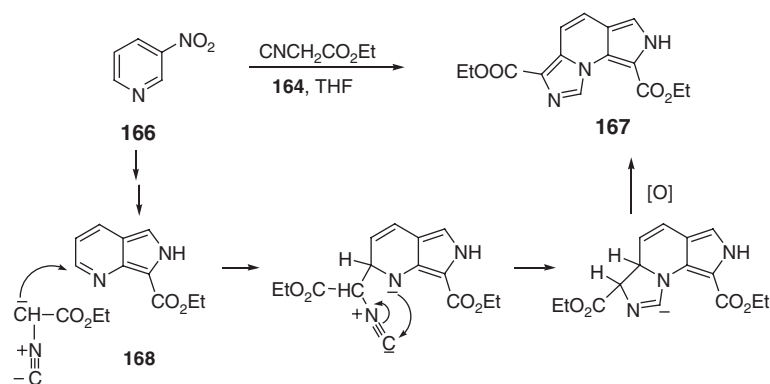
Substrate 161	Base applied	Reaction product 163	Yield (%)	Ref.
	DBU 164		- 50	00SL213
	164		a	00SL213
	DBU 164		- 44-47	96TL8391 00SL213
	DBU 164		- 26	00SL213
	DBU		53-87	94CC1019 94TL2493 95TL9441
	DBU		60	94CC1019
	DBU		21	96JCS(P1)1403
	DBU		33	96JCS(P1)1403

Table 2 (continued)

Substrate 161	Base applied	Reaction product 163	Yield (%)	Ref.
	DBU		80–91	96CC1909 97CC1873 99S1117
(2-Nitro-5,10,15,20-tetraphenylporphyrinato) nickel	DBU	Pyrroloporphyrine	a	96CC1475

^aIn original article the yield is not given.

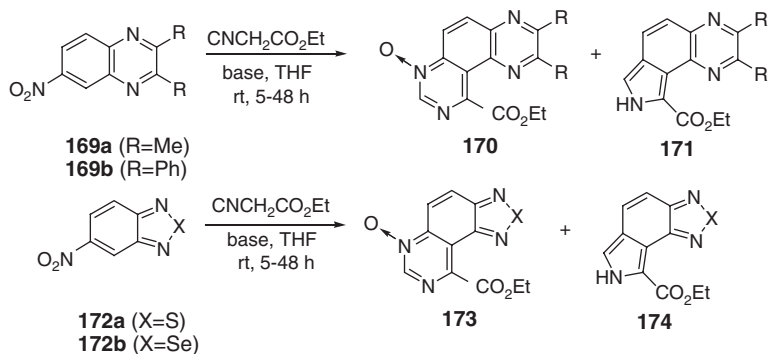


Scheme 50

3. Tandem $\text{S}_{\text{N}}\text{H}$ and S_{N} *ipso* Reactions

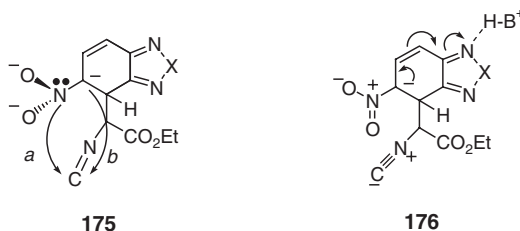
Cyclizations of this type are realized in substrates with two vicinal electron-deficient carbon atoms, one is unsubstituted and the other carries a good leaving group. Correspondingly, bifunctional nucleophiles are normally used in these reactions. The symbol $\text{S}_{\text{N}}\text{H}-\text{S}_{\text{N}}$ *ipso* means that nucleophilic replacement of hydrogen precedes *ipso* substitution. Formally, an $\text{S}_{\text{N}}\text{H}-\text{S}_{\text{N}}$ *ipso* transformation has to be an AEA'E'-process that includes two pairs of addition–elimination steps. However, the AA'E'E' sequence usually occurs and therefore cyclizations described in this section are attributed to the $\text{S}_{\text{N}}\text{H}-\text{S}_{\text{N}}$ *ipso* type in accordance with an actual result.

A typical example of such heterocyclization is the interaction of 3-phenyl-5-methoxy-1,2,4-triazine **182** with urea or *N,N*-dimethylurea in acetic or, better, in trifluoroacetic anhydride. The role of anhydride consists in converting starting molecule into a more electrophilic triazinium salt **183**, which then reacts with a bifunctional nucleophile to form imidazotriazinone **184** (Scheme 54) (00MC58, 01JHC901).



Substrate	Base	Yield, %	
		170 or 173	171 or 174
169a	DBU	15	0
	164	0	38
169b	DBU	32	0
	164	0	39
172a	DBU	21	0
	164	3	30
172b	DBU	28	0
	164	3	46

Scheme 51

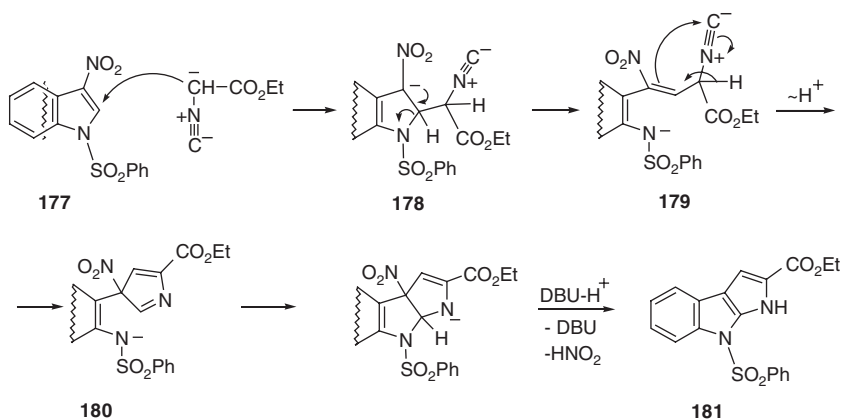


Scheme 52

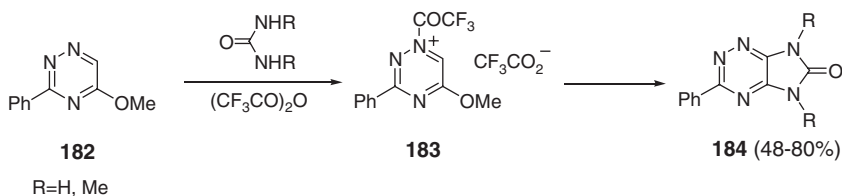
This cyclization involves consecutive formation of σ^{H} -adducts **185** and **186** with the following stepwise aromatization of **186** to **187** to **184** (Scheme 55). Moreover, it is possible to interrupt the reaction at any step by varying conditions.

In the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and under bubbling air through the reaction mixture triazine **182** also reacts with resorcinol to give benzofurotriazine **189** in 26% yield (Scheme 56) (01JHC901). Though the sequence of formation of σ^{H} - and σ^{ipso} -adducts has not been elucidated, primary attack on atom C(6) leading to **188** is thought to be more preferable sterically.

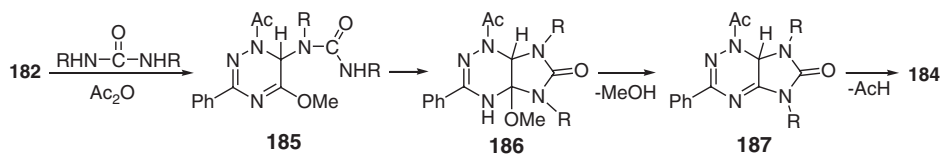
A series of similar heterocyclizations were performed with 2-chloroquinoxaline **190**. Thus, furoquinoxaline **192** was obtained in 15% yield by treating **190** with methyl-*t*-butylketone enolate **191** (Scheme 57) (82JOC1036). The pathway includes C-nucleophilic attack of the enolate ion on unsubstituted atom C(3) followed by intramolecular replacement of chlorine in dianionic σ^{H} -adduct **193**. Finally,



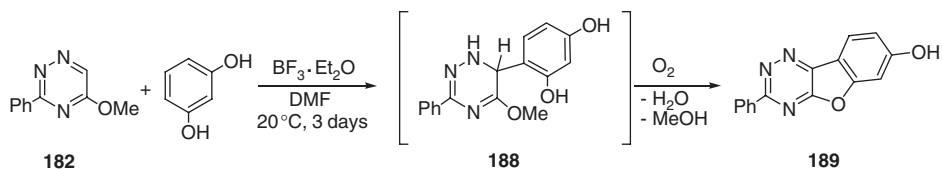
Scheme 53



Scheme 54

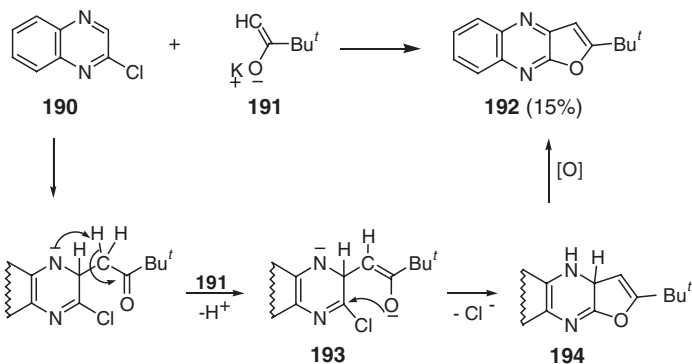


Scheme 55

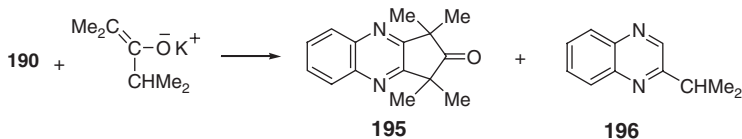


Scheme 56

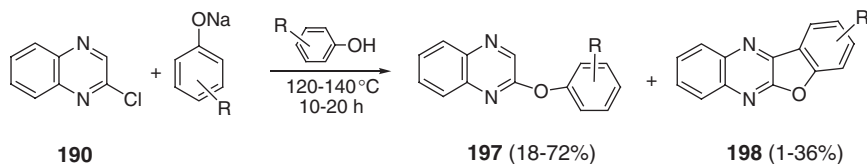
oxidative aromatization of dihydro derivative **194** occurs. It is noteworthy, that to perform cyclization of **190** to **192**, two equivalent of enolate **191** had to be used. This provides some evidence for participation of the adduct **193** in the transformation.



Scheme 57



Scheme 58



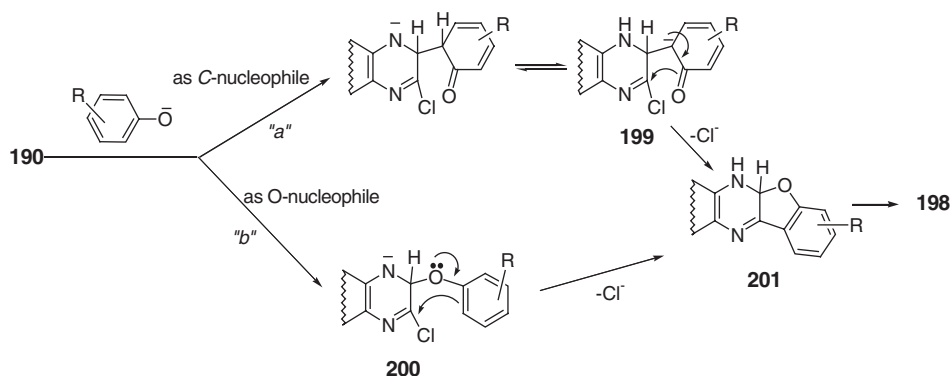
R= H, 2-Me, 3-Me, 4-Me, 3-MeO, 2,3-Me₂, 2,5-Me₂, 3,5-Me₂, 1-C₁₀H₇, 2-C₁₀H₇

Scheme 59

Interestingly, reaction of **190** with diisopropylketone enolate goes differently, producing a mixture of quinoxalino[*b*]cyclopentanone **195** and 2-isopropylquinoxaline **196** in 28 and 17% yields, respectively (Scheme 58) (82JOC1036).

Heating **190** with an excess of phenol or another phenolic reagent in the presence of one equivalent of the corresponding sodium phenolate gives a mixture of 2-aryloxyquinoxaline **197** and benzofuro[2,3-*b*]quinoxaline **198** (Scheme 59) (01JHC901). The latter usually prevails.

In principle, the construction of **198** may proceed either as a tandem S_N *ipso*-S_NH heterocyclization or as an S_NH-S_N *ipso* sequence. Since 2-aryloxyquinoxalines **197** do not cyclize under the above conditions, only the former possibility seems to be realized. Similar uncertainty exists with the phenolate nucleophile. It may react as a *C*-nucleophile (Scheme 60, path "a") or this transformation may start from *O*-nucleophilic attack (path "b"). In both cases the same cycloaddition product **201**



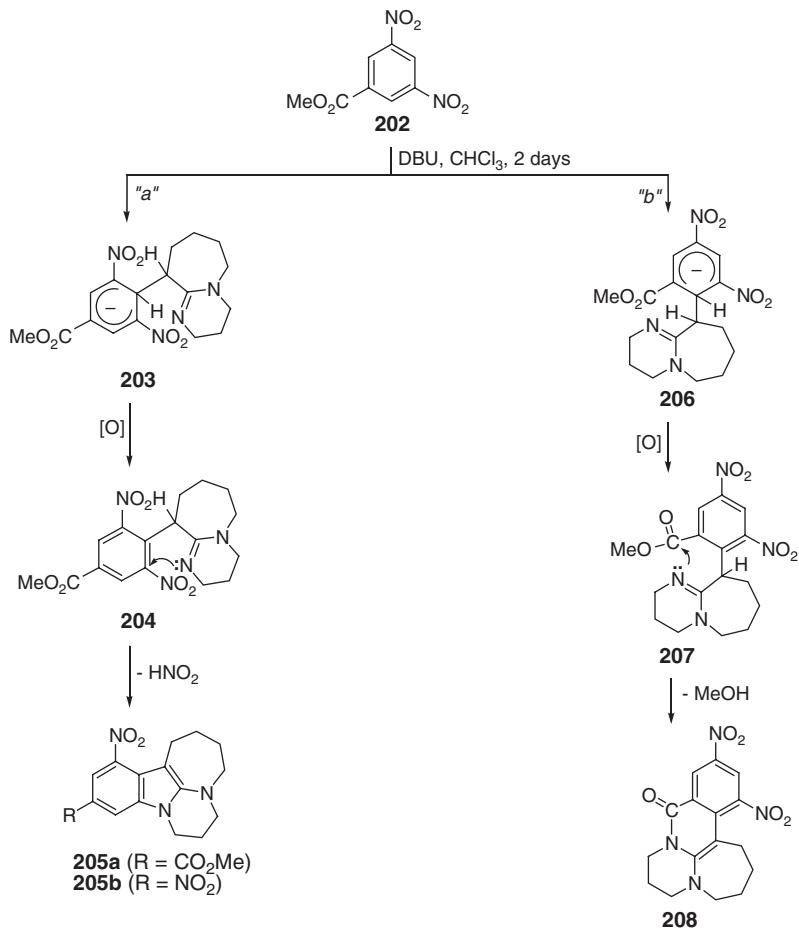
Scheme 60

has to be formed. Considering that replacement of the chlorine atom in intermediate **199** should proceed easier than with **200**, pathway “a” is preferred. Experiments with quinoxalines substituted in the benzene ring might answer this question.

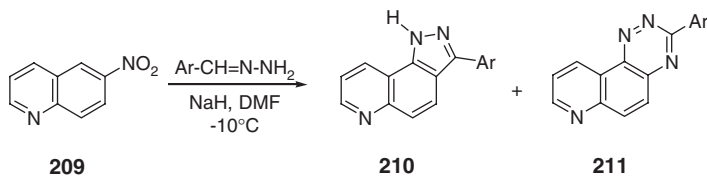
Aryloxy derivatives **197** can be cyclized into benzofuroquinoxalines **198** in 50–70% yields on prolonged heating in PPA at 140–160°C (74JCS(P1)129). Under these conditions the more electrophilic protonated form of the substrate is subjected to an intramolecular nucleophilic attack at the carbon atom *ortho* to the aryloxy group.

There are several examples of S_NH-S_N *ipso* cyclizations in nitroarenes series. Thus, 3,5-dinitromethylbenzoate **202** reacts slowly with DBU in chloroform or ethylacetate giving a mixture of pyrrole- **205a** (19%) or pyridine-centered **208** (unknown yield), both tetracyclic compounds (Scheme 61) (97CC325). Formation of **205a** can be rationalized as a result of tandem S_NH-S_N *ipso* processes initiated by C-nucleophilic attack of DBU on the C(4) atom of **202** (path “a”). Transformation of **202** to **208** starts with nucleophilic attack on the C(2) atom and is completed by intramolecular acylation (path “b”). It should be stressed that DBU behaves here as a C,N-binucleophile and in the first step the reaction is likely to proceed through equilibrium amounts of its enamine form. As to the oxidant for adducts **203** and **206**, the substrate itself may play this role. Interaction of 1,3,5-trinitrobenzene with DBU is realized by path “a” to furnish condensed pyrrole **205b** in 11% yield (97CC325). 1,3,5-Trinitrobenzene reacts similarly with other bifunctional nucleophiles such as *o*-aminophenols or *o*-aminothiophenols to produce 1,3-dinitrophenoxazines and 1,3-dinitrophenothiazines [06MC230].

6-Nitroquinoline **209** enters into a direct cyclocondensation with aromatic hydrazones in NaOH/DMF giving pyrazolo[3,4-*f*]quinolines **210** and (or) triazino[6,5-*f*]quinolines **211** in low to moderate yield (Scheme 62) (00OL413). Their ratio mainly depends on the structure of the starting hydrazone. For example, electron-donating substituents in its aryl moiety assist triazine ring closure. Evidently, pyrazoles **210** are products of two consecutive S_NH and S_N *ipso* reactions, whereas conversion of **209** into **211** looks rather complicated and better corresponds with cascade heterocyclizations considered in Section III.D.1.



Scheme 61



Scheme 62

C. TANDEM S_NH–S_NH CYCLIZATIONS

Many electron-deficient aromatic substrates have several reaction sites potentially capable of undergoing nucleophilic substitution of hydrogen including tandem S_NH–S_NH substitution. The problem is that when the first nucleophilic group has

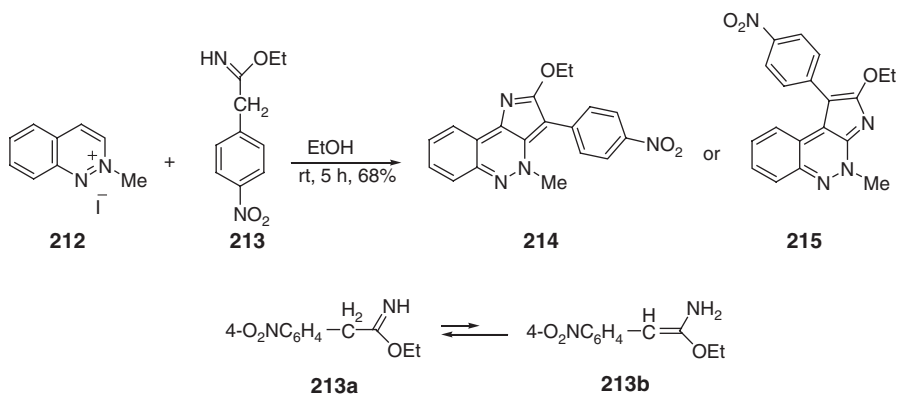
entered the substrate, it strongly deactivates the resultant molecule toward subsequent nucleophilic attack (78RCR1042, 94MI1). Pyridine, which is converted into its 2,6-diamino derivative under substantially more drastic conditions than that required for its monoamination, is an instructive example (see Scheme 1). This is one of the few cases of the multiple Chichibabin reaction. It is not surprisingly, therefore, that tandem S_NH-S_NH reactions are also very rare. The first examples in a series of azinium cations and neutral azines were discovered only recently. To the best of our knowledge no reports on similar transformations of nitroarenes still exist.

1. Azinium Cations as Substrates

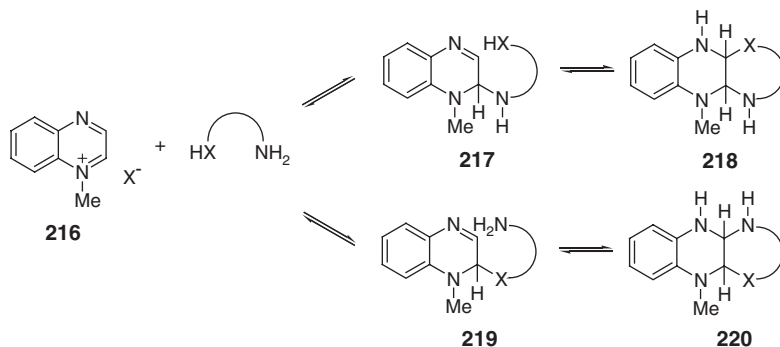
Perhaps, the only known reaction of this type proceeding in one-pot without isolation of the intermediate bis- σ^H -adduct is the conversion of *N*-methylcinnolinium iodide **212** on treatment with iminoether **213** into pyrrolocinnoline **214** (Scheme 63) (81KGS1549). Although the structure of **214** has not been proved strictly, alternative structure **215** seems less probable. The reaction may proceed via equilibrium amounts of enamine **213b**, which first acts as a *C*-nucleophile attacking the most electron-deficient C(3) position of cation **212**. Iminoether **213** used in a large-excess most likely serves as a dehydrogenating agent toward the intermediate σ^H -adduct.

In fact, all other reactions of azinium cations with various 1,3- and 1,4-binucleophiles represent A_N-A_N processes resulting in the formation of stable di- σ^H -adducts, for example **218** or **220** (Scheme 64). Thorough investigations of these adducts, mostly derived from quinoxalinium and 1,2,4-triazinium salts, were carried out by Chupakhin and Charushin (for review see (88AHC(43)301, 04PAC1621)). They established that the di-adducts **218** and **220** have the corresponding mono-adducts **217** and **219** as their precursors. All mono- and di-adducts interconvert and depending on conditions any of them can be isolated.

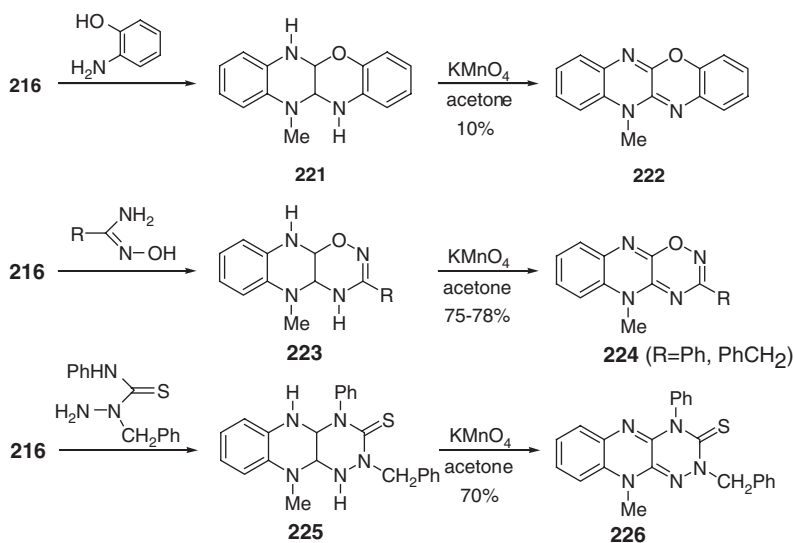
To convert the above di-adducts into fully conjugated compounds, their oxidation with potassium permanganate in acetone solution was conducted. However, such oxidation does not always proceed smoothly and successful examples are not



Scheme 63



Scheme 64



Scheme 65

numerous. Scheme 65 demonstrates adducts **221**, **223** and **225**, which were prepared from salt **216** on treating it with *o*-aminophenol, amidoxime or thiosemicarbazide derivatives and then oxidized (87KGS1118, 87KGS1260). Although the formation of products **222**, **224** and **226** was ultimately realized via substitution of two hydrogen atoms, it should be noted that cycloaddition and oxidation were performed in two separate experiments. Therefore, attributing these cyclizations to the S_NH-S_NH type seems questionable.

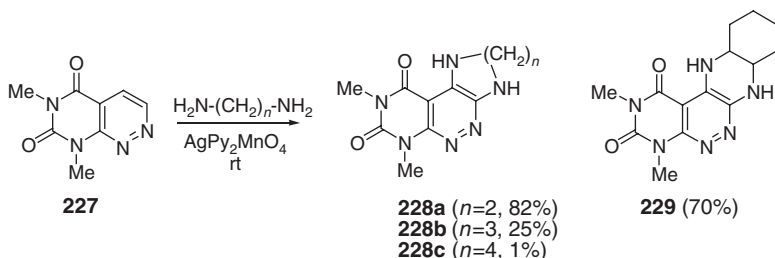
2. Neutral Azines as Substrates

Recently in our laboratory the first neutral azine substrate, namely 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione **227**, displaying a remarkable ability

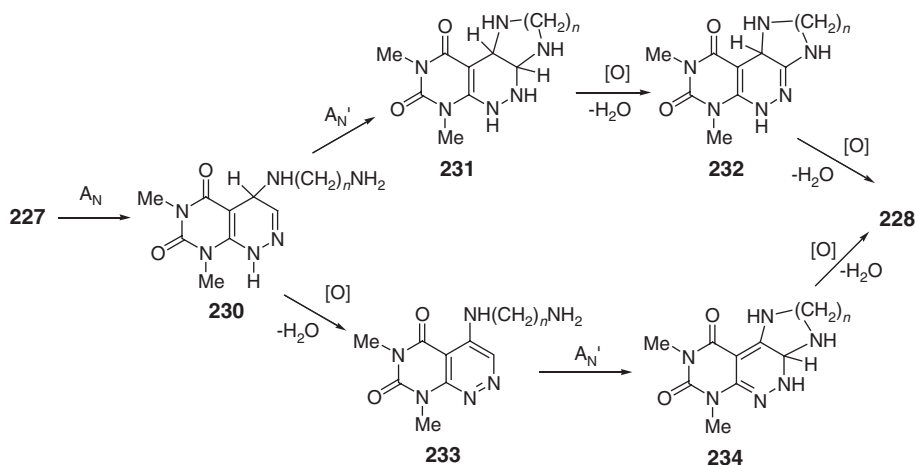
to tandem S_NH-S_NH heterocyclizations, has been discovered. Thus, its treatment with α,ω -diaminoalkanes or 1,2-diaminocyclohexane in the presence of an oxidant (complex $AgPy_2MnO_4$) results in the formation of polycyclic compounds **228a–c** and **229** (Scheme 66) (00MC150).

Taking into account that monoamination of compound **227** with liquid ammonia or primary alkylamines proceeds exclusively on the most electron-deficient position 4 (99RCB1150), the formation of mono- σ^H -adduct **230** in the first step seems likely (Scheme 67). However, further development of the pathway is not yet clear. In principle, the cyclization may proceed either through an $A_NA_{N'}EE'$ -pathway to give intermediate di-adduct **231** or via an $A_NEA_{N'}E'$ -sequence with stepwise formation and aromatization of dihydroadducts **230** and **234**. It cannot be excluded that both mechanisms are realized. A sharp decrease in yield in the case of **228b,c** is likely caused by an entropy factor that resists the second stage of cyclization owing to an increase in length of the methylene chain in the initial binucleophile.

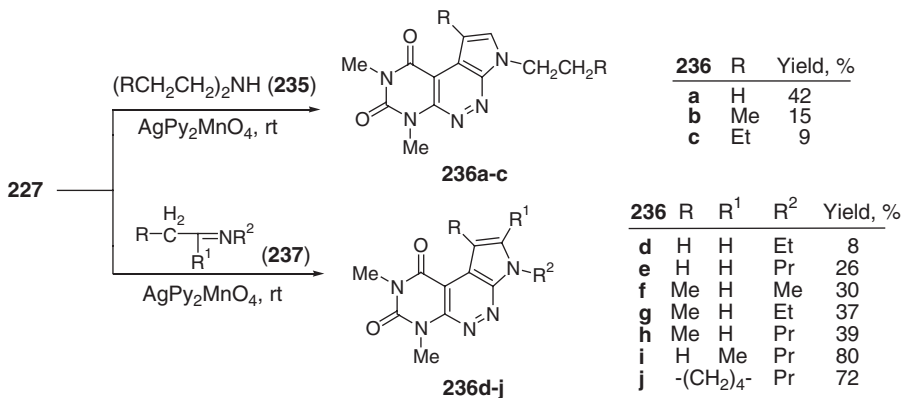
Interaction of pyrimidopyridazine **227** with acyclic dialkylamines **235** in the presence of an oxidant is even more interesting since it opens a route to condensed pyrroles **236a–c** although in quite moderate yields (Scheme 68) (01TL5981).



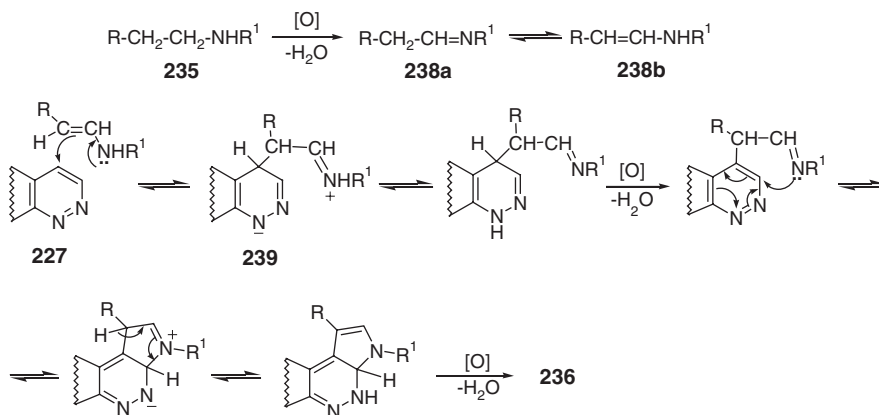
Scheme 66



Scheme 67



Scheme 68

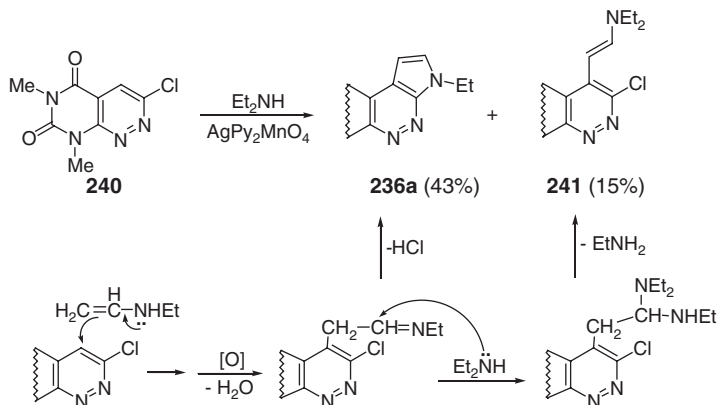


Scheme 69

Most likely, the cyclization of **227** to **236** is preceded by oxidation of dialkylamine **235** into imine **238a**, which then reacts in its enamine form **238b** as a bifunctional *C,N*-nucleophile. At first this enamine, as a *C*-nucleophile, attacks the C(4) atom of the pyridazine ring to produce σ^H -adduct **239**. Further possible development of this reaction is shown in Scheme 69 (*cf.* Scheme 67).

The participation of imines in this process has been demonstrated experimentally. In the presence of an oxidant, **227** reacts with specially prepared aldehyde imines or ketone imines **237** giving condensed pyrroles **236d-j** (Scheme 68) (01TL5981). Notably, in the case of ketimines yields of **236** are 72–80%. With aldimines they are substantially lower due to considerable tarring.

3-Chloropyrimidopyridazine **240** with diethylamine and an oxidant produces pyrrole **236a** (S_NH-S_N *ipso* process) together with quite stable enamine **241** (Scheme 70) (04RCB846). This fact suggests the mechanism presented in Scheme 70 since the formation of enamine **241** can proceed only via primary *C*-nucleophilic attack on



position 4 of chloride **240**. This example also indicates that nucleophilic addition to an unoccupied position goes easier than to a position with a chlorine atom. Therefore, if conditions for fast aromatization of σ^H -adduct are provided, the S_NH process should prevail over *ipso* substitution (94M11).

D. CASCADE SEQUENCES BASED ON S_NH REACTIONS

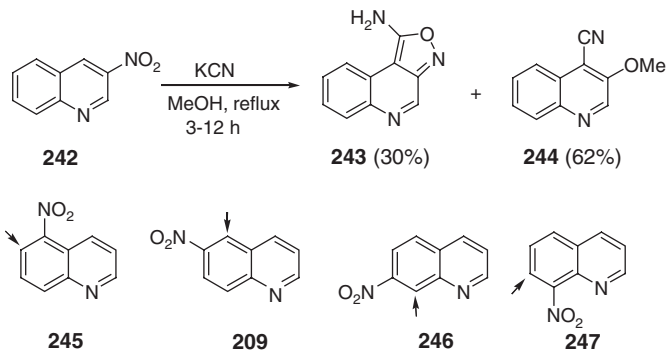
As in the above tandem reactions, cascade sequences of this type are normally initiated by an S_NH reaction. They differ from the former by having a larger number of stages and greater variety. Practically always this complexity is caused by involvement of functional groups, as a rule, via redox processes. For some time such cascades were known only for nitro derivatives of arenes and hetarenes. However, recently some novel substrates and cascade sequences have been discovered.

1. Nitroarenes and Nitrohetarenes as Substrates

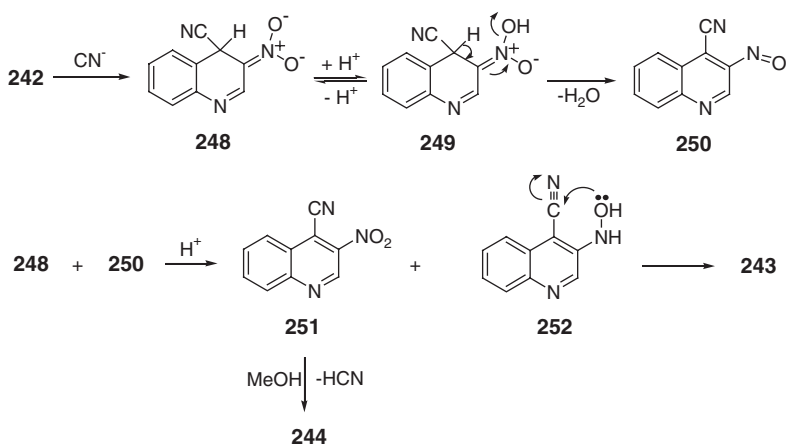
In all cascades with participation of these nitrated substrates the nitro group fulfils several important functions: (1) it activates an aromatic ring to nucleophilic attack; (2) it directly accepts hydride ion on aromatization of a σ^H -adduct and (3) it serves as a building block for the heterocycle to be formed.

Thus, interaction of 3-nitroquinoline **242** with potassium cyanide in methanol furnishes a mixture of isoxazole **243** and 3-methoxy-4-cyanoquinoline **244** (Scheme 71) (68CPB1700, 69CPB140). Isomeric nitroquinolines **207**, **245–247** enter a similar transformation (the arrow indicates the place of primary nucleophilic attack).

In the course of the reaction, cyanide ion attacks a position *ortho* to the nitro group leading to a σ^H -adduct, e.g. **248**. This initiates hydride reduction of the nitro group to a nitroso (**249** to **250**) and then to a hydroxylamino function (Scheme 72). As a result **251** and **252** are formed. In the final step, the latter is spontaneously



Scheme 71



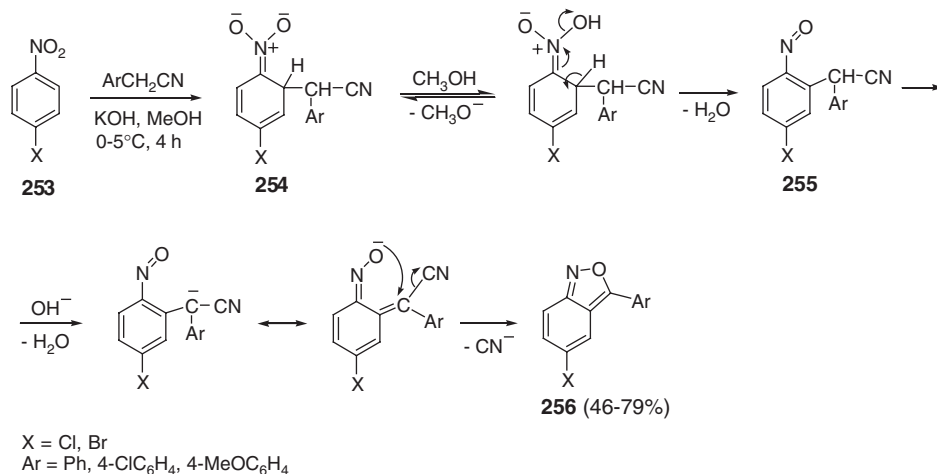
Scheme 72

cyclized into isooxazole **243** and the cyano group in **251**, strongly activated to nucleophilic substitution, is displaced by methoxide to yield **244**.

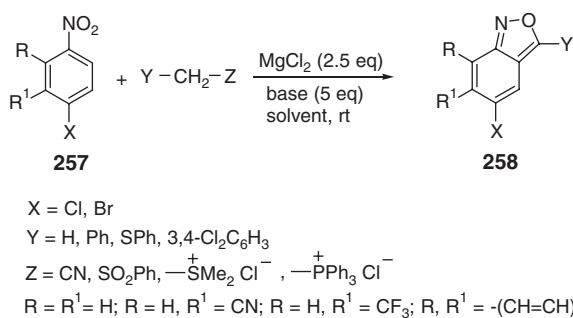
p-Nitrohalogenobenzenes **253** similarly react with benzyl cyanides in methanolic KOH to produce benzisoxazoles (anthraniles) **256** (Scheme 73) (60JOC1884).

Schemes 72 and 73 show that transformation of σ^{H} -adducts **248** and **254** into nitroso derivatives **250** and **255** needs a proton source. That is why the above cyclizations proceed easily in alcohol but are not feasible in aprotic solvents. However, to perform the cyclization of nitroarenes into benzoxazoles in aprotic solvents it is enough to add a Lewis acid. Thus, nitrobenzenes **257** with active methylene compounds bearing vicarious leaving groups Z in the presence of DBU and MgCl_2 in DMF, pyridine or even benzene provide anthraniles **258** (Scheme 74) (98PJC2384). Yields of **258** vary from trace to 83% depending on solvent, base and nature of substituents in both reagents.

This methodology was applied to annulation of the pyridine ring (see structure **260**). Nitro derivatives of benzene, naphthalene, thiophene, pyridine and quinoline



Scheme 73



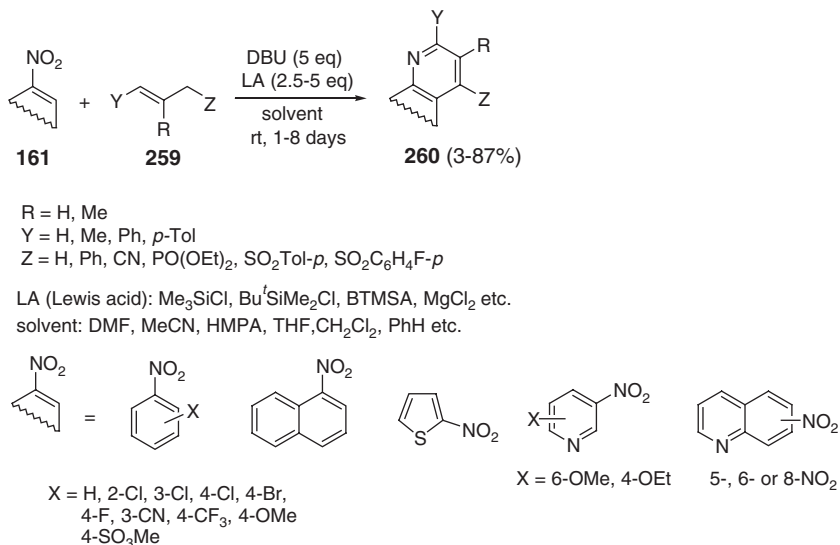
Scheme 74

were used as substrates (Scheme 75) (97TL4913, 98T2607). Allylic carbanions, generated *in situ* from alkenes **259**, served as nucleophiles.

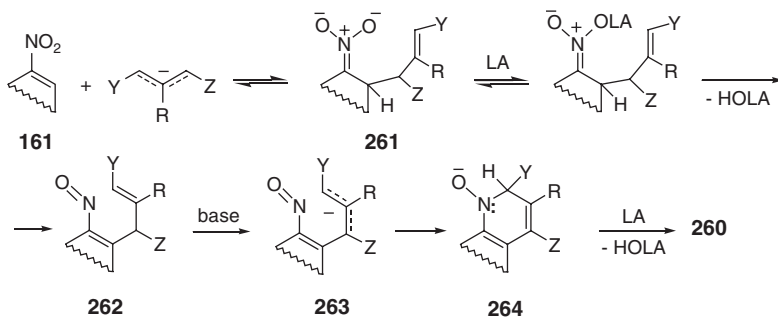
Lewis acids such as trialkylchlorosilanes, MgCl₂ and Ti(OEt)₄ are effective catalysts. They appear to facilitate aromatization of both the primary σ^H-adduct **261** and the intermediate **264** arising on electrocyclization of carbanionic species **263** (Scheme 76).

In some cases the reaction is accompanied by a five-membered heterocyclic ring closure. For example, 1-nitro-4-methoxynaphthalene **265** reacts with *p*-tolylpropenylsulfone to give benzo[*h*]quinoline **266** (35%) together with *N*-hydroxybenzopyrrole derivative **267** (14%) (Scheme 77) (00EJO521). Annulation of the pyridine ring may proceed via anion **268**, whereas the formation of benzoindole **267** occurs via neutral alkene **269**.

In similar manner, 8-nitroquinoline interacts with phenylcinnamylsulfone yielding a mixture of *o*-phenantroline **270** and isoxazolo[4,3-*h*]quinoline **271** (Scheme 78) [98T2607]. The difference is that transiently formed anions **272a,b** manifests here



Scheme 75

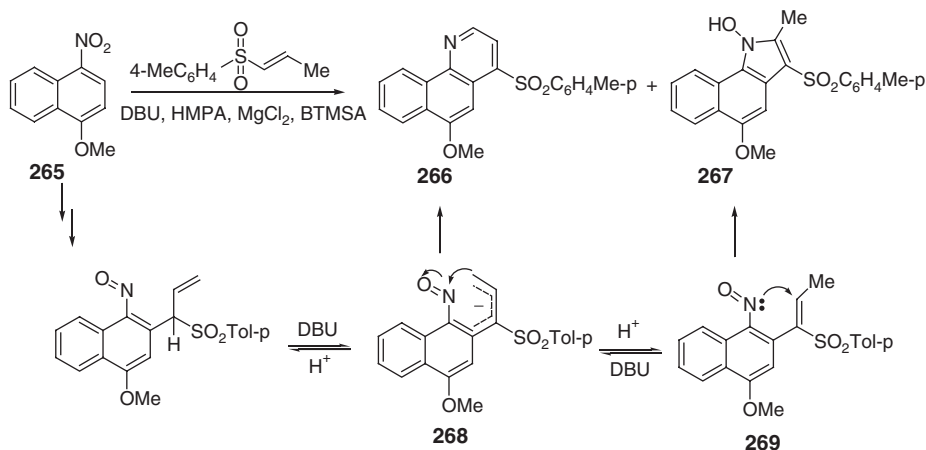


Scheme 76

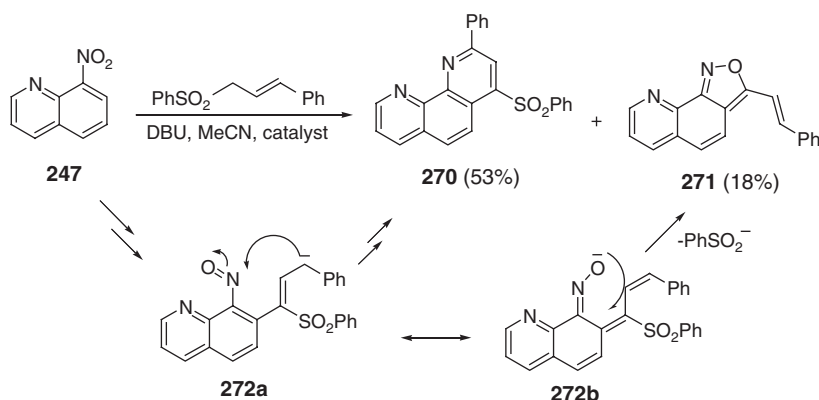
ambident properties and undergoes either electrocyclozation into **270** or intramolecular nucleophilic replacement with elimination of the phenylsulfonyl group and formation of isoxazole **271**.

An intramolecular version of such reactions is also known (00TL7365, 01T7899). In particular, *N*-(3-nitroaryl)allylsulfonamides **273** are converted by DBU and MgCl₂ in DMSO into a mixture of *peri*-cyclic sulfamides **274** and their *N*-oxides **275** (Scheme 79).

As to the formation of substantial amount of *N*-oxides **275**, one can assume that stabilization of σ^{H} -adduct **276** proceeds not only via intramolecular reduction of the nitro group (**276** to **277** to **274**), but also via air oxidation (**276** to **278** to **275**) as shown in Scheme 80. Indeed, when the experiment was performed in an inert atmosphere the yield of *N*-oxide **275** strongly decreased, while bubbling oxygen through the mixture led to the formation of **275** predominantly.



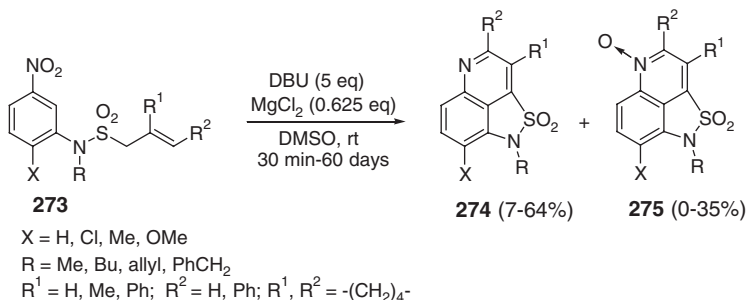
Scheme 77



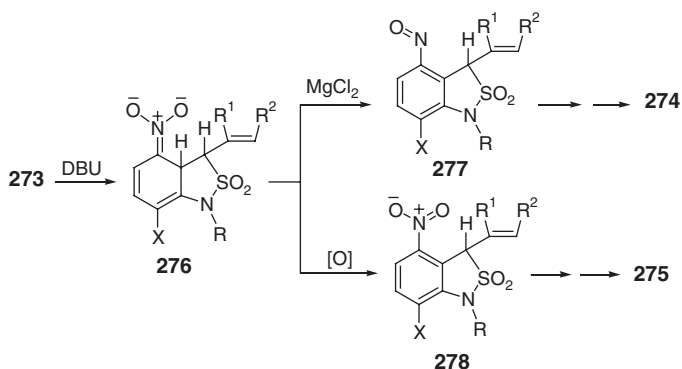
Scheme 78

Treatment of 1-nitro- and 5-nitroquinoline derivatives **279** with allyltriphenylphosphonium chloride in the presence of DBU and Ti(OPr^{*i*})₄ results in annulation of the pyrrole entity to the starting molecule (03SL1465). In the first step, the reaction probably produces 1-hydroxypyrroles **280** which are converted without isolation into pyrroles **281** and **282** after adding triethylamine and ethyl bromoacetate (Scheme 81).

The synthesis of indoles **284** by interaction of nitroarenes **283** with vinyl magnesium chloride (the Bartoli synthesis) looks like a cyclization initiated by an S_NH substitution (Scheme 82) (89TL2129, 91JCS(P2)657, 91SC611, 01JOC638, 02JOC2345). Unfortunately, its mechanism is still not fully clarified. The successful performance of the reaction requires using three equivalents of vinyl magnesium chloride. Indirect evidence of the participation of nitrosoarenes intermediates in the process exists, because their use as starting substrates leads to the same indoles even in larger yield.



Scheme 79



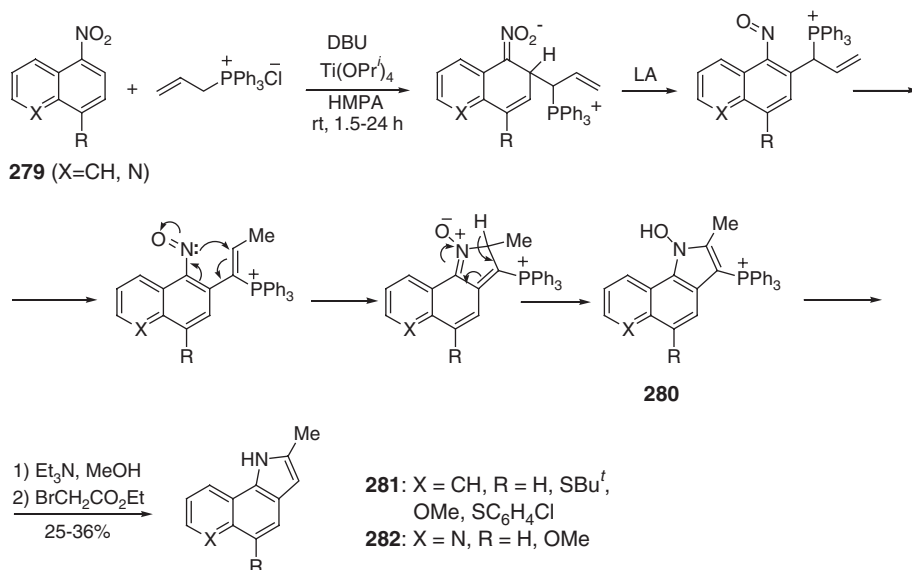
Scheme 80

From this, one can assume (91JCS(P2)657) that the first equivalent of vinyl magnesium chloride is needed to reduce the nitroarene into nitroso compound **285** (Scheme 83). Addition of another molecule of Grignard reagent to the nitroso group results in the formation of *O*-vinyl-*N*-arylhydroxylamine salt **286**. The role of the third equivalent seems unclear; probably it somehow assists the 3,3-sigmatropic rearrangement of **286** to **287**. Subsequent condensation of magnesylamine **287** accompanied by hydrolysis gives indole **284**.

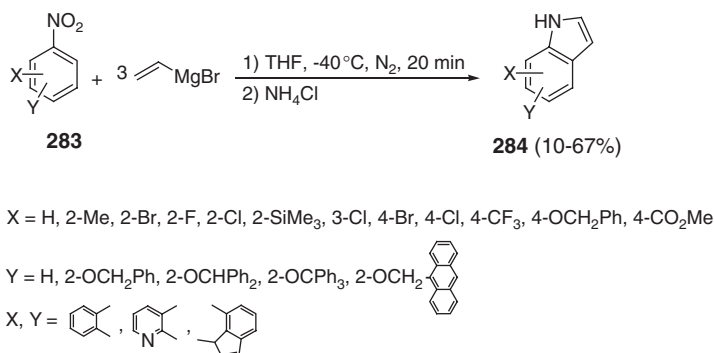
Reaction of 5-*R*-1-nitronaphthalenes and 5-nitroquinoline **288** with α -chloropropyl-*p*-tolylsulfone in NaOH/DMSO leads to oxazinones **289**, although in diminished yields (Scheme 84) [86LAC69, 87LAC711].

Taking into account the vicarious nature of the nucleophile the authors suggested that ring closure occurs inside alkenic σ^{H} -adduct **290** with participation of the nitro group. However, in principle, the reaction might proceed via the formation of nitroso compound **291** with subsequent electrocyclization into oxazine **292** and hydrolytic exchange of the *p*-tosyl group (Scheme 85).

In several related transformations, guanidines and hydrazones were employed as nucleophiles instead of carbanions that then leads to annulation of the 1,2,4-triazine ring. For example, 2-nitronaphthalene with guanidine, in the presence of an excess



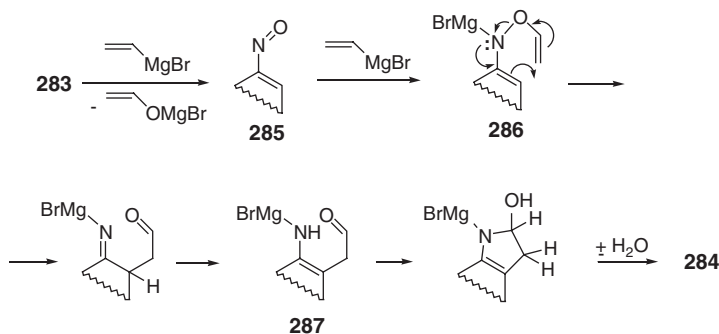
Scheme 81



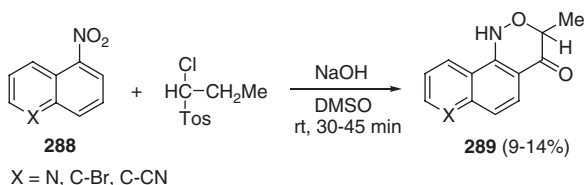
Scheme 82

of NaH or *t*-BuOLi, furnishes naphtho[1,2-*c*]-1,2,4-triazine **296** in ~40% yield (Scheme 86) (99JOC3361). 1-Nitronaphthalene, 1-nitro-4-chloronaphthalene as well as 5-, 6-, 7- and 8-nitroquinolines react similarly. In the case of 2-nitronaphthalene the (1-nitro-2-naphthyl)guanidine **294** was isolated in 6% yield as a side product. This can be interpreted in favor of stabilization of σ^{H} -adduct **293** not via its ordinary conversion into a nitroso compound but rather via air oxidation. Thus, the triazine ring closure must proceed with participation of the NO₂ group to give at first *N*-oxide **295**. Indeed, the corresponding triazine *N*-oxide has been obtained as a single product in 69% yield in the reaction of 7-nitroquinoline with guanidine.

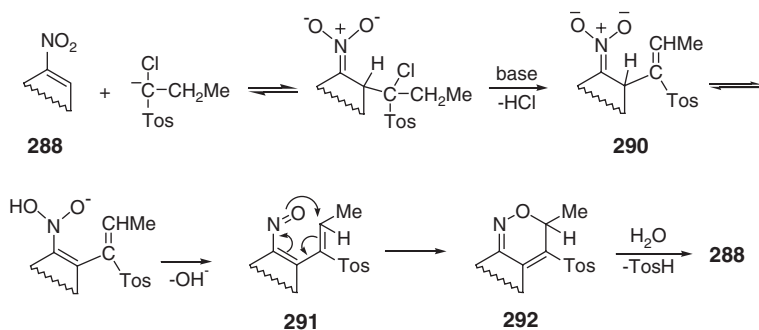
Interaction of 6-nitroquinoline **209** with amidines proceeds similarly to form condensed triazine **297** (Scheme 87) (99JOC3361).



Scheme 83



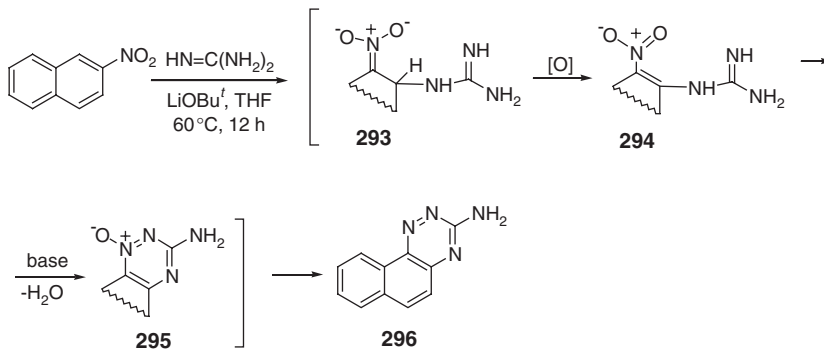
Scheme 84



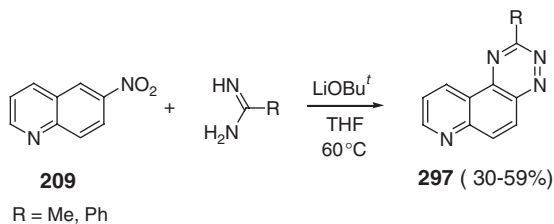
Scheme 85

As it was mentioned in Section III.B.3, 6-nitroquinoline **209** reacts with arylhydrazones giving a mixture of pyrazoloquinolines **210** and triazinoquinolines **211**. The formation of the latter can be considered to involve a cascade process taking its course via intermediate nitroso compound **298**, which then undergoes a base-catalyzed heterocyclization (Scheme 88) (00OL413).

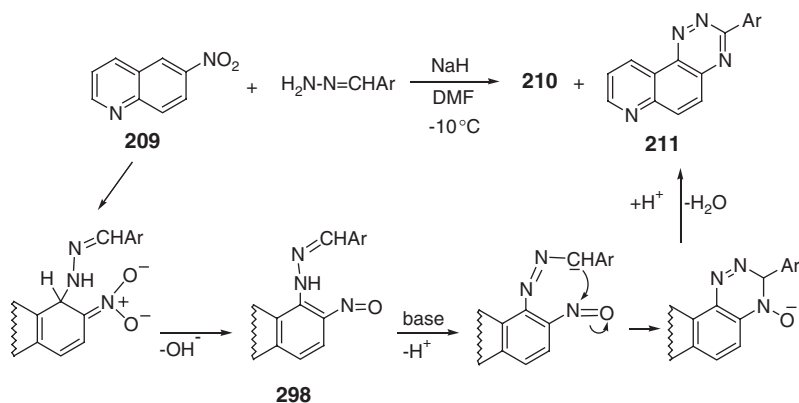
Nitronaphthalenes and nitroquinolines **299** react with dimethylphosphite in basic medium to afford a mixture of anilines **300** and **301** together with azepines **302** (85CC1792). Although the azepine ring is constructed here not by annulation but by means of a ring expansion process, this conversion is interesting because it starts



Scheme 86



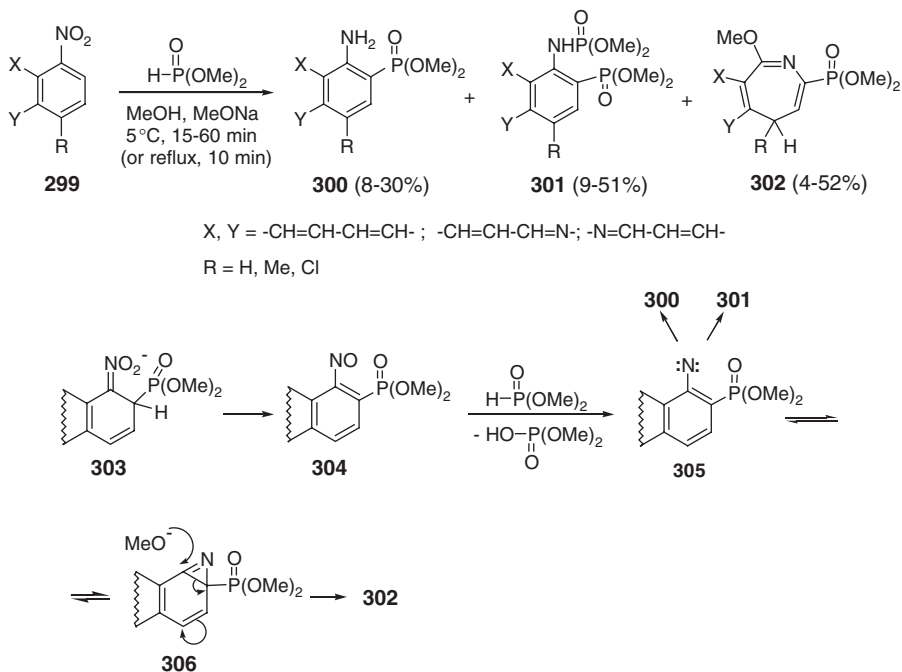
Scheme 87



Scheme 88

from nucleophilic substitution of hydrogen with the formation of intermediate σ^{H} -adduct **303** and nitroso compound **304**. The latter reacts with dimethylphosphite to generate nitrene **305** that produces **300–302** (Scheme 89).

According to this mechanism, the authors suggested that nitrene **305** might be completely transformed into the azepine in the presence of a nucleophile more active



Scheme 89

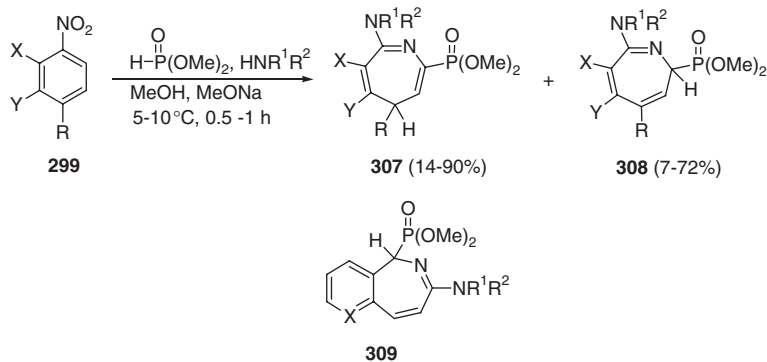
than methoxide ion (91JOC1283). Indeed, interaction of nitroarenes **299** with dimethylphosphite in the presence of ethylamine, dimethylamine or pyrrolidine resulted in the formation of isomeric azepines **307** and **308** exclusively (Scheme 90). Under the same conditions 2-nitronaphthalene and 6-nitroquinoline were converted into condensed azepines **309** (91JOC1283).

2. 6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones as Substrates

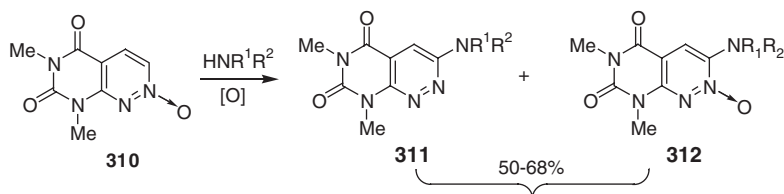
Recently, in our laboratory, a novel kind of cascade S_NH heterocyclization has been discovered (02MC157, 03T7669, 05JHC375, 06T652). All are based on using the 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione **227** derivatives as substrates subjected to the action of alkylamine/AgPy₂MnO₄.

Pyrimidopyridazine *N*₍₂₎-oxide **310** reacts with a variety of alkylamines in the presence of AgPy₂MnO₄ to give a mixture of 3-alkylamino derivatives **311** and **312** with predominance of *N*-oxides **312** (Scheme 91) (00CHE1213).

Unexpectedly, on using cyclohexyl- or isopropylamine, a change in reaction course took place and along with 3-amino-*N*₍₂₎-oxides **312i,j** about ~5% of the corresponding imidazoline ring annulation **315a,b** was formed (02MC157, 03T7669). A plausible mechanism of the imidazoline ring annulation can include the following steps (Scheme 92): (i) alkylation of **310** with deoxidized 3-alkylaminopyrimidopyridazine **311i** or **311j** formation; (ii) independent oxidation of cyclohexylamine or isopropylamine



Scheme 90

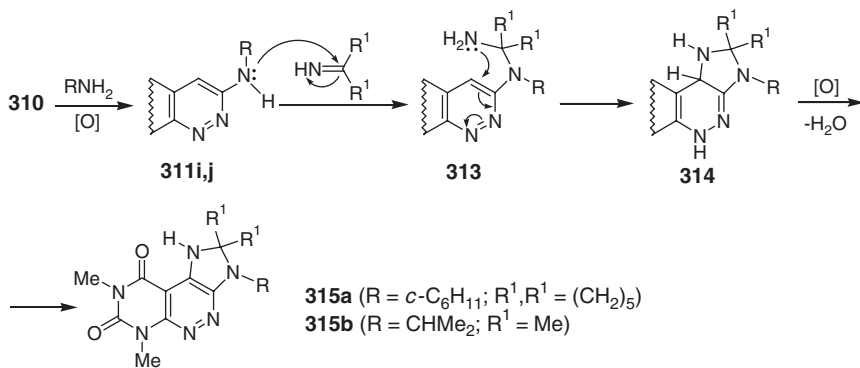


NR ¹ R ²	Ratio 311:312, %
a: NMe ₂	0:100
b: piperidino	37:63
c: morpholino	40:60
d: NHMe	61:39
e: NHEt	33:67
f: NHPr	13:87
g: NHCH ₂ Ph	37:63
h: NH ₂	0:100
i: NHC ₆ H ₁₁ -c	0:100
j: NHPr ⁱ	0:100

Scheme 91

into the corresponding imine; (iii) addition of 3-alkylamino derivative **311i** or **311j** to the imine C=N bond leading to *gem*-diamine **313** and, finally (iv) intramolecular oxidative amination (**313** to **315**). This scheme was proved by an experiment in which interaction of 3-alkylamino derivative **311i** with cyclohexylamine and oxidant afforded imidazoline **315a** in 65% yield.

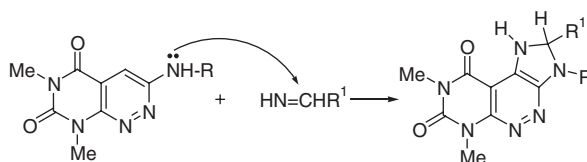
Formation of imidazolines **315a,b** namely with cyclohexylamine and isopropylamine can be explained by the comparative ease of their oxidation and the relative stability of the corresponding ketimines. Similar heterocyclizations have been shown to proceed with other combinations of 3-alkylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(*6H,8H*)-diones **311** and primary alkylamines. Their directionality is determined by the relative ease of oxidation of the amine reagent and the substrate amino group. Two general possibilities leading to isomeric imidazolines exist



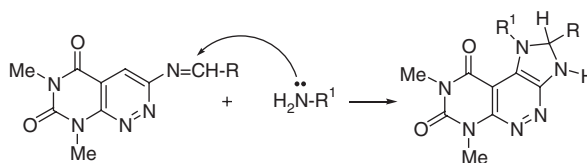
Scheme 92

Possible combinations of substrate and reagent :

1. Azomethine function as reagent



2. Azomethine function as substrate



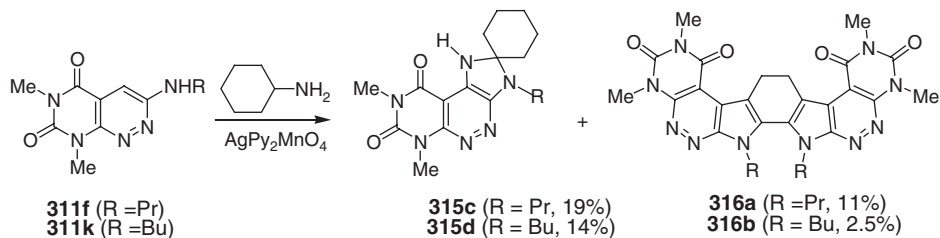
Scheme 93

depending on whether an azomethine function arises from the reagent or the substrate (Scheme 93).

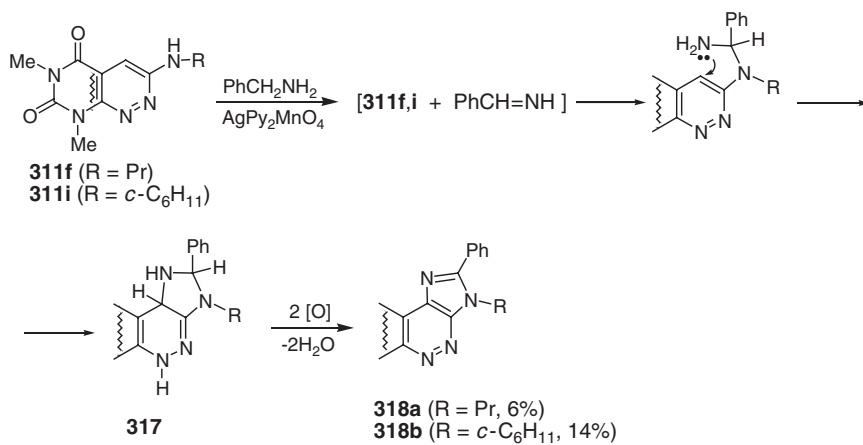
In the above example, the first possibility is realized. The same is true for reactions of 3-propylamino- **311f** or 3-butylamino derivatives **311k** with cyclohexylamine producing imidazolines **315c,d** together with polycyclic compounds **316a,b** (Scheme 94) (02MC157, 03T7669).

Reactions of 3-alkylaminopyrimidopyridazines **311f,i** with benzylamine and an oxidant are similar with one exception: intermediate imidazolidines **317** are oxidized twice to furnish condensed imidazoles **318a,b** (Scheme 95).

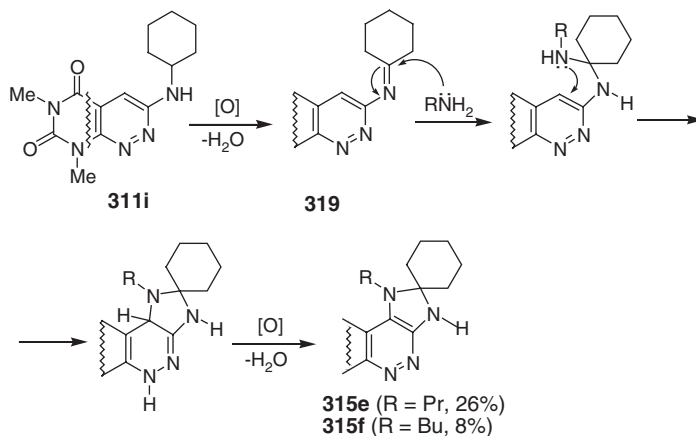
A reversed combination of reactants, when 3-cyclohexylaminopyrimidopyridazine **311i** is used as a substrate and propylamine or butylamine as a nucleophile, provides imidazolines **315e,f** isomeric to **315c,d**. Clearly, the azomethine arises as a result of oxidation of the substrate (**311i** to **319**) as depicted in Scheme 96.



Scheme 94



Scheme 95



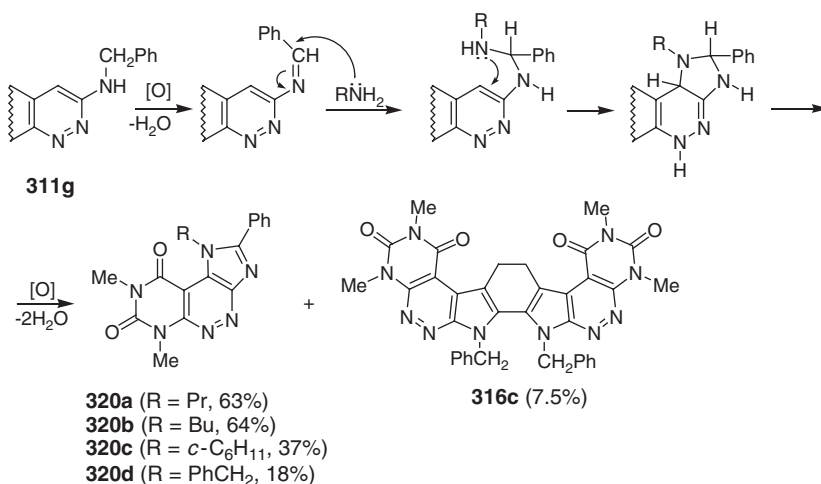
Scheme 96

Similarly, 3-benzylamino derivative **311g** reacts with alkylamines to afford imidazoles **320a–d** in moderate to good yield (Scheme 97). Upon using cyclohexylamine polycyclic compound **316c** is also formed.

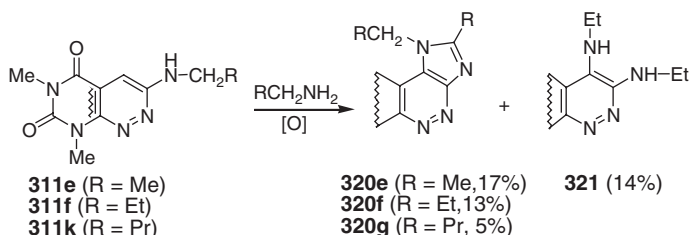
Notably, 3-alkylamino derivatives **311e,f,k** can also be converted into imidazoles **320e,f,g** though in quite low yield. In the case of **311e**, 3,4-di(alkylamino) derivative **321** was also obtained (Scheme 98).

Thus, one can conclude that the 3-benzylamino group in **311g** as well as benzylamine itself is oxidized into their corresponding imines easier than ordinary alkylamines. When both reactants do not contain a benzylamino fragment, the cyclohexylamino group is oxidized first. If both benzylamino and cyclohexylamino functions are absent in the reactants, the process starts from oxidation of a 3-alkylamino group as in **311e,f,k**. Heterocyclizations described here represent a novel approach to condensed imidazoles and imidazolines.

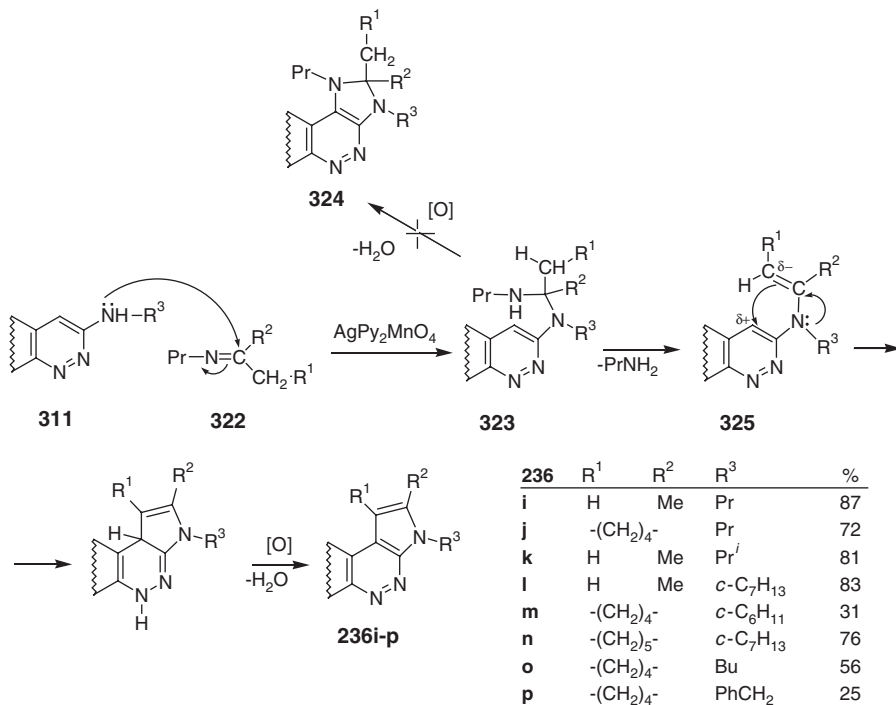
On interaction of 3-alkylaminopyrimidopyridazines **311** with specially prepared *N*-propylketimines **322** in the presence of an oxidant, only condensed pyrroles **236i–p** were obtained in 31–87% yields instead of expected imidazolines **324** (Scheme 99)



Scheme 97



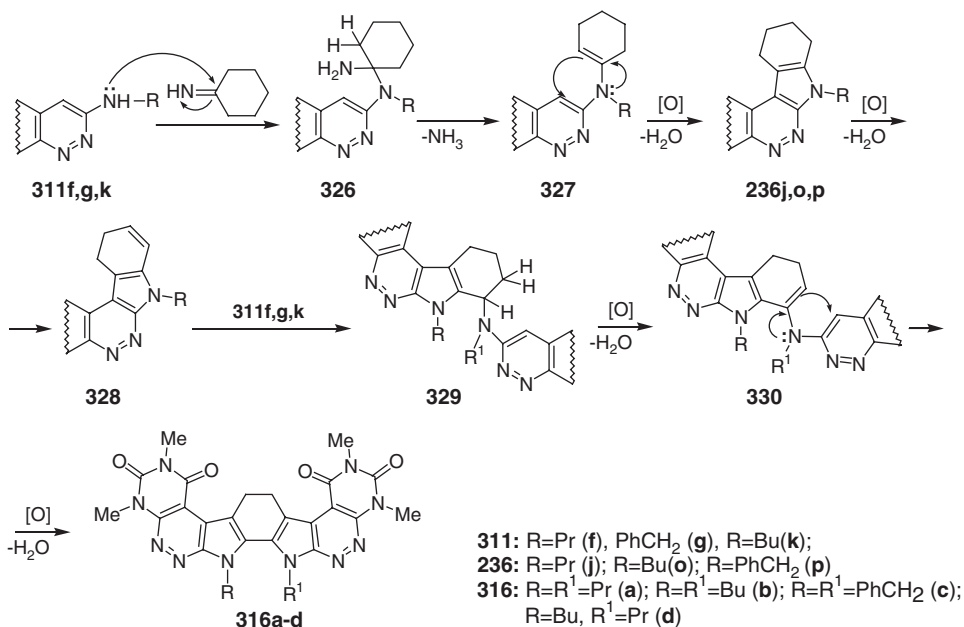
Scheme 98



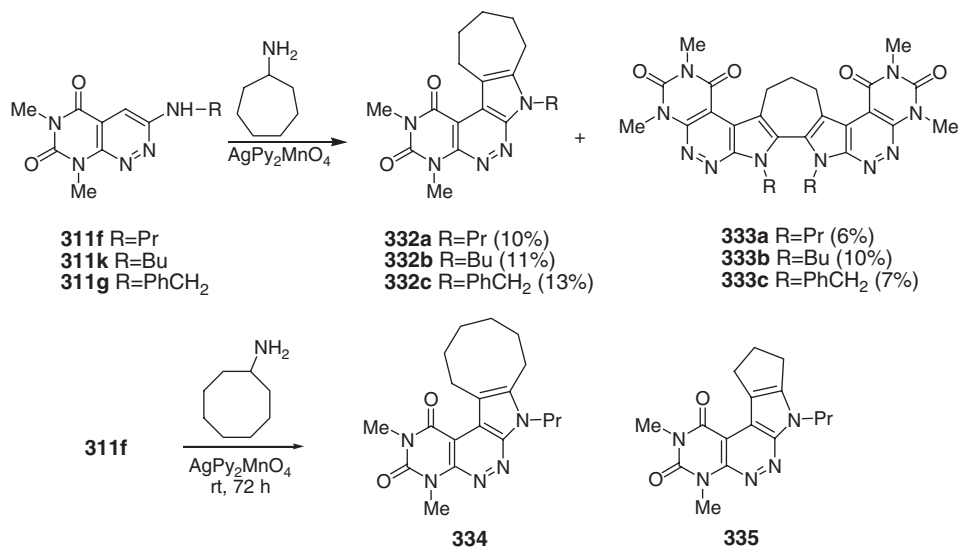
Scheme 99

(03T7669). Apparently, the first-formed intermediates **323** fail to cyclize into imidazolines **324** due to insufficient stability and steric hindrance. Instead, they lose a propylamine molecule giving enamine **325** that is then converted into pyrrole **236** via the oxidative S_NH reaction. Interestingly, the sequence of steps leading to the pyrrole ring annulation in this case is opposite to that in the reaction of pyrimidopyridazine **227** with enamines (see Scheme 69).

The formation of polycyclic compounds **316** in reactions of 3-alkylaminopyrimidopyridazines **311f,g,k** with cyclohexylamine looks especially intriguing. Presumably, after oxidation of cyclohexylamine into cyclohexanone imine, heterocyclization proceeds in accordance with the pathway depicted in Scheme 100. It includes: (i) addition of 3-alkylaminopyrimidopyridazine **311** to the cyclohexanone imine C=N bond; (ii) departure of an ammonia molecule from *gem*-diamine **326** resulted in the formation of enamine **327**; (iii) S_NH cyclization of **327** into tetrahydroindole **236**; (iv) oxidation of the latter into alkene **328**; (v) addition of the starting molecule **311** to the C=C bond in alkene **328** led to intermediate **329**; (vi) generation of alkene **330** and, finally, one more oxidative S_NH cyclization of **330** to **316**. Participation of pyrroles **236** in this conversion has been confirmed experimentally. Authentic pyrroles **236j,o,p** react with one equivalent of the corresponding 3-alkylaminopyrimidopyridazine **311f,g,k** in cyclohexylamine/AgPy₂MnO₄ to provide polycyclic compounds **316a-c** in 48–50% yield. Moreover, by varying starting pyrrole **236** and 3-alkylamino derivative **311** one can obtain not only symmetric compounds **316a-c** but also asymmetric ones,



Scheme 100



Scheme 101

e.g. **316d**. A more detailed discussion of this reaction can be found elsewhere (03T7669, 06T652).

Interaction of 3-alkylaminopyrimidopyridazines **311f,g,k** with cycloheptylamine proceeds similarly to produce cycloheptane-centered polycycles **333a,b,c** (6–10%)

together with cycloheptapyrroles **332a,b,c** (10–13%) (Scheme 101) (06T652). The yield of **333** may be increased up to 25–30% by using pyrrole **332** and compound **311** as reactants. Attempts to obtain cyclooctane- and cyclopentane-centered analogues of polycycles **316** and **333** resulted only in formation of cycloocta- **334** and cyclopentapyrroles **335**.

No doubt, heterocyclizations of **311** to **316** and **311** to **333** are the most complicated transformations, based on nucleophilic substitution of hydrogen, known at present. In spite of moderate yields, the method permits one to obtain in a single preparation step compounds that are otherwise very hard to obtain. Another feature is that for the first time an oxidant serves here not only for aromatization of σ^{H} -adducts but also for modification of both reactants before each next stage. This tremendously expands the synthetic possibilities of such reactions that obviously need further extensive development.

IV. Conclusions

In summary, $\text{S}_{\text{N}}\text{H}$ based heterocyclizations allow the synthesis of a great variety of heterocyclic structures differing in ring size, number of heteroatoms and their type, degree of unsaturation, etc. Various arenes as well as hetarenes with appropriate electron deficiency can be used as substrates. The method is quickly progressing and about 70% of our quoted articles have appeared after 1990. Since a large number of known $\text{S}_{\text{N}}\text{H}$ cyclizations deals with the pyrrole ring closure a search for new substrates, reagents and cyclization schemes for the annulation of other heterocyclic rings is desirable. It is equally important to optimize reaction conditions since many existing transformations do not provide high enough yields. In general, there is no doubt that $\text{S}_{\text{N}}\text{H}$ based cyclizations have broad perspectives for heterocyclic chemistry and will intensively develop in nearest future.

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34JA1748
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The Chemistry of Thienopyridines

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I. Introduction

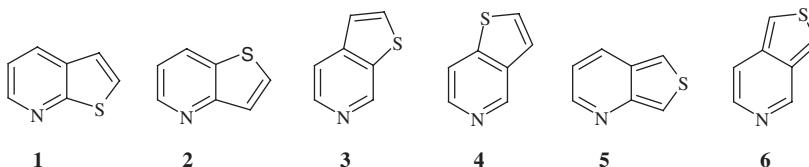
Derivatives of pyridine attract considerable interest because of their great practical usefulness, primarily, due to their various biological activities. Among pyridine derivatives, fused analogs are often of much greater interest biologically than the corresponding monocyclic compounds. Qualitatively the new properties of fused molecules with greater possibilities of varying pharmacophoric groups in different positions, and their ability to react with a wider range of receptors play a decisive role. In addition, these factors are supplemented with variations due to annulation at different positions of the heterocyclic fragments. Among these heterocyclic systems, thienopyridines occupy a special place and have attracted considerable attention, reflected in their reviews (1977AHC65, 1981H1349, 1986DK215, 1987KFZ536, 1989JHC1167, 1989MI1, 1987MI2, 1987MI3, 1987MI4, 1991KGS1155, 1991MI1, 1991MI2, 1992KGS435, 1992KGS781, 1992SR1, 1993PS139, 1994KGS1603, 1994S123, 1996KGS1026, 1996MI1, 1996MOL236, 1997KGS1603, 1997KZA83, 1997THC37, 1998AHC89, 1998AHC225, 1998MI1, 1998RCR442, 1999JHC333, 1999KGS437, 1999KGS579, 1999RCR45, 1999RCR817, 2000H941, 2000JHC519, 2000KGS435, 2000RCR218, 2001KGS41, 2001RCR343, 2002UKZ67, 2003MI1), monographs (1985MI1, 1987MI1, 2001MI1, 2005MI1) and other publications.

This notwithstanding, their data have been summarized only within narrow-subject areas. However, recent years have witnessed a tremendous growth in the number of publications on different aspects of the chemistry and pharmacological actions of thienopyridine derivatives. For example, approximately 150 studies were published during the first 60 years after the synthesis of thieno[2,3-*b*]pyridine in 1913 by Steinkopf and Lutzkendorf (1913CZ379, 1914LA45) using the Skraup reaction starting from 2-aminothiophene up to the publication of the most comprehensive

review (1977AHC65) by Barker in 1977. More than 800 publications, including patents, have appeared in the literature during the last 10 years. The importance of this field and the lack of a summary analysis of its current state gave impetus to the present review where data on the synthesis, reactivity, and biological activities of isomeric thienopyridines, primarily in the last 10–15 years, are systematized and analyzed for the first time. Prominence is given to studies in which the most general and promising approaches to the synthesis of target structures were considered and data on the properties and biological activities were published. The scope of the review does not include all publications on the chemistry of thienopyridines and a complete bibliography. Only the most interesting studies in narrow-subject areas are considered.

II. Thienopyridines

Six isomeric thienopyridine structures characterized by different annulation modes are known: thieno[2,3-*b*]pyridine (**1**), thieno[3,2-*b*]pyridine (**2**), thieno[2,3-*c*]pyridine (**3**), thieno[3,2-*c*]pyridine (**4**), thieno[3,4-*b*]pyridine (**5**), and thieno[3,4-*c*]pyridine (**6**). The first four thienopyridines were studied in detail. Data on the “isostructural” isomers **5** and **6** are scarce and are beyond the scope of the present review.



A. THIENO[2,3-*b*]PYRIDINES

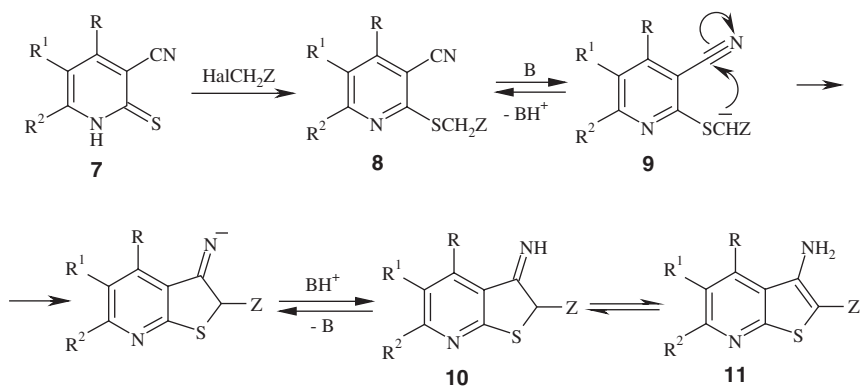
Thieno[2,3-*b*]pyridines (and thienopyridines, as such) were mentioned for the first time in 1913 (1913CZ379, 1914LA45). Nowadays, after 90 years, the chemistry of the [2,3-*b*]-isomer is best known. This is associated primarily with a great practical importance of many derivatives of thieno[2,3-*b*]pyridine (**1**). The spectrum of biological activities of this class of compounds is broad and includes antiinflammatory, antidepressant, antibacterial, antimicrobial, antiviral, and antitumor activities. In addition, certain derivatives of **1** hold promise for the treatment of osteoporosis and serve as tachykinin antagonists, 5-lipoxygenase inhibitors with a broad spectrum of action, antagonists for gonadotropine releasing hormone (GnRH), vasodilators, acetylcholine esterase inhibitors, inhibitors of atherosclerotic coronary artery aneurysm, allosteric modulators of adenosine receptors, telomerase inhibitors, anti-convulsants and mutagens, drugs for the treatment of dysmnnesia, modulators of endothelin activity, inhibitors of prolactin secretion, agents for the treatment of

rheumatism and autoimmune diseases, inhibitors of pronounced glutamate release from brain cells, antipsychotic medications, agents for the treatment of Alzheimer's disease, protein tyrosine phosphatase inhibitors with a broad spectrum of action, and ligands of γ -aminobutyric acid receptors.

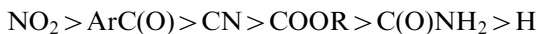
The available ingenious and preparatively convenient methods for the synthesis of **1** and its analogs **2–4** have played a considerable role in the development of their chemistry. These approaches include thiophene ring closure based on pyridine derivatives and the pyridine ring closure based on thiophene derivatives.

1. Thiophene Ring Closure in Pyridine Derivatives

Among these methods, Thorpe isomerization of substituted 2-alkylthio-3-cyanopyridines is of considerable interest. The advantages of this approach are that the starting 3-cyanopyridine-2(*1H*)-thiones (**7**) are readily accessible, diverse 3-cyanopyridine-2(*1H*)-thiones can be used, one-pot procedures can be employed, and the final products are prepared in high yields. The mechanism of this transformation can be represented by the Scheme (1985MI1, 1989MI2):



The electron-withdrawing effect of the substituent Z responsible for stability and the concentration of carbanion **9** is the main factor determining the cyclization rate. The tautomeric equilibrium $\text{10} \rightleftharpoons \text{11}$ is completely shifted to the amino form. It was empirically established that the activity of the electron-withdrawing substituents Z increases in the following series (1989MI2, 1992SR1):

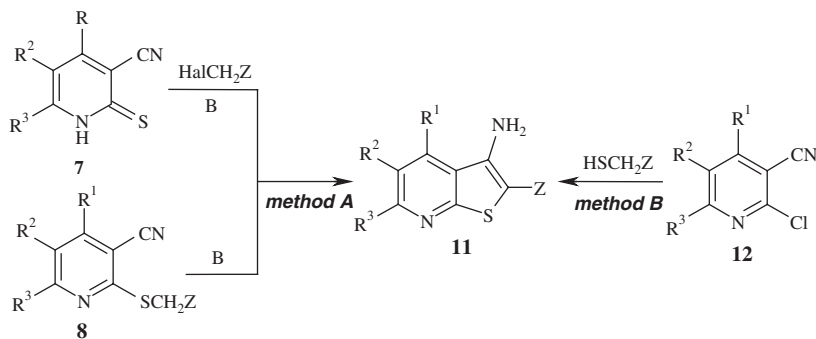


Some general preparative aspects of cyclization, such as a choice of catalysts, solvents, etc., have been described earlier (1989MI2, 1992SR1). However, numerous new examples of the use of the Thorpe reaction in the synthesis of thienopyridine

derivatives have been reported in recent years. Hence, there is a need to supplement and generalize the available information.

The reaction conditions can be varied widely. Generally, cyclization occurs in a basic medium, whereas acid catalysis is used more rarely. A 10% aqueous KOH/DMF solution, as well as KOH/EtOH, K_2CO_3 /EtOH, K_2CO_3 /DMF, and EtONa/EtOH are reagents of choice. The Na_2CO_3 /EtOH (1992MI1), K_2CO_3 /acetone (1991AP853, 1992PS127), 7% MeONa/EtOH (1996KGS59), KOH/EtOH/ H_2O (2002IZV1432, 2003JHC689), AcONa/anhydrous EtOH (1992PS219), Et_3N /dioxane (2002KGS1525), Et_3N /EtOH (1991SL27, 1999IZV1150, 2002KGS1525, 2003IZV2069), and Et_3N /DMSO (1997GEP19601264) systems are used more rarely. Both excess and catalytic amounts of bases are used. Sometimes, the ring closure occurs spontaneously when attempting to alkylate thiones **7** in the presence of equimolar amounts of bases; in these processes, intermediates **8** cannot be isolated. Generally, thienopyridines can be easily synthesized at room temperature, although heating is required in certain reactions. Examples of cyclization in refluxing pyridine (1992PS127, 1997IJC79) and under phase-transfer conditions <2000PS29, 2000PS91> with the use of $Bu_4N^+ Br^-$ are known.

Based on the structures of the starting reagents, several main pathways of formation (*A–C*) of the thiophene ring by the Thorpe reaction can be proposed.



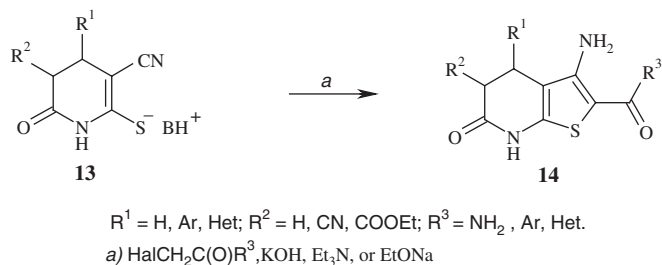
Method A. Thieno[2,3-*b*]pyridines **11** are generated by isomerization of 2-alkylthio-3-cyanopyridines **8**, which are traditionally prepared from 3-cyanopyridine-2(1*H*)-thiones **7** (or the corresponding thiolates) and an alkylating agent containing an electron-withdrawing substituent in the α -position with respect to the halogen atom. The often-used modification is based on cyclization without isolation of intermediate structures analogous to sulfides **8**. In most cases, this modification makes it possible to obtain the final reaction products in higher yields.

Method B. The reactions starting from 2-chloro-3-cyanopyridines **12** and thioglycolic acid derivatives involve nucleophilic substitution followed by thiophene ring closure in the presence of a basic catalyst.

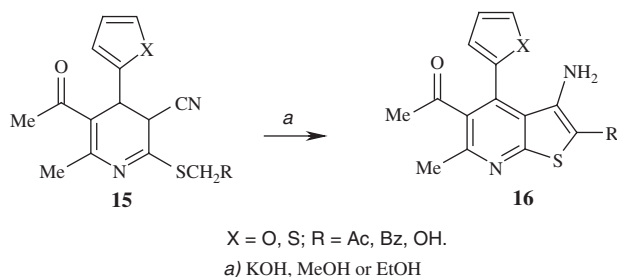
Method C. The bicyclic thienopyridine system is constructed from various acyclic precursors by a multicomponent one-pot process.

Method *A* has a very wide application and was used to prepare various derivatives of **1** and related systems, such as quinoline, isoquinoline, and cyclopentano[*b*]pyridine (pyridine).

The Thorpe reaction was successfully used also in the synthesis of partially hydrogenated thienopyridines starting from tetrahydro- or 1,4-dihydropyridine-2-thiolates, the corresponding pyridinethiones, or their *S*-alkyl derivatives. The reactions with tetrahydro derivatives **13** occur with retention of the initial saturated structure and, as a rule, without complications to give lactams **14** as the final products (1997IZV1029, 1997IZV1852, 1998KGS1381, 1999ZOR966, 2003KGS117).

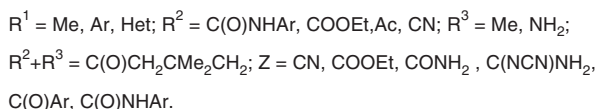
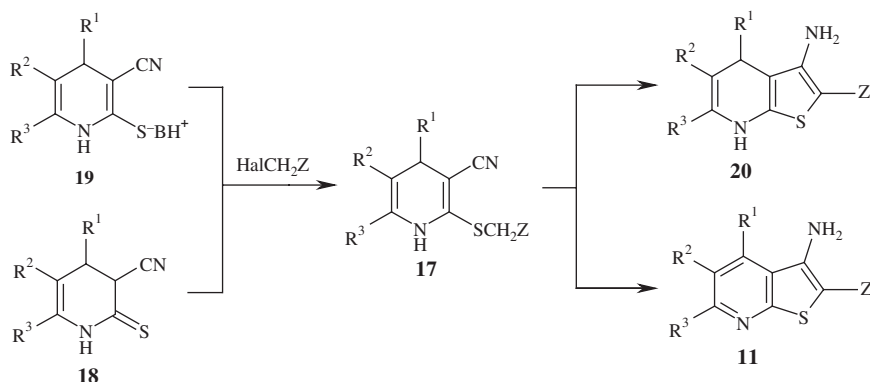


The reactions of dihydropyridine analogs are less unambiguous. For example, cyclization of 3,4-dihydropyridines **15** under the action of bases is accompanied by aromatization to give thienopyridines **16** (1996PS1, 1996PS31). However, numerous data on the synthesis of partially hydrogenated pyridine-2(1*H*)-thiones and their derivatives summarized in the reviews (1989MI2, 1999KGS579) suggest that the 3,4-dihydropyridine structure assigned to compounds **15** is erroneous and the latter should be considered as the 1,4-dihydro isomers.

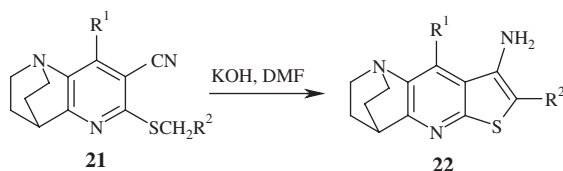


Transformations of 2-alkylthio-1,4-dihydropyridines **17** under conditions of Thorpe isomerization were considered. These compounds are easily formed by alkylation of pyridinethiones **18** or the corresponding thiolates **19** and can be used in reactions without preliminary isolation. Cyclization afforded both 4,7-dihydrothieno[2,3-*b*]pyridines **20** (1992KFZ40, 1996KGS553, 1997KGS666, 1997ZOR1088, 1998ZOR750, 2000KGS794, 2003PS2201) and their aromatic analogs **11** (1996KGS1243, 1997KGS672, 1997KGS909, 1998ZOR927, 1999PS189,

2000KGS345) generated due, evidently, to oxidation of the hydrogenated pyridine by atmospheric oxygen. The conditions under which the reaction produces compounds **11** were not reliably determined. Most likely, the stability of structures **20** against oxidation *in situ* depends on a number of factors, such as the structures of substituents in the pyridine ring, particularly, at position 4, the nature of the solvent, the reaction temperature, the nature of the catalyst, and the structure of the alkylating agent. However, no unambiguous conclusions about the cyclization pathway of dihydropyridines **17** can be drawn based on the available data.

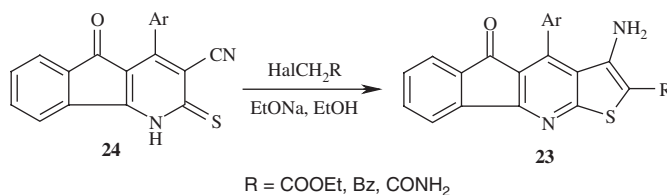


The Thorpe reaction of 2-alkylthiopyridoquinuclidines **21** resulting in its isomerization to form the corresponding thienopyridoquinuclidines **22** (1989ZOR1980, 1994KGS122) is another example of the construction of the thieno[2,3-*b*]pyridine system according to method *A*.



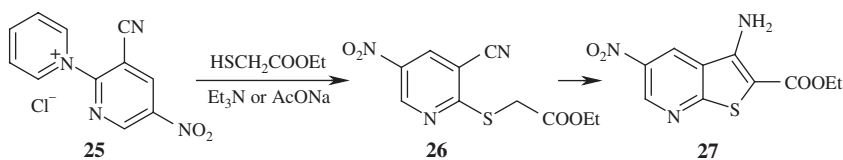
Recently, a method has been developed for the synthesis of thieno[2,3-*b*]indeno[2,1-*e*]pyridine derivatives **23** by the Thorpe reaction starting from thiones **24** (2000SC3883). It should be noted that compounds **23** were synthesized according to the same procedure three years earlier (1997M11). However, the latter study is

not original, because this transformation was described (1990KGS115) as early as 1990.

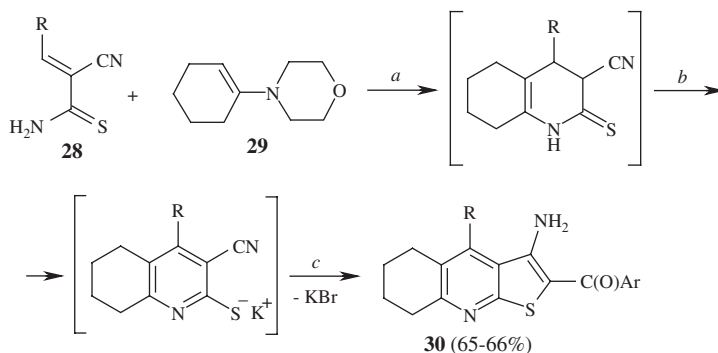


Method **B**, which involves the replacement of the halogen atom with a sulfur-containing nucleophile in 2-chloro-3-cyanopyridines **12** followed by Thorpe cyclization, is used more rarely (see, for example, 1991MI3, 1992IJC492, 1992MI1, 1992MI2, 1993PS91, 1994H1299, 1996KFZ36, 1996PH937, 1997KFZ18, 1997KFZ44, 1998HEC245, 1998T5775, 2001PS49). Evidently, the reason is that *S*-nucleophiles, viz., thioglycolic acid derivatives, are less accessible compared to diverse alkylating agents used in method **A**. Another important factor is that convenient procedures were developed for the synthesis of thiones **7** and 2-alkylthiopyridines **8**, which serve as the starting compounds for the preparation of the thieno[2,3-*b*]pyridine system in alternative approaches. Besides, while giving the final products in comparable yields, method **B**, on the whole, requires that cyclization be performed under more drastic conditions. As a rule, thienopyridines are prepared by refluxing a mixture of chloride **12** and a thioglycolic acid derivative (usually an ester) in alcohol (EtOH or MeOH) in the presence of an excess of a base over a long period of time. In this reaction, MeONa (1992MI2), EtONa, (2001PS49, 2001S97), Na₂CO₃ (1991MI3, 1997IZV1029, 1997IZV1852, 1998KGS1381, 1999ZOR966, 2003KGS117), or K₂CO₃ (1994H1299) can be used. A decrease in the heating time (1994H1299), the use of the AcONa–EtOH system at room temperature (1996KFZ36, 1997KFZ18), or the reaction in DMF in the presence of KOH (1992IJC492) or K₂CO₃ (1993PS91) allow isolation of intermediates **8**, which undergo cyclization under the action of EtONa in hot ethanol. Nevertheless, in some cases (1997KFZ44) spontaneous cyclization occurs even under mild conditions (K₂CO₃, DMF, 60 °C), and intermediate sulfide **8** cannot be obtained. Presumably, the possibility of isolating the latter is determined by the degree of electrophilicity of the cyano group at position 3 of the pyridine ring.

Nucleofuges, other than the chlorine atom, can be involved in these reactions. For example, 1,2-bipyridinium chloride **25** reacts with ethyl thioglycolate with elimination of pyridine to form sulfide **26**, whose isomerization to thienopyridine **27** occurs under conditions of the Thorpe reaction (1998T5775).

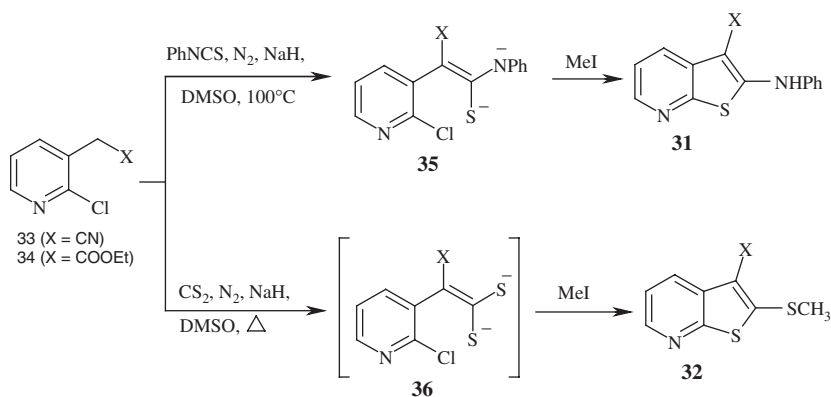


Examples of the synthesis of thieno[2,3-*b*]pyridines according to method *C* are scarce. In this case, the synthesis of the starting 3-cyanopyridine-2(1*H*)-thione, its *S*-alkylation, and cyclization of an intermediate occur as a multicomponent one-pot process. For example, the reaction of thioamides **28** with 1-(4-morpholino)cyclohexene (**29**) in anhydrous ethanol followed by treatment with a twofold excess of KOH and then with α -bromo ketones produced thienoquinolines **30** (1997KGS1384).



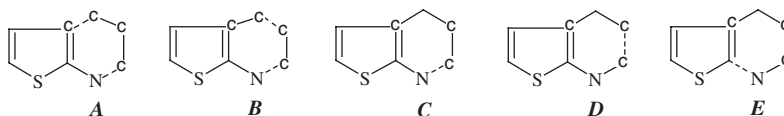
R = 2-(5-Ph-furyl), 2-thienyl; Ar = 4-ClC₆H₄, 4-MeC₆H₄.
 (a) EtOH, 20 °C, 4 h; (b) 10% KOH (2 equiv.), EtOH; (c) ArC(O)CH₂Br, EtOH.

A method used to prepare four of six possible thienopyridines (1992S528, 1997S949, 1998S1095) holds considerable promise. In particular, the synthesis of thieno[2,3-*b*]pyridine derivatives **31** and **32** involves the reaction of 2-chloro-3-(cyanomethyl)pyridine (**33**) and ethyl 2-chloro-3-pyridylacetate (**34**) with heterocumulenes, such as carbon disulfide and phenyl isothiocyanate. The reaction proceeds through the formation of the corresponding dianions **35** and **36** followed by cyclization through intramolecular nucleophilic substitution of the chlorine atom.

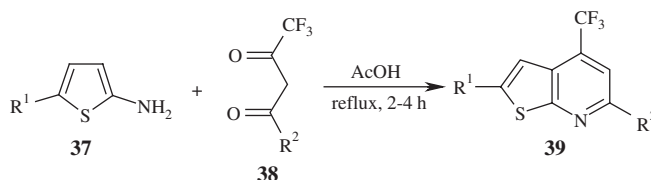


2. Pyridine Ring Closure in Thiophene Derivatives

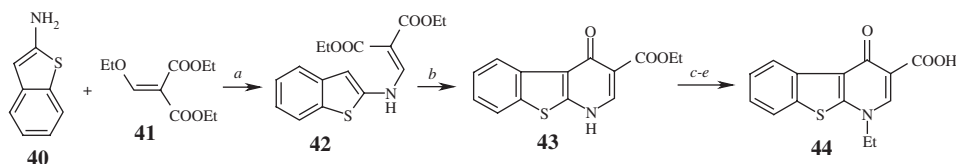
Widely employed methods for the construction of the pyridine ring are based on 2-aminothiophene derivatives. Some examples of the construction of **1** were given in reviews (1987KFZ536, 1997KZA83, 1998MI1). All synthetic routes can be divided into several main groups (A–E), according to the strategy of the pyridine ring construction. In our opinion, this tentative classification is most convenient for the discussion.



Method **A** is based on 3-unsubstituted 2-aminothiophenes or their precursors. For example, heating 2-aminothiophenes **37** and dicarbonyl compounds **38** led to their regioselective cyclocondensation to form 4-trifluoromethylthieno[2,3-*b*]pyridines **39** (2003S1531).



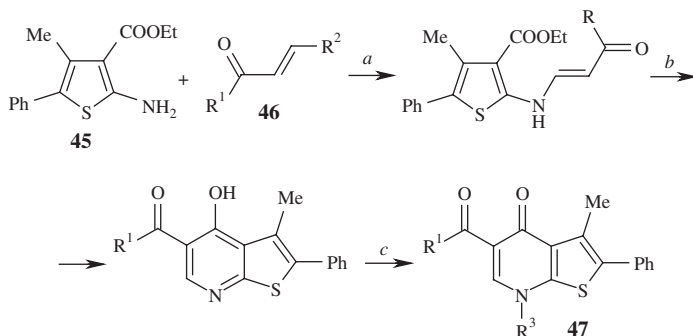
Another example of this approach is based on the modified Gould–Jacobs reaction. For instance, 2-aminobenzothiophene (**40**) reacts with diethyl ethoxymethylenemalonate (**41**) to give aminomethylenemalonate **42**, whose high-temperature cyclization yields benzothienopyridin-4-one **43** (1993JHC1085). The latter was transformed in three steps into acid **44**, which is a potential bactericide.



a) 140 °C, 0.5 h; *b*) (BuOCH₂CH₂)₂O, AT, 245 °C, 10 min; *c*) EtI, K₂CO₃, DMF, 100–110 °C, 5 h; *d*) 10% NaOH, EtOH, 2 h; *e*) 10% H₂SO₄, pH 2.

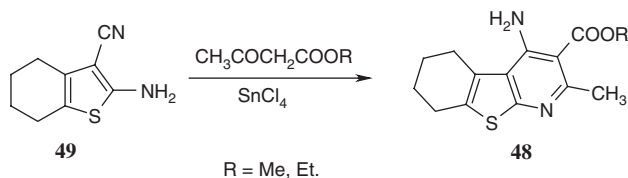
Method **B** assumes pyridine ring construction by the reaction of 3-*R*-2-aminothiophenes with the so-called 2C-component (a component serving as a source of two carbon atoms). As a rule, readily accessible malonic, cyanoacetic, and acetoacetic acid derivatives are used as such 2C-components. The CN or COOEt groups are generally present as substituents at position 3 of the thiophene ring. An important factor stimulating the development of such methods is the high pharmacological

potential of compounds prepared according to the method **B**. In particular, several syntheses of GnRH antagonists were documented; one of these compounds, viz., 4-oxothieno[2,3-*b*]pyridine **45**, was synthesized by cyclocondensation of enamino ester **46** with α,β -unsaturated ketone **47** followed by *N*-alkylation (1999PCT9909033, 2002UKZ67, 2003USP6437132).

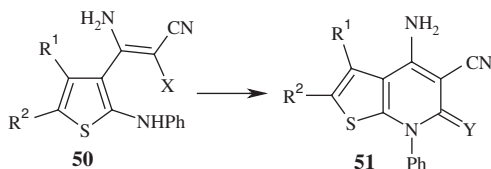


$R^1 = Pr^i$; $R^2 = MeO$; $R^3 = 2,6-F_2C_6H_3CH_2$;
 (a) $TsOH \cdot H_2O$, PhMe, 20°C, 2.5 h; (b) Ph_2O , reflux, 4 h;
 (c) R^2Br , DMF, K_2CO_3 , 20°C, 4 h.

The tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine **48** was easily obtained from tetrahydrobenzo[*b*]thiophene **49**, methyl acetoacetate (or ethyl acetoacetate) and stannic chloride (2005MI1).

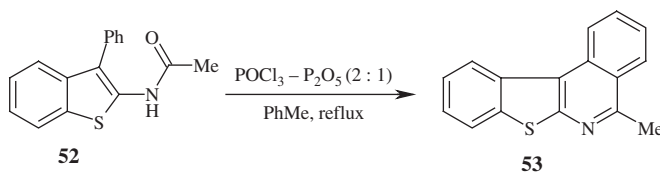


Method **C** is based on intramolecular cyclization of 2-aminothiophenes containing a substituent with the electrophilic γ -carbon atom at position 3. This class of compounds, for example, amines **50**, can be prepared by multicomponent cascade heterocyclization of phenyl isothiocyanate, CH-acids, and alkylating agents (1991SL229, 1992G147, 1992M341, 2001PS215). Cyclization of compounds **50** affords 6-oxo(imino)-6,7-dihydrothieno[2,3-*b*]pyridines **51** as the final products.

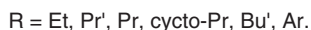
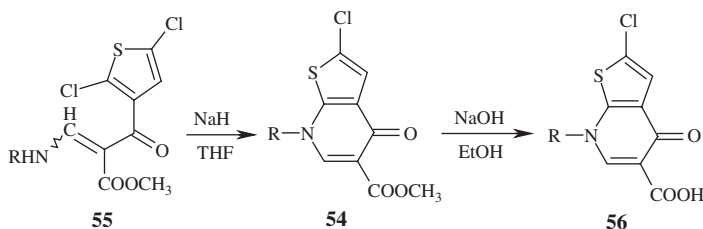


$X = CN, COOEt$; $Y = NH, O$; $R^1 = Ph$; $R^2 = OH, NH_2$.

Among the studies published in the last 10 years, we found only one example (2000JOC(E)1353) of the synthesis of thieno[2,3-*b*]pyridines according to method *D*. The pyridine fragment was constructed by intramolecular Bischler–Napieralski cyclization of 2-(acetamido)benzothiophene **52**. The maximum yield of the target isoquinoline derivative **53** was achieved with the use of P_2O_5 – $POCl_3$ as a condensing agent.



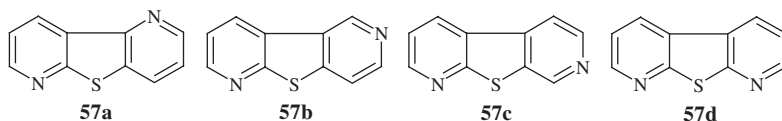
Method *E*, which assumes the N(7)–C(7a) bond formation in the cyclization step, is also rarely used in the synthesis of thienopyridines. For example, the method (1997H255, 1998JMC(E)33, 1998PS21) for the preparation of 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid esters **54** is based on intramolecular *N*-nucleophilic substitution of (*E/Z*)-aminomethylene derivatives of (2,5-dichloro-3-thenoyl)acetic acid esters **52** in the presence of a strong base. Esters **52** and products of their alkaline hydrolysis **56** have an antibacterial action; the influence of the substituents on the biological activity of the resulting compounds was studied.



3. Syntheses of Tri- and Polycyclic Systems Based on Thieno[2,3-*b*]pyridines

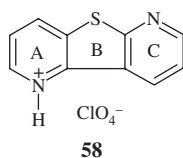
We restrict our consideration of the reactivities of thieno[2,3-*b*]pyridines to annulation reactions giving rise to tri- and polycyclic heterocycles. Information on such transformations has been systematized for the first time in the late 1980s (1987KFZ536, 1989MI2) and published more recently (1992SR1, 1993PS139, 1997KZA83, 1999KGS579, 2000KGS435, 2001MI1). Since the synthesis and properties of annulated thienopyridines have been particularly extensively studied recently, the need arose for a tentative generalization of the available data.

a. Pyridothienopyridines. Methods for the preparation of only pyrido[3',2':4,5]thieno[3,2-*b*]pyridines **57a** derived from one of four isomeric dipyridothiophene structures (**57a-d**), which are possible annulation products of thieno[2,3-*b*]pyridines, and their properties were documented. Evidently, this is associated with the fact that the starting 3-aminothieno[2,3-*b*]pyridines are readily accessible and can be varied. In some cases, the latter are generated *in situ* from monocyclic or acyclic precursors.

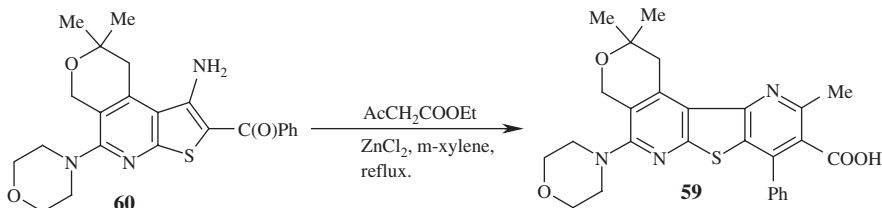


Data on the biological actions of dipyridothienopyridines are scarce. Information is lacking in the review (1987KFZ536), where considerable attention was given to the pharmacological aspect of the use of thienopyridine derivatives. The anticonvulsive activity of substituted pyrido[3',2':4,5]thieno[3,2-*b*]pyridine, which has low toxicity, was documented (1996RFP1417446).

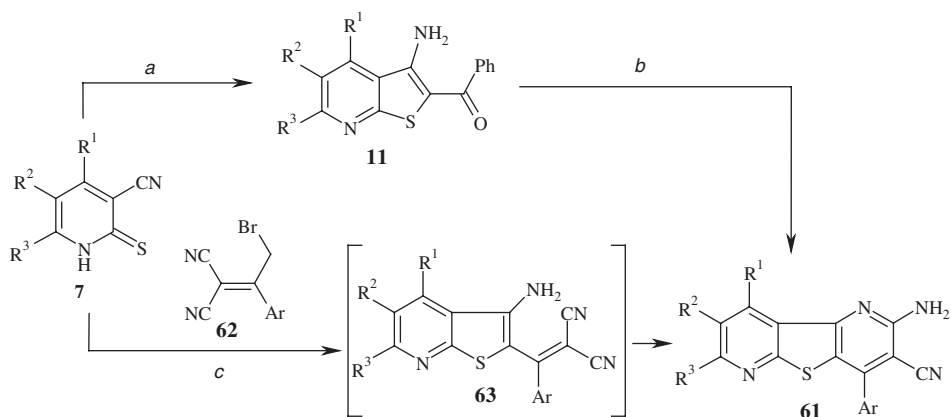
The structures of the simplest thieno[2,3-*b*:4,5-*b'*]dipyridine (**57a**) and its monohydroperchlorate **58** were studied (2000JHC763). Only the N atom of the ring A in compound **57a** is subjected to protonation.



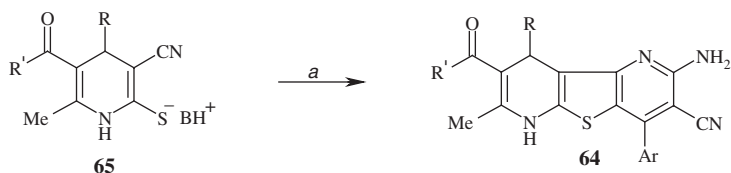
As mentioned above, amines of the thienopyridine series synthesized by the Thorpe reaction always contain an electron-withdrawing substituent (acyl, alkoxy-carbonyl, etc.) at position 2. The presence of the *o*-aminocarbonyl fragment in these compounds makes these compounds useful as synthons for pyridine ring construction in the Friedlaender synthesis. Generally, condensation occurs in the presence of a basic catalyst. The acid-promoted synthesis can be exemplified by the preparation of tetracyclic structure **59** from pyranthienopyridine **60** (1996RFP1417446).



The problem of the synthesis of substituted pyridothienopyridines was successfully solved using a method based on cascade transformations of 3-cyanopyridine-2(1*H*)-thione derivatives (**7**) (1996KGS115). On the whole, this type of heterocyclization has the following advantages over the conventional method of annulation based on the Friedlaender synthesis: the cascade process occurs more rapidly and under milder conditions and affords the target products in higher yields in a one-pot fashion. For comparison, alkylation of thiones **7** is accompanied by ring closure through the Thorpe reaction to form thienopyridines **11** ($Z = C(O)Ph$). Prolonged refluxing of the latter in pyridine in the presence of an excess of malononitrile affords tricyclic Friedlaender cyclocondensation products **61** (67–75%). At the same time, compounds **61** can be successfully prepared within two minutes from the same thiones **7** and 2-aryl-3-bromo-1,1-dicyanopropenes **62** in 57–95% yields; the intermediate, viz., thienopyridine **63**, was subjected to cyclization *in situ* and cannot be isolated (1996KGS115).

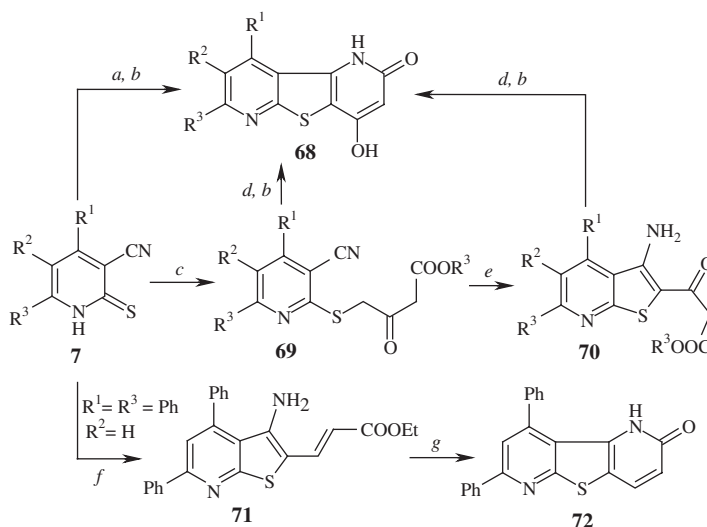


More recently, an approach based on bromides **62** was employed in the synthesis of other dipyridothiophenes (1996KGS553, 1997T13351). In particular, 6,9-dihydro-pyrido[3',2':4,5]thieno[3,2-*b*]pyridines **64** were prepared for the first time from thiolates **65**. It should be emphasized that cascade heterocyclization occurs spontaneously in the absence of a basic catalyst (1996KGS553).



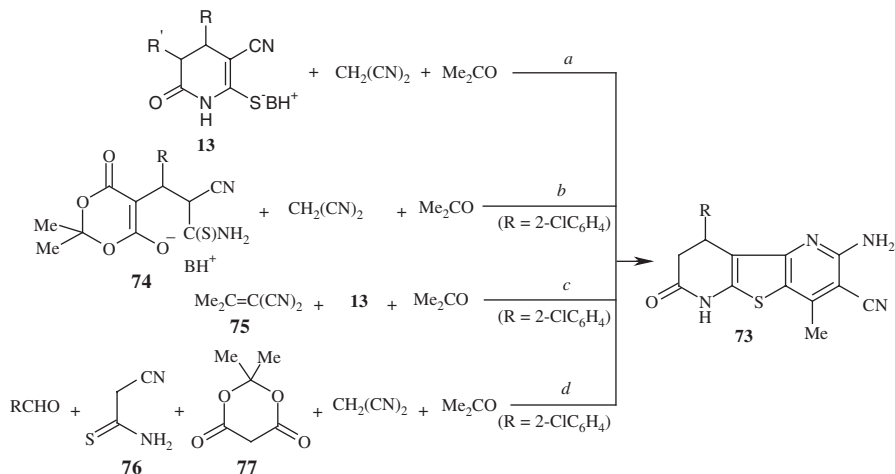
$\text{R} = 4\text{-MeOC}_6\text{H}_4, 2\text{-NO}_2\text{C}_6\text{H}_4, 2\text{-thienyl}; \text{R}' = \text{EtO}, \text{Me}; \text{Ar} = 4\text{-BrC}_6\text{H}_4; \text{B} = \text{piperidine}.$
a) **62**, EtOH, 40 °C, 10 min; -20 °C, 16 h.

In addition to dicyanobromopropenes **62**, γ -chloroacetic acid esters ($\text{ClCH}_2\text{C}(\text{O})\text{CH}_2\text{COOR}$) (**66**) (1998IZV365, 2003IZV428, 2003IZV2069, 2003IZV2087) and 4-bromoethylcrotonate ($\text{BrCH}_2\text{CH}=\text{CHCOOEt}$) (**67**) (1998KGS263) are also used as alkylating agents in heterocyclization reactions giving rise to fused thienopyridine derivatives. The cascade reaction of substituted pyridine-2(1*H*)-thiones **7** and γ -chloro- β -keto esters **66** in refluxing ethanol in the presence of KOH or EtONa is a method of choice for the preparation of dipyridothiophenes **68**. If the reaction is performed under milder conditions, intermediates, such as pyridine **69** and thieno[2,3-*b*]pyridine **70**, can be isolated, and the latter are readily subjected to heterocyclization under the action of bases to form target products **68** (2000IZV347). Analogously, thienopyridine **71** prepared by the reaction of thione **7** ($\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{H}$) with crotonate **67** can be transformed into dipyridothiophene **72** (1998KGS263).

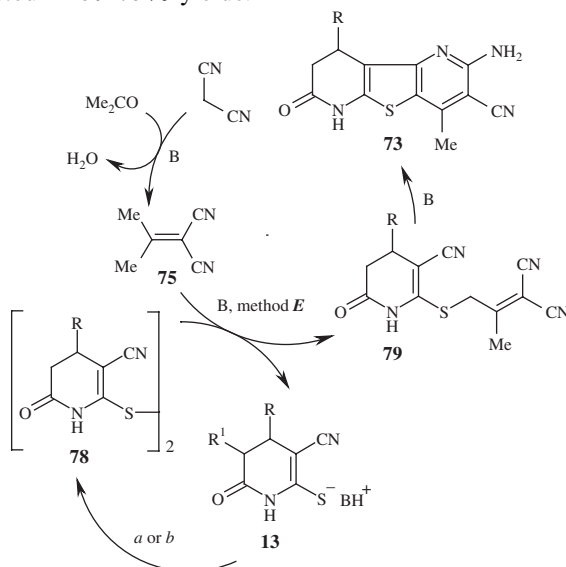


a) **66** ($\text{R} = \text{Et}, \text{Pr}^1$), KOH or EtONa, EtOH, reflux; *b)* 10% HCl; *c)* **66**, 10% KOH, DMF; *d)* KOH or EtONa, EtOH, reflux; *e)* Et_3N , EtOH, reflux; *f)* **67**, KOH or EtONa, EtOH; *g)* HCl, MeOH, reflux, 8 h.

The multicomponent approach to the synthesis of substituted 6,7,8,9-tetrahydropyrindo[3',2':4,5]thieno[3,2-*b*]pyridines **73** is based on the reaction of pyridinethiolates **13**, malononitrile, and acetone (method *A*) (2002IZV339, 2003IZV918, 2003MC267). Attempts to modify this method by performing the reaction with precursors of thiolates **13**, viz., Michael adducts **74**, instead of thiolates by themselves (method *B*), using isopropylidene malononitrile **75** instead of malononitrile (method *C*), or performing multicomponent cyclocondensation of 2-chlorobenzaldehyde, cyanothioacetamide **76**, Meldrum's acid **77**, acetone, and malononitrile (method *D*) resulted in a decrease in the yields of the above-mentioned target products with a simultaneous increase in reaction time (2002IZV339).



The above-described reaction (method A) occurs only in the presence of atmospheric oxygen (2003M11, 2004MC30). These data suggest the following reaction mechanism: pyridinethiolate **13** is oxidized to the corresponding bis(pyrid-2-yl) disulfide (**78**), which reacts with the isopropylidene malononitrile anion **75** (derived *in situ* from malononitrile and acetone) resulting in S-S bond cleavage and the formation of dicyanoallyl sulfide **77** and thiolate **13**. The latter is again oxidized to disulfide, and compound **79** is involved in cascade heterocyclization giving rise to the dipyridothiophene. The possibility of this reaction pathway was confirmed by the independent synthesis of compounds **73** from disulfides **78** (method E), which were prepared in virtually 100% yields by mild oxidation of thiolates **13**; the target products were isolated in 60–75% yields.

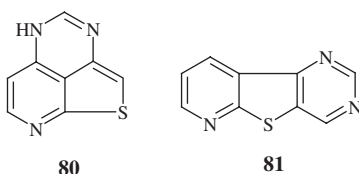


B is N-methylmorpholine; R = Ar, Het; R' = H.

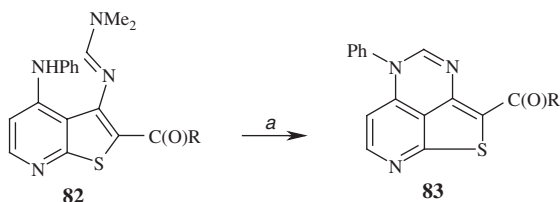
a) O₂, EtOH (in situ); b) I₂ > EtOH-H₂O, 24 h, 90-100%.

b. Pyridothienopyrimidines. Of all fused thienoazines derived from **1**, pyridothienopyrimidine derivatives have received the most study. Representatives of this class serve as bactericides, fungicides, or immunomodulators, exhibit antianaphylactic, antiallergic, anticonvulsive, analgetic, or antiinflammatory activities, and are used (or are suitable) as intermediate products in chemical and pharmaceutical industry. Selected data on biological activities of pyridothienopyrimidine derivatives were given in the review (1986DK215). Here we analyze information on the chemistry of pyridothienopyrimidines considering them as a special class of thienopyrimidine derivatives.

All pyridothienopyrimidines prepared by annulation of thieno[2,3-*b*]pyridines are derivatives of two regioisomeric structures, namely, 5*H*-thieno[2,3,4-*e,d*]pyrido[4,3-*d*]pyrimidine (**80**) or pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (**81**).

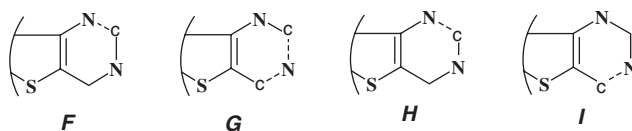


Compounds with structure **80** can be synthesized by intra or intermolecular cyclization of substituted 3,4-diaminothieno[2,3-*b*]pyridines. For example, heating (*N,N*-dimethylaminomethylene)amines **82** affords tricyclic pyrimidine derivatives **83** via intramolecular cyclocondensation (1993KFZ40).

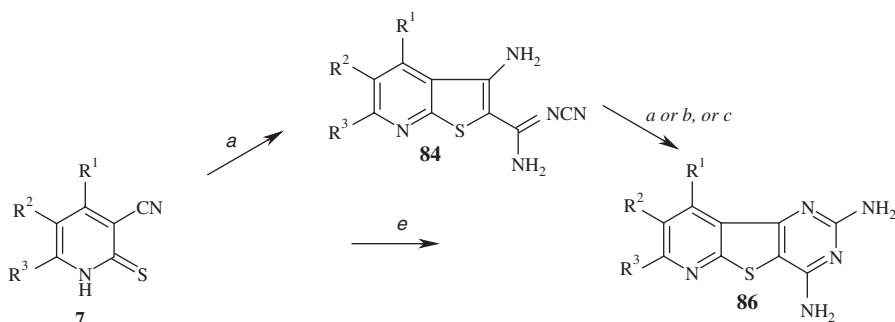


R = OEt, N=CH(NMe₂); R' = OEt (87%), NHC(O)H (94%).
a) 70% AcOH, 100 °C, 0.5 h.

There is a large body of data on the synthesis and properties of pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine derivatives (**81**). All methods used for the construction of the pyrimidine ring can be classified into several types (**F-I**).

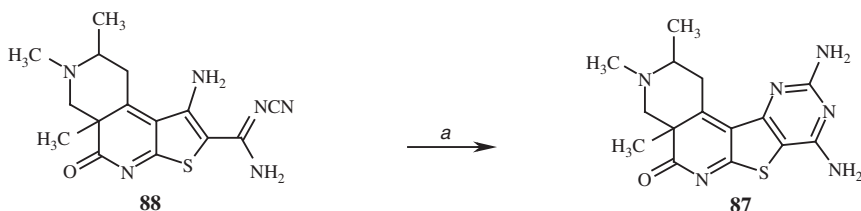


Approach **F** is based on intramolecular cyclization of 3-aminothienopyridines containing a γ -electrophilic substituent at position 2, resulting in the formation of the N(1)–C(2) bond of the pyrimidine ring. Examples were given in (1993MC149, 1994KGS122, 1996KGS553, 1996T1011). For instance, thienopyridines **84** derived from 3-cyanopyridine-2(1*H*)-thione derivatives **7** and *N*-cyanochloroacetamide (**85**) are subjected to both base- and acid-catalyzed cyclization giving rise to tricyclic 2,4-diaminopyridine derivatives **86** where the yields average 60–90%. The latter can also be synthesized directly from thiones **7** and chloride **85** by one-pot cascade heterocyclization. Transformations of **86** were studied (1994KGS122).



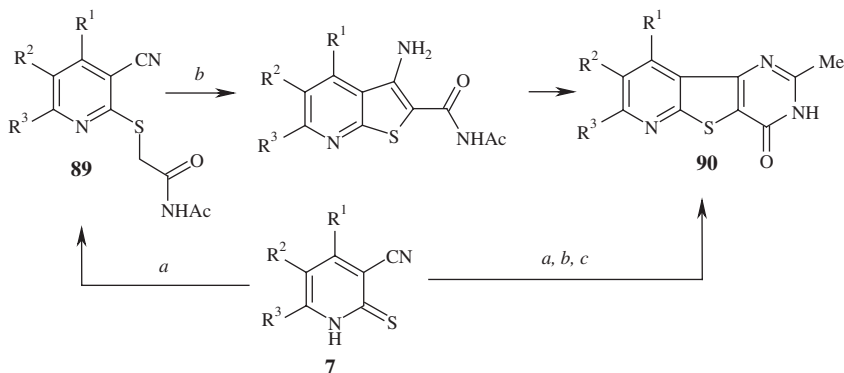
- a) C1CH₂C(NCN)NH₂ (**85**), KOH, DMF; b) EtONa, EtOH, reflux, 6 h; c) 35% HCl, MeOH, 0.5–12 h; d) Ac₂O, reflux, 6 h; e) 1) EtOH, KOH, ~20 °C; 2) **83**, ~20 °C; 3) EtONa, EtOH, reflux, 2 h.

6,9-Dihydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines were successfully prepared using the corresponding 1,4-dihydropyridine-2-thiolates **19** instead of thiones **7** (1993MC149, 1996KGS553). This approach made it possible to prepare pyrimidothieno[2,7]naphthyridine derivative **87** starting from tricyclic structure **88** (1995MI1).



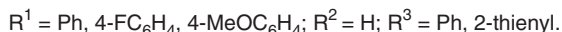
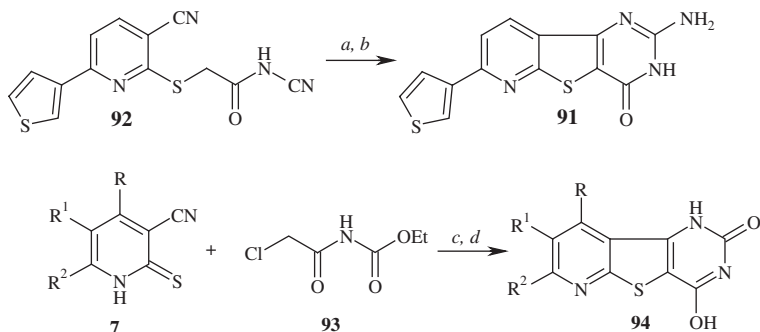
- a): 1) 35% HCl, MeOH, reflux, 1 h; 2) Na₂CO₃, H₂O.

In a basic medium pyridines **89** are involved in cascade heterocyclization giving rise to fused pyrimidines **90**. The starting compounds **89** can be generated *in situ* from 3-cyanopyridine-2(1*H*)-thiones **7** (1997KGS837).



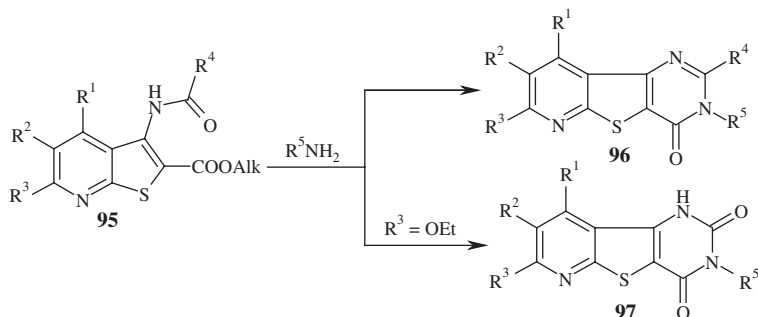
a) $\text{ClCH}_2\text{C(O)NHAc}$, 10% KOH, EtOH, 50 °C, 30 min; b) 10% KOH, EtOH, reflux for 1.5 h; c) HCl, pH 7.

Analogously, pyrido[3',2:4,5]thieno[3,2-*d*]pyrimidine **91** is derived from *N*-cyanoamide **92** in moderate yield under mild conditions (1998IZV365). The treatment of pyridinethiones **7** ($R^1, R^3 = \text{Ar}, R^2 = \text{H}$) with *N*-(ethoxycarbonyl)chloroacetamide **93** provides a convenient one-pot method for the synthesis of tricyclic thienoazines **94** (2003IZV2087).



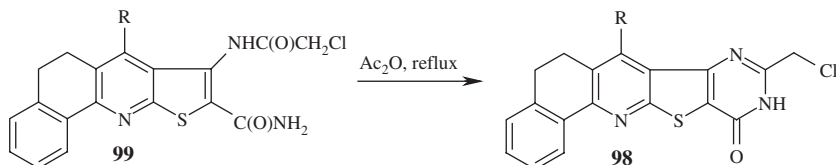
a) EtOH, HCl, 5 °C, 24 h; b) 10% Na_2CO_3 ; c) EtONa, EtOH-DMF (1 : 1), reflux, 2 h; d) 10% HCl, 20 °C.

Approach **G** involves the successive formation of the N(3)–C(4) and C(2)–N(3) bonds of the pyrimidine ring during cascade heterocyclization. Such transformations can be exemplified by condensation of substituted 2-alkoxycarbonyl-3-(R^2 -carbonyl)aminothieno[2,3-*b*]pyridines **95** with primary amines or hydrazine giving rise to fused pyrimidin-4(3*H*)-ones **96** (1993PH26, 1997KGS847). In the case of $R^4 = \text{EtO}$, the reaction gives pyrimidine-2,4-dione derivatives **97** as the final products (1993PH95).



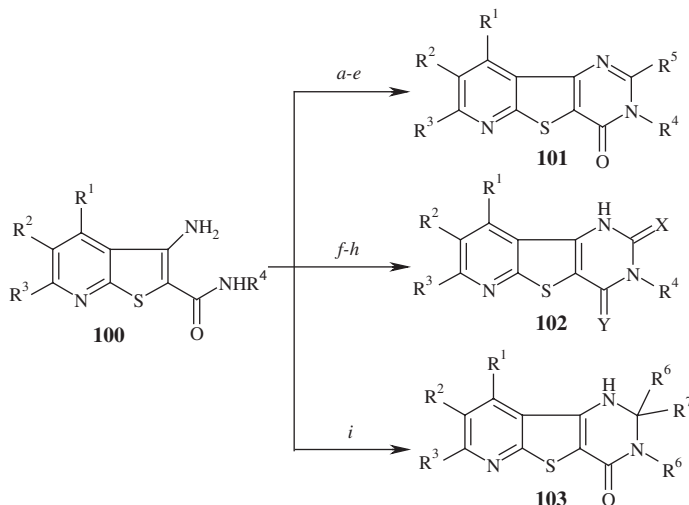
$R^1 = \text{H, Alk, Ar, COOEt}$; $R^2 = \text{H, Ph, Me}$; $R^3 = \text{Me, Et}$; $R^4 = \text{NH}_2, \text{H, Alk, (CH}_2)_2\text{NEt}_2, (\text{CH}_2)_n\text{OH, } n = 2, 3$; $R^4 = \text{Me, Ph}$; $R^5 = \text{H, NH}_2, \text{Ar, PhNH, NHC(S)NH}_2$.

The *H* mode of the pyrimidine ring construction assuming the stepwise formation of the N(1)–C(2) and C(2)–N(3) bonds as a result of the insertion of a component serving as the source of the C(2) atom is more often used in practice. The simplest modification involves intramolecular condensation of 3-(acylamino)thienopyridines produced by acylation of 3-amino-2-carbamoylthieno[2,3-*b*]pyridines or their structural analogs (1995PS83). An example is the synthesis of pyrimidothienobenzoquinoline **98** from chloroacetamide **99**.



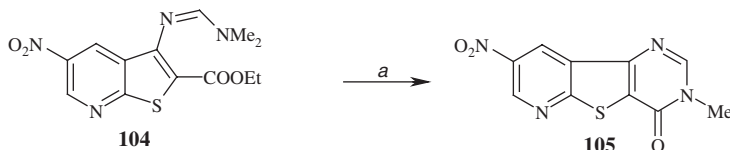
R = 2-furyl

However, methods based on the successive one-pot formation of the N(1)–C(2) and C(2)–N(3) bonds of the pyrimidine ring are more convenient. For this purpose, 3-amino-2-carbamoylthienopyridines or their derivatives **100** are subjected to reactions (usually, under drastic conditions, e.g., reflux or fusion) with various mono-carbon components. Acetic anhydride, carboxylic acid chlorides, the Vilsmeier reagent, formic acid, trimethyl and triethyl orthoformates, carbon disulfide, urea, aldehydes, ketones, ethyl chloroformate, DMF dimethyl or diethylacetal, and diethyl oxalate can serve as such components. In particular, this method was used to prepare annulated structures **101–103** containing different substituents in the pyrimidine ring. These approaches are also suitable for the preparation of polyfused systems containing the partially hydrogenated pyridine fragment (2003KGS117). It was demonstrated (1994IZV181, 1994IZV489) that pyrimidinones **101** can exist in part as the 4-hydroxy tautomers. Refluxing certain 3-amino-2-cyanothieno[2,3-*b*]pyridines with CS₂ in pyridine leads to the transformation of the CN group into the thiocarbamoyl group to give tetrahydropyrimidine derivatives **102** (X = Y = S, R⁴ = H) (1991PS189). Compounds **103** (R⁴ = H, R⁶ = Ar, Alk, R⁷ = H) were oxidized to annulated pyrimidin-4(3*H*)-ones **101** (1992JHC1693).



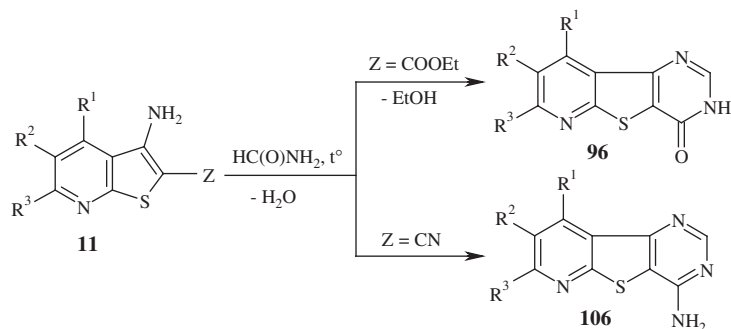
- a) Ac_2O , reflux, $\text{R}^5 = \text{Me}$; b) $\text{R}^5\text{C}(0)\text{Cl}$, AcOH or fusion, $\text{R}^5 = \text{Me}$, ClCH_2 , Ar ;
 c) $\text{POCl}_3\text{-DMF}$, $\text{R}^1 = \text{H}$; d) HCOOH , reflux, $\text{R}^1 = \text{H}$; e) $\text{HC}(\text{OMe})_3$ or $\text{HC}(\text{OEt})_3$, Ac_2O , reflux, $\text{R}^1 = \text{H}$;
 f) CS_2 , pyridine, $100\text{ }^\circ\text{C}$, or dioxane, $\text{X} = \text{S}$, $\text{Y} = \text{S}, \text{O}$; g) $(\text{NH}_2)_2\text{C}(\text{O})$, fusion, $\text{X} = \text{Y} = \text{O}$;
 h) ClCOOEt , $\text{X} = \text{Y} = \text{O}$; i) $\text{R}^6\text{C}(\text{O})\text{R}^7$, reflux in AcOH or PhMe-TsOH (cat.), $\text{R}^6 = \text{Ar, Alk}$;
 $\text{R}^7 = \text{H}$, or $\text{R}^6 + \text{R}^7 = (\text{CH}_2)_n$, $n = 5, 6$.

Method *I* is based on reactions giving rise to the pyrimidine ring by N(3)–C(4) bond formation. Generally, cyclization is preceded by the formation of one more bond, for example, of C(2)–N(3). For instance, the reaction of formamidine **104** with MeNH_2 provides a convenient approach to the synthesis of pyridothienopyrimidine **105** (1997KFZ18).

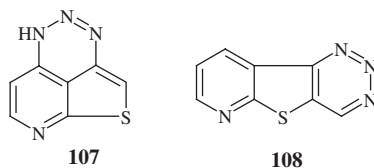


- a) 15% $\text{MeNH}_2/\text{MeOH}$, $120\text{ }^\circ\text{C}$, 15 h.

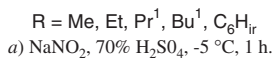
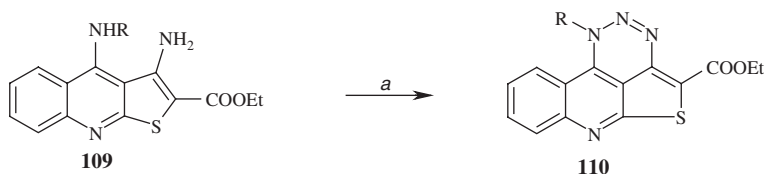
The one-step reactions resulting in N(1)–C(2) and N(3)–C(4) bond formation are obviously useful. Various 3-aminothienopyridines **11** and formamide most often serve as the starting compounds. Formamide acts also as the solvent; the final products can be prepared in high yields by refluxing **11** in formamide for several hours. This method for the preparation of pyridothienopyrimidine derivatives was included in the synthetic arsenal from the early 1970s (1989MI2). In recent years, this method was used to prepare a series of polyfused azines with general formulas **96** and **106** (1994IZV181, 1995KGS851, 2000PS149, 2000SC3883).



c. Pyridothienotriazines. Scarce data on the synthesis of this class of compounds were reported in reviews (1989M12, 1999KGS579) in connection with an investigation of the properties of their precursor 3-cyanopyridine-2(1*H*)-thiones. Investigation of the properties of pyridothienotriazines and the development of procedures for their preparation hold promise taking into account that some compounds belonging to this class possess analgetic, anticonvulsive, antimicrobial, antifungal, anti-tumor, antianaphylactic, and antiallergic activities. In spite of a considerable body of data on the synthesis of pyridothienotriazines, there are just a few synthetic approaches to the triazine ring in the thieno[2,3-*b*]pyridine series. Only derivatives of the 1,2,3-triazine system represented by two isomers **107** and **108** were documented.

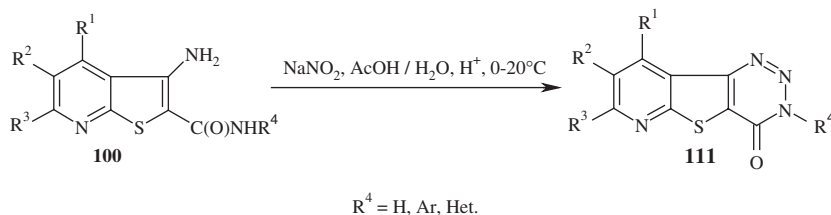


Under diazotization conditions, 3,4-diaminothienoquinolines **109** are transformed into derivatives of a new heterocyclic system, namely, 1*H*-5-thia-1,2,3,6-tetraazaacephenanthrylene **110**, in high yields (2001PS49, 2001S97).



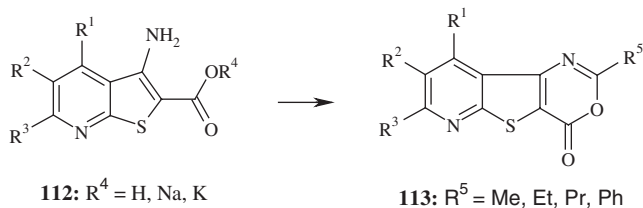
The same approach to the triazine fragment was used in the synthesis of all pyrido[3',2':4,5]thieno[3,2-*d*][1,2,3]triazines with the structure of isomer **108**. Nitrous acid generally serves as a source of the N(2) atom. This acid is generated *in situ* from

NaNO₂ and AcOH, often in the presence of HCl or H₂SO₄; the reaction proceeds under mild conditions and gives the final products in good yields averaging 60–80%. Isoamyl nitrite was used as the source of the nitrogen atom in one study (1995H37). However, it should be noted that diazotization with the NaNO₂–AcOH system seems to be preferable because this reaction affords the target products in higher yields. Besides, isoamyl nitrite is more expensive than sodium nitrite. The synthesis of 1,2,3-triazin-4(3*H*)-ones **111** from 3-amino-2-carbamoylthieno[2,3-*b*]pyridine derivatives **100** has been studied most extensively (1992PS219, 1993BCJ3716, 1993PH514, 1993PH576, 1995H37, 2000PS289, 2002SC3493).



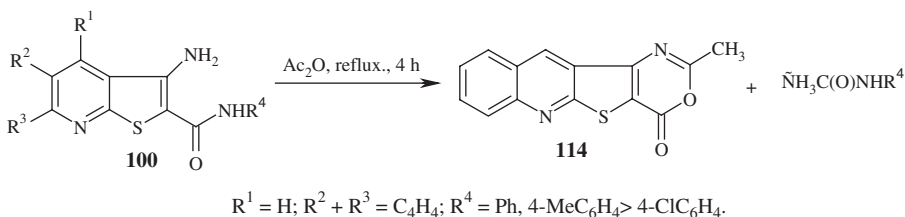
d. Pyridothienooxazines. Some aspects of the synthesis and reactions of pyridothienooxazines were covered in reviews (1989MI2, 1999KGS579). Information on this class of compounds has not been previously generalized. Data on biological activities of pyridothienooxazines and their fused derivatives are scarce. For example, this type of compounds was not included in the review devoted to the pharmacological properties of thienopyridine and its annulated analogs (1987KFZ536). More recently, their antibacterial (1996RFP1282510) and possible antitumor and radioprotector (1998PS57, 1998PS447) actions have been documented.

In practice, pyrido[2',3':5,4]thieno[3,2-*d*]oxazine derivatives are most often synthesized by the method based on cyclocondensation of 3-aminothieno[2,3-*b*]pyridine-2-carboxylic acids **112** (or the corresponding salts **112**) with carboxylic acid anhydrides (usually, Ac₂O) by refluxing (1990PH731, 1993BCJ3716, 1993CCC1457, 1993PH63, 1994IZV181, 1995KGS250, 1996RFP1282510, 1996JHC431, 1996PS31, 1998PS447). The yields of products **113** are, on the average, 60–75%.



In another modification of this approach (1992CCC2359), the corresponding anilides **100** ($R^1 = \text{H}$, $R^2 + R^3 = \text{C}_4\text{H}_4$) are used instead of acids **112**. This method was employed to prepare oxazinothienoquinoline **114**. However, it should be noted that numerous data suggest that (see Section II.A.3.b) pyrimidine derivatives **96**, rather than 1,3-oxazine derivatives, would be expected to be produced under these

conditions. Apparently, to resolve this contradiction, additional investigations are required.

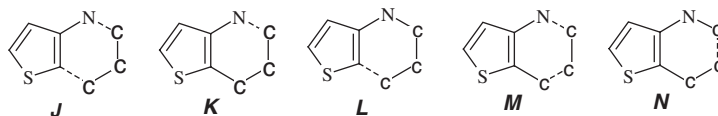


B. THIENO[3,2-*b*]PYRIDINES

Methods for the preparation of thieno[3,2-*b*]pyridine derivatives (**2**) and their properties are less well described in the literature compared to [2,3-*b*]-isomer **1**. Scarce data on the synthesis of thienopyridine **2** and its fused analogs are available in reviews (1985MI1, 1987KFZ536, 1987MI1, 1991MI2, 1994KGS1603, 2000KGS435, 2001KGS41). The transformations of the [3,2-*b*]-isomer were discussed in more detail in the review (1977AHC65).

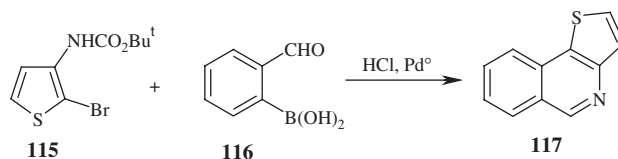
The biological actions of compounds containing the thieno[3,2-*b*]pyridine structural fragment are well known. Certain representatives of this class serve as endothelin receptor antagonists, ligands of γ -aminobutyric acid receptors, immunoregulators, calcium channel blockers, α -1-adrenoreceptor antagonists, agents of chemical control over synaptic transmission, topoisomerase and 5-lipoxygenase inhibitors, inhibitors of binding of neuron growth factor to p75NGF receptors, and leukotriene antagonists. In addition, representatives have antiinflammatory, antiallergic, analgetic, anticancer, antitumor, or antiasthmatic/bronchodilatory actions, exhibit anticonvulsive or anticholinesterase activities, serve as gastrointestinal regulators, acetylcholine esterase inhibitors improving memory, medicines suitable for the treatment of nervous system disorders, or bactericides. In the general case, the antibacterial activity of thieno[3,2-*b*]pyridines is higher than the activity of derivatives of the [2,3-*b*]-isomer (1987KFZ536, 1991JMC(E)3). Undoubtedly, the diversity of biological activities gave impetus to the development of convenient synthetic approaches to the construction of the thieno[3,2-*b*]pyridine system.

Most of the known methods for the synthesis of these compounds are based on the use of readily accessible 3-aminothiophenes or their *N*-derivatives. The following main ways of the pyridine ring construction (**J–N**) are possible:

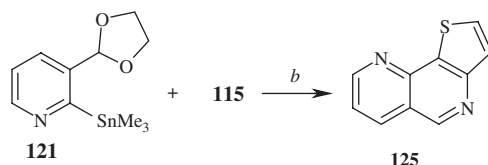
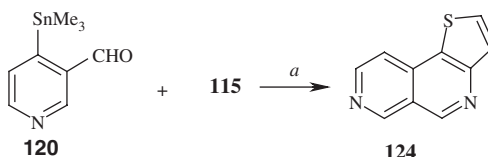
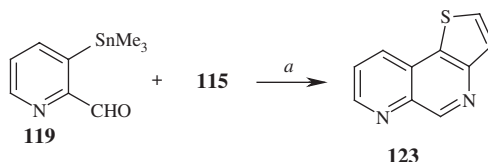
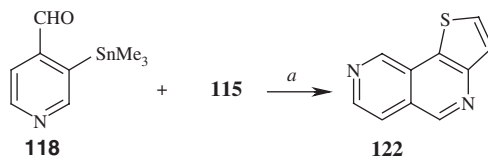


Approach **J** is often used in organic synthesis and assumes the formation (sometimes, stepwise) of the N(1)–C(2) and C(4)–C(5) bonds of the pyridine fragment in reactions of 3-aminothiophenes with various 3C-components. In particular, this type

of heterocyclization provides the basis for methods developed for the preparation of the simplest [3,2-*b*]-fused thioazines. For example, the modified Suzuki reaction of carbamate **115** with *o*-formylphenylboronic acid **116** produces unsubstituted thieno[3,2-*c*]quinoline **117** (1990JHC1127).

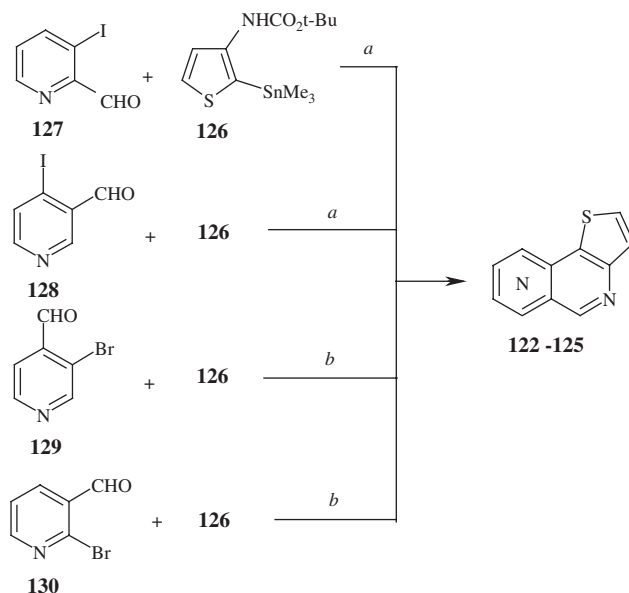


The Stille cross-coupling reactions of thienyl-3-carbamate **115** with *o*-formyl (trimethylstannyl)pyridines **118–120** (1994JHC1161) or acetal **121** (1992MI3, 1994JHC1161, 1994JOMC127) afford a series of isomeric thienonaphthyridines **122–125**. The addition of CuO to the reaction mixture leads to an increase in rate (1993JOMC127).



a) PdCl₂(dppb), CuO, N₂, DMF, 100 °C; *b*) Pd(PPh₃)₄, CuO, N₂, DMF, 100 °C, HCl, 3 h; (PdCl₂ (dppb) is dichloro(diphenylphosphinebutane)palladium(II)).

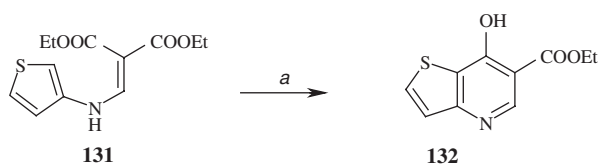
An alternative cross-coupling process based on the reaction of 2-(trimethylstannyl)-3-thienylcarbamate **126** with *o*-halopyridinecarbaldehydes **127–130** afforded the same products in higher yields (1995JHC751).



a) PdCl₂(dppb), N₂, DMF, 100 °C, 2 h; *b*) PdCl₂(dppb), CuO, N₂, DMF, 100 °C, 2 h.

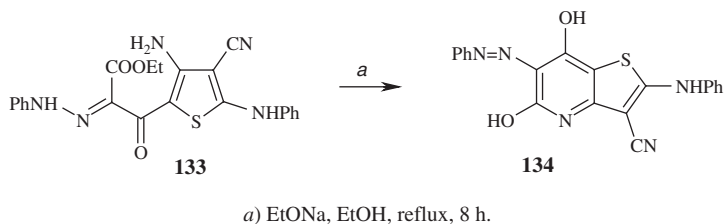
It was also demonstrated (1997HC183) that the reactions can be performed under analogous conditions not only with pyridine **130** but also with 2-chloro-formylpyridine *N*-oxide or 2-bromo-3-(1,3-dioxolan-2-yl)pyridine *N*-oxide. The latter reactions produce the corresponding thieno[*b*][2,5]naphthyridine *N*-oxides, which can also be prepared by oxidation of the parent systems with *m*-chloroperoxybenzoic acid.

The pyridine ring can also be constructed by the Gould–Jacobs reaction (1991JMC(E)3, 1998JAP10251264, 2000PH595, 2002JHC783). This formation of the thienopyridine system can be exemplified by intramolecular cyclization of enamino diester **131** giving **132**, which possesses antihypertensive and antibacterial actions (1998JAP10251264).

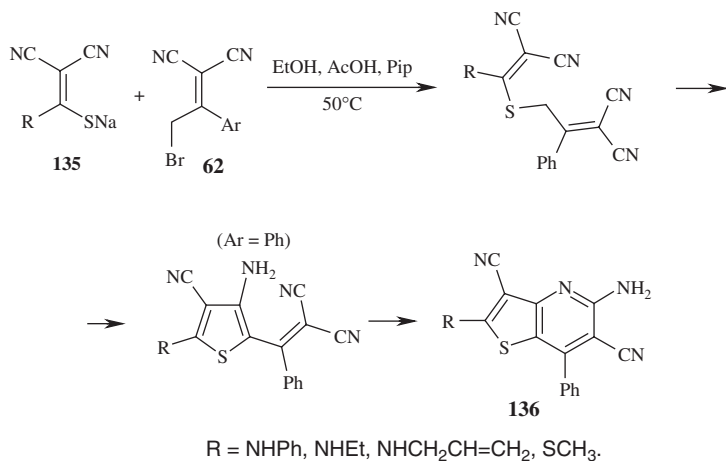


a) TsOH, Ac₂O, xylene, reflux, 26 h.

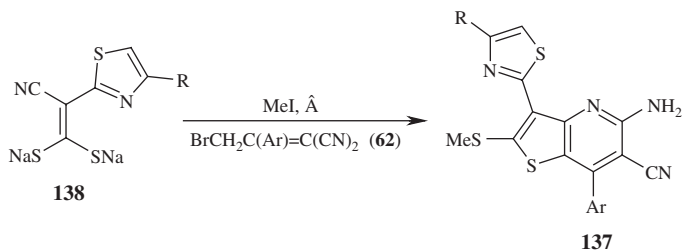
The cyclocondensation reaction of substituted thiophene **133** giving rise to **134** (1991SL229) is a good example of the use of approach **K** based on intramolecular cyclization of 3-aminothiophenes containing a γ -functionalized substituent at position 2 to form the N(4)–C(5) bond.



However, the synthesis of thieno[3,2-*b*]pyridines by cascade heterocyclization of simple and readily accessible reagents **62** and **135** holds more promise. In this process, the thiophene ring and then the pyridine ring are successively formed in the presence of a basic catalyst to give finally polyfunctionalized thieno[3,2-*b*]pyridine **136** (1996KGS413).

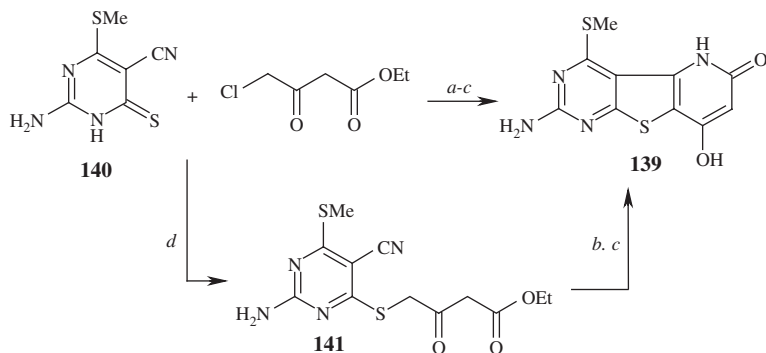


More recently, this approach was used in the synthesis of 3-(thiazol-2-yl)thieno[3,2-*b*]pyridines **137** from the corresponding ethylenedithiolates **138** (2003MI2).



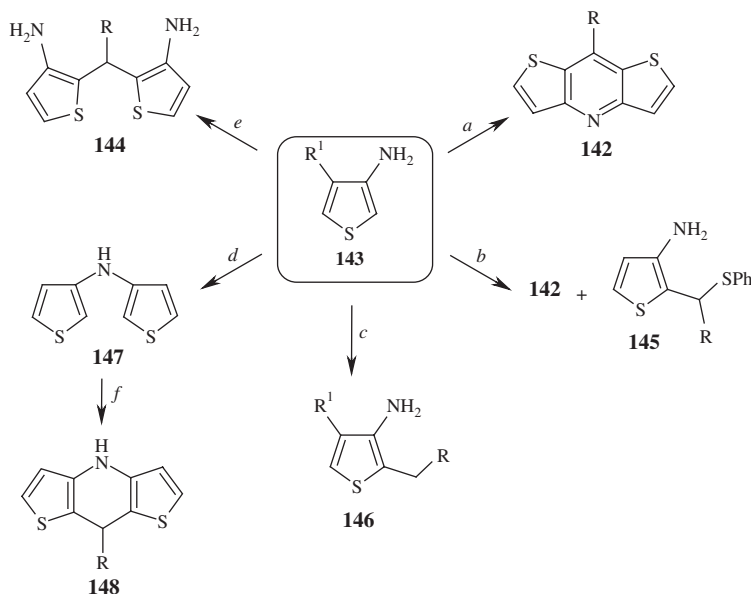
Ar = 4-ClC₆H₄; R = Ph, 4-ClC₈H₄, 4-MeOC₆H₄, 4-BrC₆H₄; B is a base.

This approach was also employed for pyrido[3',2':4,5]thieno[2,3-*b*]pyrimidine derivative **139**, which can be prepared according to the following two procedures: by the one-pot base-catalyzed reaction of pyrimidinethione **140** with ethyl 4-chloroacetoacetate or by cascade heterocyclization of pyrimidine **141** (2003IZV2069).



a) KOH, EtOH, 20 °C; *b*) 2 equiv. of KOH, EtOH, reflux; *c*) HCl; *d*) KOH, DMF.

Dithieno[3,2-6:2',3'-*e*]pyridine derivatives **142** can be prepared by the acid-catalyzed reaction of 3-aminothiophene or its 4-BocNH derivative **143** with aldehydes followed by transamination and dehydrogenation of bis(3-amino-2-thienyl)methane intermediates **144** (1993TL5715, 1993TL5719, 1996JHC9, 1997T10331). This reaction in the presence of PhSH was accompanied by the formation of thiophene **145** (1996JHC9), whereas the reaction with selenophenol yielded only the reductive alkylation products 2-alkyl-3-aminothiophenes **146** (1993TL5715, 1996JHC9, 1997T10331). Bis(3-thienyl) amine (**147**) that formed by self-condensation of amine **143** can also be involved in a condensation with aldehydes to give dihydrodithienopyridines **148** (1993TL5719). In this case, the pyridine ring construction occurs via pathway *L*.

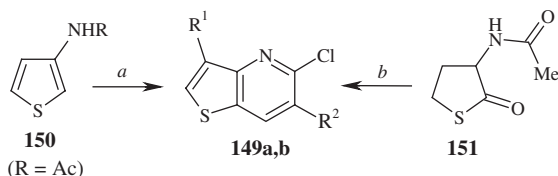


R = H, Me, Et, Ar; R' = H, BocNH.

a) RCHO (0.5 equiv.), THF; *b*) RCHO (R = Me, Et), PhSH, TsOH, ~20°C;

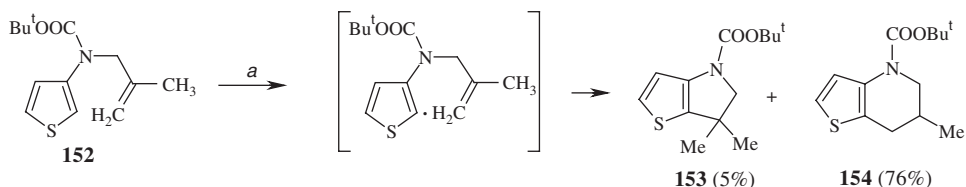
c) RCHO (1 equiv.), PhSeH, CH₂Cl₂, H⁺; *d*) AcOH, PhH, A; *e*) RCHO (0.5 equiv.), TsOH; *f*) RCHO, H⁺, 0°C.

Approach **L** assumes the formation of the C(4)–C(5) bond of the pyridine ring in the final step of cyclization. Thienopyridine **149a** was prepared from 3-(*N*-acetylthiophene (**150**, $R^1 = \text{Ac}$) by the Vilsmeier–Haack reaction (1987USP4593099). *N*-acetylhomocysteine thiolactone **151** undergoes an analogous transformation, cyclocondensation being accompanied by formylation of the thiophene ring, to give 5-chlorothieno[3,2-*b*]pyridine-3-carbaldehyde (**149b**) as the final product (1993TL4249).



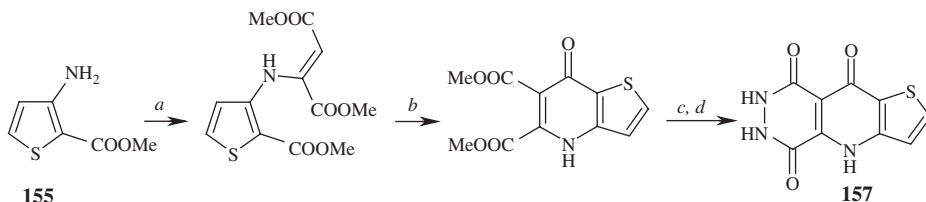
a) $R^2 = \text{H}$, $R^3 = \text{CN}$; POCl_3 , DMF, reflux, 1.5 h; $\text{NH}_2\text{OH} \cdot \text{HCl}$; b) $R^2 = \text{CHO}$, $R^3 = \text{H}$; POCl_3 , DMF, 90 °C.

Radical cyclocondensation of *tert*-butyl-*N*-(2-bromo-3-thienyl)-*N*-metallylcarbamate (**152**) affords a mixture of 5-*exo* (**153**) and 6-*endo* products (**154**), the latter predominating (2001JCS(P1)37).



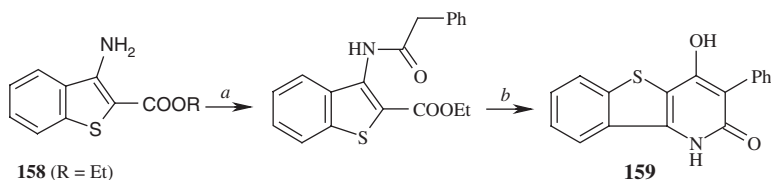
a) Bu_3SnH , AIBN, PhCH_3 , reflux, 8 h.

The construction of a thieno[3,2-*b*]pyridine by pathway **M** involves the successive formation of the N(1)–C(2) and C(3)–C(4) bonds of the pyridine fragment. Various 3-aminothiophene-2-carboxylic acid derivatives are most often used as the starting reagents with 2C-components, which introduce carbon atoms C(2) and C(3) into the pyridine ring. For example, the reaction of amino ester **155** with dimethyl acetylenedicarboxylate (**156**) involves intramolecular cyclocondensation followed by hydrazinolysis to give derivatives of the new heterocyclic system thieno[2',3':5,6]pyrido[2,3-*d*]pyridazine (**157**) (1991JHC205, 1990SPH203).



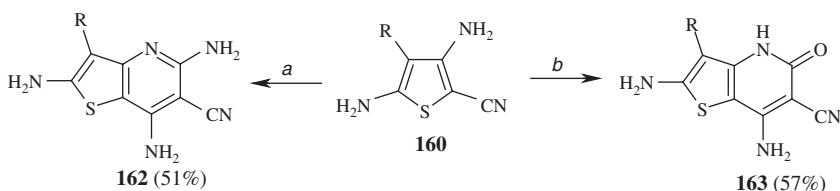
a) **156**, MeOH, reflux, 16 h; b) $\text{Bu}'\text{OK}$, $\text{Bu}'\text{OH}$, t° ; c) N_2H_4 , MeOH, reflux, 72 h; d) 2 N HCl , t° .

Phenylacetyl chloride can be used as the 2C-component in the *M*-type reactions. Here, N(1)–C(2) bond formation occurs due to the acylation of 3-amino-2-ethoxycarbonylbenzothiophene (**158**); cyclization of the resulting amide in a basic medium affords the target benzothienopyridine **159** (2002H317).



a) PhCH₂C(O)Cl, Et₃N, THF, 0 °C → ~20 °C; *b*) LiN(SiMe₃)₂, THF, ~20 °C → reflux.

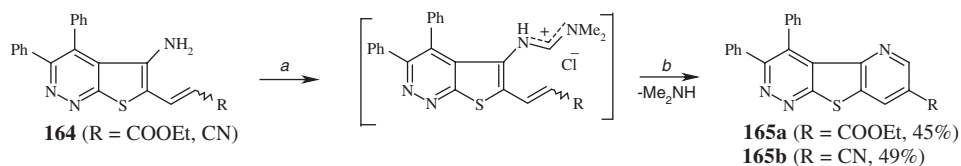
Thieno[3,2-*b*]pyridines **162** and **163** were prepared starting from *o*-aminonitrile **160** and methylene-active compounds **161** (1996M955).



R is benzothiazol-2-yl.

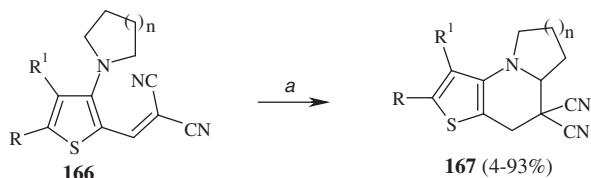
a) NCCCH₂CN (**161a**), AcOH, reflux, 4 h; *b*) NCCCH₂COOEt (**161b**), dioxane, Et₃N, reflux, 3 h.

The C(2)–C(3) bond formation provides the basis for the construction of thieno[3,2-*b*]pyridines according to method N. Scarce examples were, as a rule, based on nontrivial synthetic approaches. For example, thienopyridazines **164** undergo an unusual cyclization to give pyridothienopyridazines **165** under the conditions of the Vilsmeier–Haack reaction (2001T5413).



a) 1) POC₁₃, DMF, -10 - 0 °C, 1 h; 2) ~20 °C, 12 h; *b*) DMF, reflux, 24 h.

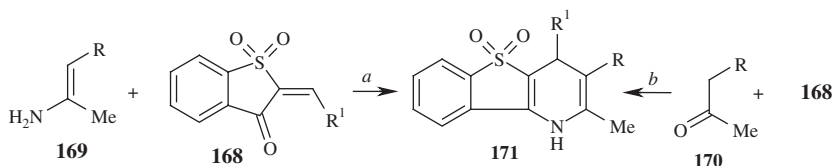
An ingenious method for the construction of the pyridine ring based on the “*tert*-amino effect” was used (1990RTC481) in the synthesis of a series of [3,2-*b*]annulated thienoazines. Prolonged refluxing of diene aminodinitriles **166** in butanol affords thieno[3,2-*b*]indolizines and thieno[2,3-*e*]quinolizines of general formula **167**.



R, R' = H, Me, Ph, or R + R' = C₄H₄; n = 1, 2.

a) BuOH, N₂, reflux, 35–120 h.

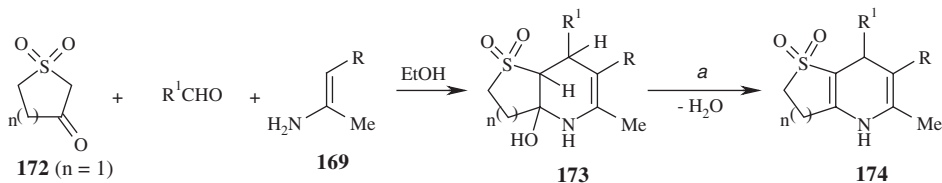
In addition to procedures for pyridine ring closure based on the use of 3-aminothiophene derivatives, there are alternative ring methods for the construction of thieno [3,2-*b*]pyridines. One approach made use of cyclic β-keto sulfones, which proved to be convenient synthons for the modified Hantzsch synthesis of fused pyridines (1986KGS1563, 1990JHC1453, 2000MI1, 2002USP6191140). For example, the reactions of benzothiophene 1,1-dioxide **168** with enamines **169** or methylene-active compounds **170** in the presence of NH₄OAc produced fused dihydropyridines **171** (1990JHC1453).



R = COOMe, COOEt, Ac, CN, C(O)SEt, C(S)OEt, C(S)SEt; R' = Ar, PhCH=CH.

a) AcOH, reflux, 0.5 h; b) NH₄OAc, AcOH, reflux, 10 min.

Three-component cyclocondensation of keto sulfone **172** (*n* = 1), enamino ester **169** (R = CO₂Me), and 2-nitrobenzaldehyde unexpectedly afforded hexahydrothieno [3,2-*b*]pyridine **173** (*n* = 1) instead of the 1,4-dihydropyridine derivative. Heating the latter led to its dehydration to thienopyridine **174** (*n* = 1), which serves as a calcium channel blocker with a broad spectrum of biological activities (2000MI1).

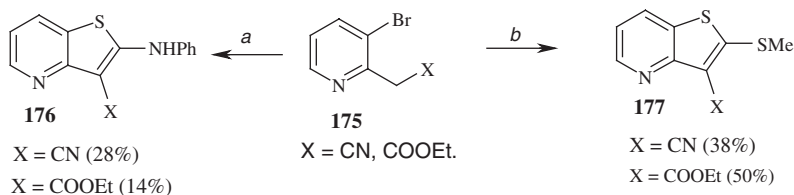


R = COOMe, R' = 2-NO₂C₆H₄; n = 1.

a) PhCH₃, reflux, 24 h.

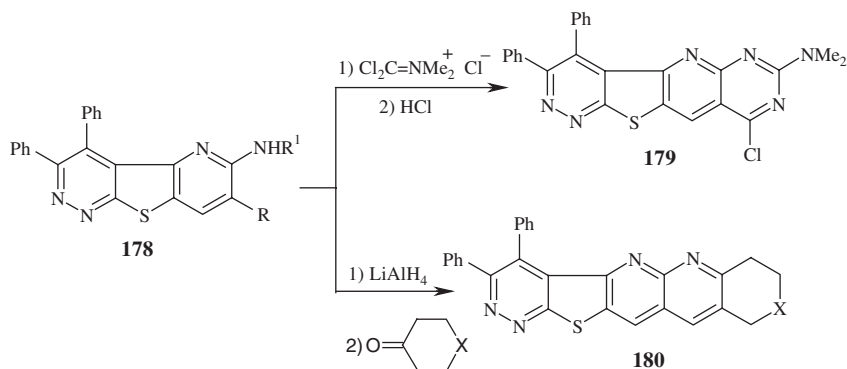
The method based on the reaction of 3-bromo-2-cyanomethylpyridine (**175**, X = CN) or ester **175** (X = COOEt) with heterocumulenes, such as phenyl isothiocyanate or CS₂ (1992SS28, 1997S949, 1998S1095) is of interest. The reaction

proceeds through the formation of the dianions of ketene S,N-acetal or ketene S,S-acetal, respectively, and involves the intramolecular replacement of the bromine atom to produce fused structures **176** and **177**. Low yields of the final products are attributed to the low lability of the halogen atom at position 3 of the pyridine ring.



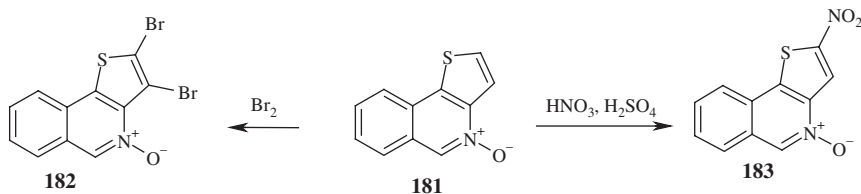
a) 1) PhNCS, N₂, NaH, DMSO, 110 °C; 2) Mel;
b) 1) CS₂, N₂, NaH, DMSO, 90 °C; 2) Mel.

The reactivity of thieno[3,2-*b*]-pyridine derivatives is less well studied compared to the transformations of regioisomeric thienopyridines. As mentioned above, thieno[3,2-*b*]pyridines have a wide variety of useful properties, the nature and arrangement of the substituents playing an important role. Hence, the introduction of new groups or transformations of the available groups are of considerable practical interest and, as a rule, focuses the attention of researchers on chemical transformations of thieno[3,2-*b*]pyridines. In particular, transformations of the carboxy or ethoxycarbonyl groups of some thieno[3,2-*b*]pyridines were investigated with the aim of preparing biologically active compounds, and the results of these studies were patented (1992EUP505058, 1994EUP560348, 1994USP5219867, 1995GEP4227747, 1996USP5352685, 2003EUP1256581). The use of nucleophilic substitution reactions (1987USP4593099, 1995JAP0753557, 1998PCT9847903, 2001USP6166203) and halogenations (2001USP6166203) was patented. Transformations giving annulated products are of more interest. For example, reactions yielding polyfused thienopyridine-containing compounds were documented (1997H1733). For example, tetra and pentacyclic **179** and **180** were prepared by different approaches starting from **178**.

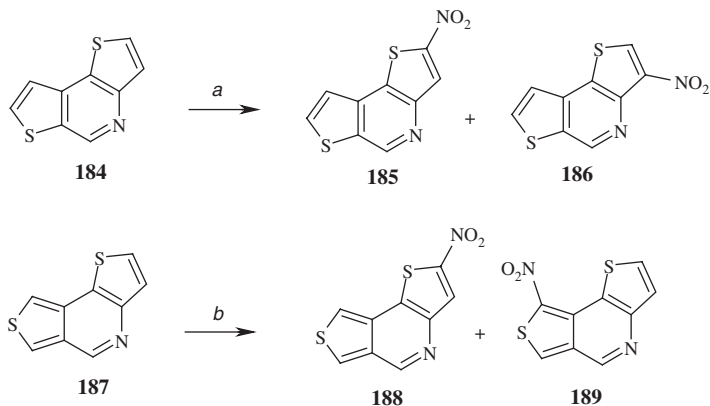


R = CN; R¹ = H; X = CH₂, NBz, O, S.

Bromination and nitration of some annulated thieno[3,2-*b*]pyridines were investigated. The reaction of thieno[3,2-*c*]isoquinoline *N*-oxide (**181**) with bromine yields 2,3-disubstituted product **182**, whereas treatment of **181** with HNO₃ affords 2-nitro derivative **183** (1989CS305, 1989CS309).



Nitration of dithieno[3,2-*b*:3',2'-*d*]pyridine (**184**) occurs at both positions of the [3,2-*b*]-annulated thiophene ring to form a mixture of isomers **185** and **186** in a ratio of 40:60 (1993JHC561). For dithieno[3,2-*b*:3',4'-*d*]pyridine (**187**), the replacement occurs predominantly at the 3,4-annulated ring. The 2-nitro- and 8-nitro isomers **188** and **189**, respectively, were obtained in a ratio of 33:67.



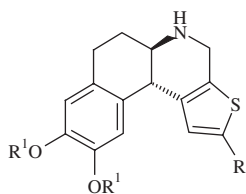
a) TFA, HNO₃, (NH₂)₂C(O), 73 °C, 4 h; b) TFA, HNO₃, (NH₂)₂C(O), 25 °C, 7 h.

C. THIENO[2,3-*c*]PYRIDINES

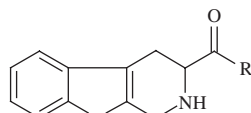
More than two hundred studies devoted to the synthesis and transformations of thieno[2,3-*c*]pyridines have been published during the period under consideration. In several reviews (1977AHC65, 1987KFZ536, 1991MI2, 1997KZA83, 1999JHC333, 1999KGS437, 2000RCR218), considerable attention was given to their chemistry. This interest is equally associated with prospects for their use as synthons for the preparation of polycyclic structures and for their biological activities. The spectrum of practical applications is wide. Thus, compounds possessing cardioprotective, anti-proliferation, cerebro and neuroprotective, vasodilatory, fungicidal, antiallergic,

anticonvulsive, antitumor, antiviral, hypnotic, anxiolytic, antiinflammatory, analgetic, antiulcerous, psychotropic, and neurotropic actions were found. In addition, some representatives of thieno[2,3-*c*]pyridine derivatives serve as kappa-receptor agonists, inhibitors of topoisomerase II catalytic activity, modulators of neurotransmitter functions with antidepressant activity, 5-lipoxygenase inhibitors, tachykinin antagonists, drugs enhancing erythropoiesis, cGMP-specific phosphodiesterase 5 inhibitors, antagonists of cell adhesion molecule expression, regulators of β -amyloid peptide activity, allosteric modulators of adenosine receptors, dilators of nephrovascular tract, platelet activation factor antagonists, inhibitors of interleukin 2 production, and appetite suppressants.

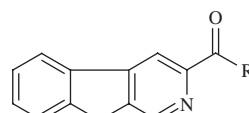
A series of related polyfused [2,3-*c*]annulated thienoazines exhibiting specific biological activities were documented. For example, tetracyclic **190** belong to a new class of selective dopamine agonists (1995JMC3445, 1995PCT9422858, 1997JMC1585, 1997USP5659037, 1998USP5597832, 1999BMC(L)1341, 1999SC1835). Pyrimidine derivatives **191** having affinity for serotonin receptors were proposed for the treatment of central nervous system diseases (1988GEP19636769, 2001GEP19900673, 2002GEP10031389). A group of benzothienopyridine derivatives **192** and **193** exhibit psychotropic (anxiolytic) activity (1992JAP04154785, 1992USP5126448, 1993JAP04264087, 1994JAP05163278, 1994PCT9321189, 1995JAP07109281, 1995PCT9413679, 1998USP5621103) and have strong ability to bind the 5-HT_{1A} receptor (1993JMC3526). Numerous studies (predominantly, patents) were devoted to the synthesis and transformations of pyridothienodiazepines **194** and, particularly, their triazolo[4,3-*a*]-fused derivatives **195**. These compounds are strong antagonists of platelet aggregation factor (1991CPB3215, 1991GEP4010315, 1991GEP4010316, 1991GEP4010361, 1991GEP4015137, 1992CPB521, 1992CPB762, 1992FRP2661911, 1995EUP624588, 1995FNP93120), ligands of somatostatin receptors (2000FRP2779652, 2000PCT0061587, 2001FRP2791980), and benzodiazepine receptor antagonists (1992FRP2661911, 1992FRP2660311) and also possess antiallergic, antiischemic, antiasthmatic, and some other activities (1991BRP2229723, 1991BRP2229724, 1992BRP2242427, 1993AUP394562B, 1993BRP2243829, 1993GEP4015136, 1993SWP681010, 1994NOP173140, 1995NOP173504, 1995USP5304553, 1995USP5221671, 1996FNP95035, 1996USP5382579, 1997USP5409909, 1997USP5468740, 1997USP5438045, 1997USP5482937, 1999PCT9858930, 2003USP6433167). Earlier data on the biological activities of thieno[2,3-*c*]pyridines and related structures were summarized in review (1987KFZ536).

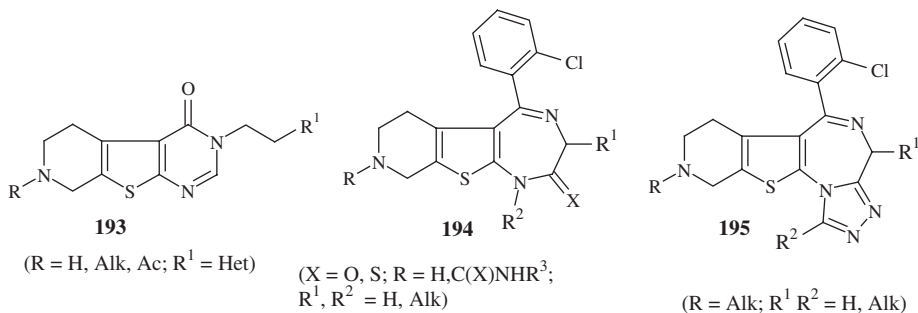


(R = H, Alk, Ph; R¹ = H, Me, Ac)



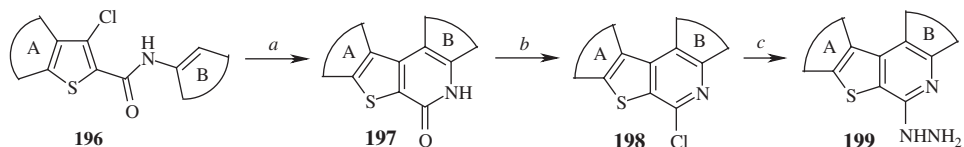
(X = S, SO, SO₂; R = NHR¹, OAlk, NHNH₂)





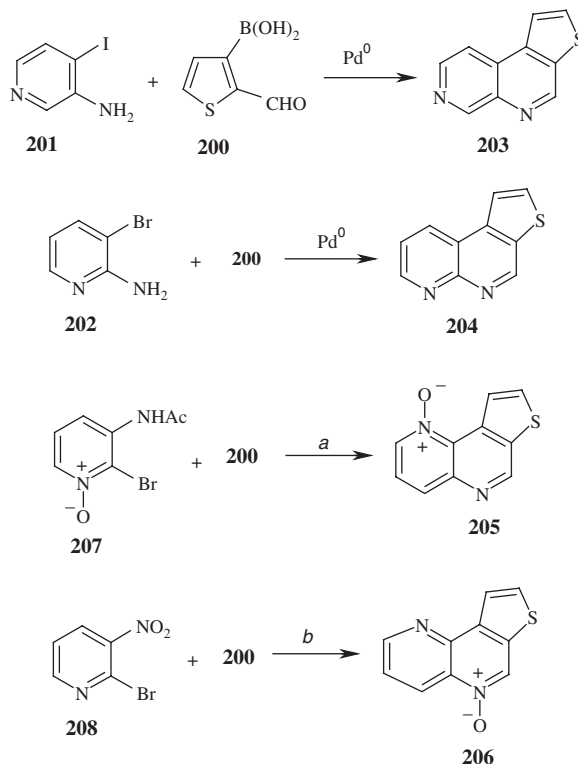
The majority of methods for the synthesis of thieno[2,3-*c*]pyridines and related fused structures can be tentatively divided into two groups based on the construction of the pyridine or thiophene rings, respectively.

Oxidative photochemical cyclization of *N*-aryl(hetaryl)-substituted 3-chlorothiophene-2-carboxamides **196** is one of the best approaches involving pyridine ring construction. Although this method was known since the late 1970s (1979H489) and was successfully used by other researchers (1995H1659, 1995H2691, 1995M1253, 1996HCO213), Castle and coworkers have made the most prominent contributions to this field of thienozines. They succeeded in preparing new parent heterocyclic systems along with a large number of derivatives (1987JHC231, 1988JHC1363, 1990JHC1031, 1990JHC2047, 1991JHC203, 1991JHC737, 1991JHC1825, 1991JHC1997, 1992JHC963, 1992JHC1613, 1993JHC153, 1993JHC453, 1993JHC487, 1993JHC653, 1993JHC1167, 1994JHC553, 1995JHC317, 1995JHC659, 1995JHC1735, 1996JHC179, 1996JHC185, 1996JHC727, 1996JHC923, 1997JHC1597, 1997JHC1829, 1998JHC1441, 2000JHC171, 2000JHC997, 2001JHC137) and performed experiments on the complete assignment of their ¹H and ¹³C NMR spectra (1992JHC1805, 1992JHC1869, 2000JHC821). Photocyclization products of amides **196**, viz., lactams **197**, were successively transformed into chlorides **198** and hydrazines **199** according to common procedures.



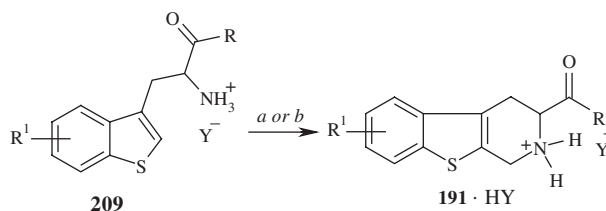
a) *hν* (UV), O₂, PhH or PhH-C₆H₁₂, or C₆H₁₂, Et₃N, 4-12 h; *b*) POC1₃, 100-120 °C, 4-24 h;
c) N₂H₄, EtOH-PhH (1 : 1), reflux.

Isomeric thienonaphthyridines were synthesized using the Suzuki reaction. For example, 2-formyl-3-thiopheneboronic acid (**200**) with aminopyridines **201** and **202** produced thieno[2,3-*c*][1,7]naphthyridine (**203**) and thieno[2,3-*c*][1,8]naphthyridine (**204**) (1994JHC11). This method was also used to synthesize (1993H245) isomeric *N*-oxides **205** and **206** from pyridine *N*-oxides **207** and **208**, respectively.



a) $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , $(\text{MeOCH}_2)_2$, reflux, 2 h; b) 1) $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 ; 2) $\text{FeSO}_4 \cdot \text{NH}_4\text{OH}$.

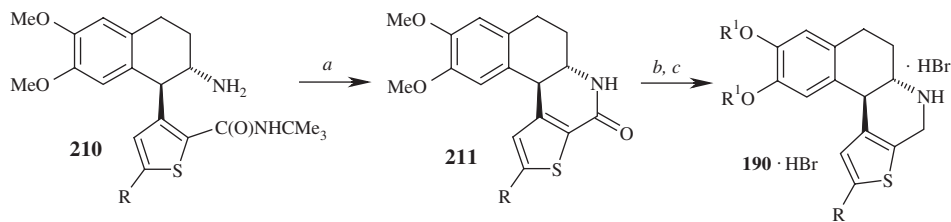
Thieno[2,3-*c*]pyridine derivatives are often prepared according to methods based on the Pictet–Spengler reaction. For example, thiotryptophane esters and amides **209** undergo cyclocondensation with formaldehyde to give biologically active benzothienopyridines **191** (as tosylates or hydrochlorides) (1989JAP63-96188, 1991JAP1100172, 1992JAP04154785, 1992USP5126448, 1993JAP04264087, 1993JMC3526, 1994JAP05163278, 1994PCT9321189, 1995JAP07109281, 1998USP5621103).



Y = Cl, TsO; R = OH, OMe, OEt, NHR^3 .

a) HCHO, EtOH— H_2O , reflux; b) 35% HCHO, HCl, MeOH— H_2O , 70–90 °C.

Multistep syntheses of dopamine agonists **190** were documented (1995JMC3445, 1995PCT9422858, 1997JMC1585, 1997USP5659037, 1998USP5597832, 1999BMC(L)1341, 1999SC1835). The pyridine ring can be constructed by either the Pictet–Spengler reaction (1997USP5659037) or by alternative methods. For example, intramolecular cyclization of compound **210** occurs in the presence of an acid catalyst to give lactams **211** in 60% yield; subsequent reduction and demethylation afford tetracyclic structure **190** ($R = H$, $R' = Bu'$) as hydrobromide (1997JMC1585). The potent medicine A-86929 was synthesized analogously (**190**, $R = Pr$, $R' = H$) (1995JMC3445).

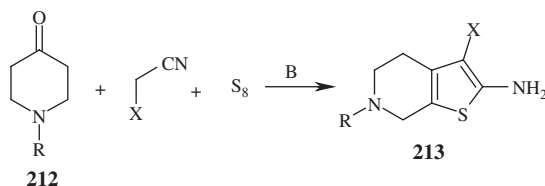


$R = Pr$; $R' = H$; $R = H$; $R' = Bu'$.

a) $TsOH \cdot H_2O$, $PhCH_3$, reflux, 48 h; b) $BH_3 \cdot THF$, reflux, 14 h; c) BBr_3 , CH_2Cl_2 , $-78^\circ C \rightarrow$ heating.

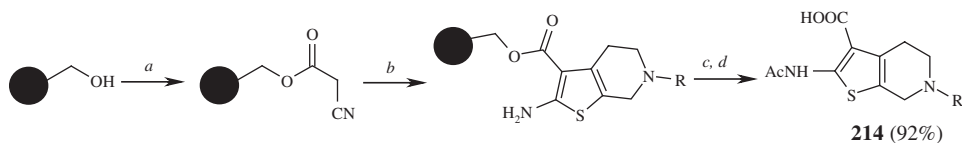
Noteworthy are also the patent data on the combinatorial solid-state synthesis of libraries of imidazo[3',4':1,2]pyrido[3,4-*b*]benzothiophenes (1998PCT9834112, 1999USP5856107).

A smaller number of methods for the construction of thieno[2,3-*c*]pyridines is based on the formation of the thiophene fragment. Undoubtedly, the well-studied multi-component Gewald reaction of *N*-substituted piperidin-4-ones **212** ($X = NR$), elemental sulfur, and methylene-active nitriles in the presence of secondary amines is the most popular. This approach was employed in more than 30 patents (see 1991CPB3215, 1992CPB762, 1993JCT(B)15, 1994MI1, 1997MI2, 1999CPB993). Data are also available in the last review (1999JHC333) devoted to this reaction. The conditions of the synthesis of thieno[2,3-*c*]pyridines by the Gewald reaction can be varied over a wide range. Ethanol, DMF, or MeOH are most often used as the solvent; Et_2NH , morpholine, or Et_3N are generally used as the catalyst; the reaction is usually performed with moderate heating (40 – $60^\circ C$) or, rarely, at 70 – $80^\circ C$. The yields of the target tetrahydrothienopyridines **213** are, as a rule, 60 – 85% . The products thus prepared serve as convenient precursors for the synthesis of various polyfused systems.



$B = Et_2NH$, morpholine; $X = CO_2Et$, CN , $C(O)Ar$, $CONH_2$; $R = Me$, Et , Pr^1 , Bn , $COOAlk$, Ac , $C(O)Ar$.

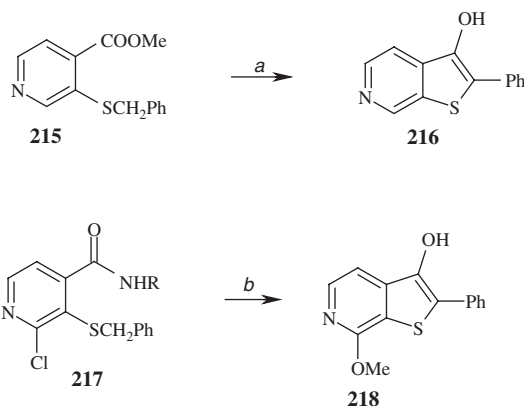
The solid-state synthesis of thienopyridines by the Gewald reaction was documented. For example, **214** was prepared in 92% yield by cyanoacetylation of a polymer support and the reaction of the resulting ester on the polymer support with sulfur and piperidin-4-one **212** followed by acylation and elimination of the polymer matrix (2001TL7181).



● - Argogel Wang Resin; R = (CH₂)₅COOH.

a) NCCH₂CO₂H, PrⁱN=C=NPrⁱ, DMAP, CH₂Cl₂; b) **212** (X = NR), S₈, morpholine, EtOH, t^o;
c) AcCl, CH₂Cl₂, EtNPrⁱ₂; d) TFA, H₂O, CH₂Cl₂.

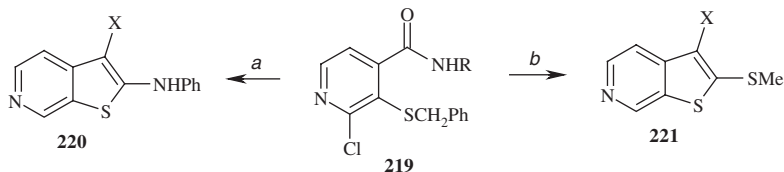
Cyclocondensation of 3-(alkylthio)isonicotinic acid derivatives catalyzed by strong bases also provides a convenient method for thiophene ring closure. For example, treatment of isonicotinate **215** with sodium hydride produced thienopyridine **216** (1991USP4904672). Cyclization of isonicotinamide **217** in the presence of an excess of MeONa is accompanied by the nucleophilic substitution of the chlorine atom to give finally 3-hydroxy-7-methoxy-2-phenylthieno[2,3-*c*]pyridine (**218**) (1993TL2875).



R = 4-MeOC₆H₄.

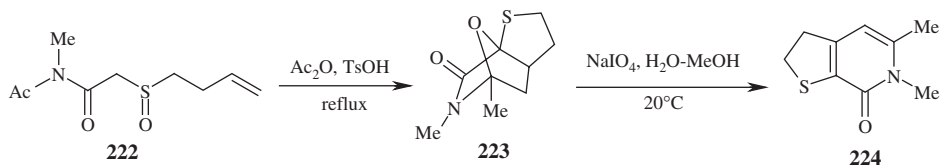
a) NaH, DMF-THF, 60 °C, 3 h; b) 5 equiv. of MeONa, DMF, 100 °C.

The above general approach to the synthesis of various thienopyridines (1992S528, 1997S949, 1998S1095), including [2,3-*c*]-annulated derivatives, deserves more attention. The method is based on the reaction of halopyridines **219** with CS₂ or PhNCS. Unfortunately, the yields of the target products **220** and **221** are low due, evidently, to low mobility of the bromine atom at position 3 of the pyridine ring.

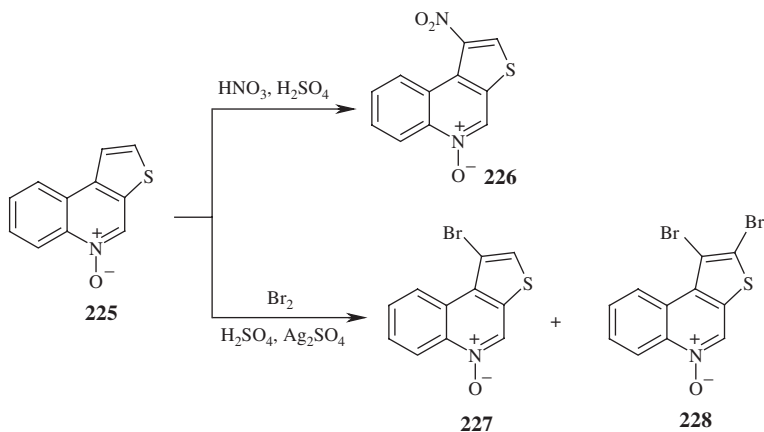


a) 1) PhNCS, N₂, NaH, DMSO, 100 °C; 2) MeI, -20 °C; b) 1) CS₂, N₂, NaH, DMSO, 90 °C; 2) MeI, -20 °C.

Methods for the construction of the thieno[2,3-*c*]pyridine skeleton based on the formally simultaneous formation of both the pyridine and thiophene rings were documented. Under the Pummerer rearrangement conditions, β-sulfinylamide **222** underwent a cascade transformation into **223**, which was oxidized to fused lactam **224** in low yield (1999JOC2038). Data on the use of cascade transformations, including the Pummerer rearrangement – cycloaddition sequence, in the synthesis of complex heterocyclic systems were summarized in a review (1997S1353).



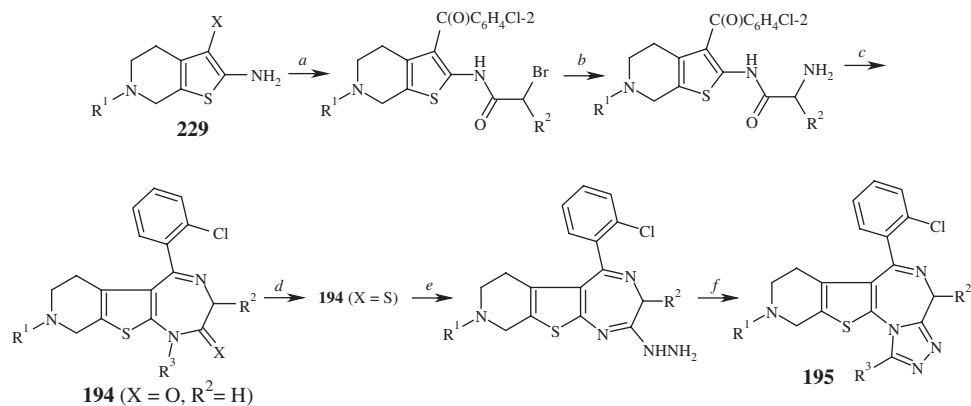
In recent years, the reactivities of thieno[2,3-*c*]pyridine and its fused analogs have received considerable attention. Nitration of thieno[2,3-*c*]quinoline 5-*N*-oxide (**225**) gives rise to 1-nitro derivative **226** (1989CS305), whereas bromination affords a mixture of bromide **227** and dibromide **228** (1989CS309).



Annulation reactions, in which thieno[2,3-*c*]pyridines and, in particular, tetrahydrothienopyridines of general formula **229**, serve as building blocks, are of considerable interest. This choice is associated primarily with the ease of preparation of these compounds by the Gewald reaction, as well as with the presence of two vicinal functional groups, favorable for the formation of additional rings.

In addition, many annulation products of thienopyridines possess interesting biological activities. The studies (1991CPB3215, 1991BRP2229723, 1991BRP2229724, 1991GEP4010315, 1991GEP4010316, 1991GEP4010361, 1991GEP4015137,

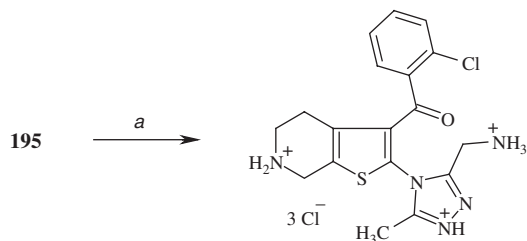
1992BRP2242427, 1992CPB521, 1992CPB762, 1992FRP2661911, 1993AUP394562B, 1993BRP2243829, 1993GEP4015136, 1993SWP681010, 1994NOP173140, 1995NOP173504, 1995FNP93120, 1995USP5221671, 1996FNP95035, 1996USP5382579, 1997USP5409909, 1997USP5468740, 1997USP5438045, 1997USP5482937, 1999PCT9858930, 2000FRP2779652, 2000PCT0061587, 2001FRP2791980, 2003USP6433167) were devoted to the synthesis of tetracyclic antagonists of platelet aggregation factor **195**. One of the most typical approaches is presented in the Scheme



X = 2-ClC₆H₄C(O); R¹ = COOEt, Ac, etc.; R² = H, Me; R³ = Alk.

a) BrCH(R)C(O)Br, HCCl₃; b) NH₃; c) pyridine, N₂, reflux; d) Lawesson's reagent (LR) or P₂S₅; e) N₂H₄; f) R⁴C(OEt)₃.

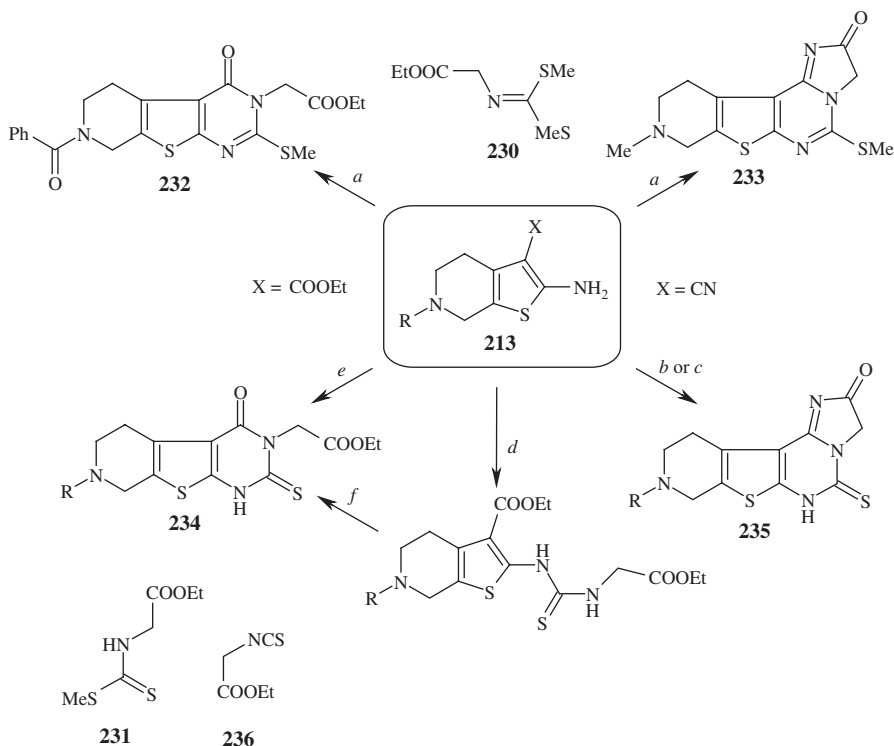
Hydrolysis of the ester group (R¹ = CO₂Et) in one of the steps affords compounds **194** and **195** (R¹ = H), which give a wide range of biologically active compounds upon treatment with various electrophilic reagents. Interestingly, compounds **195** can be subjected to partial destruction in a strongly acidic medium to give a product of the diazepine ring opening in quantitative yield (2000JHC127).



195: R¹, R² = H, R³ = Me.

a) HCl, H₂O, 20 °C, 16 h.

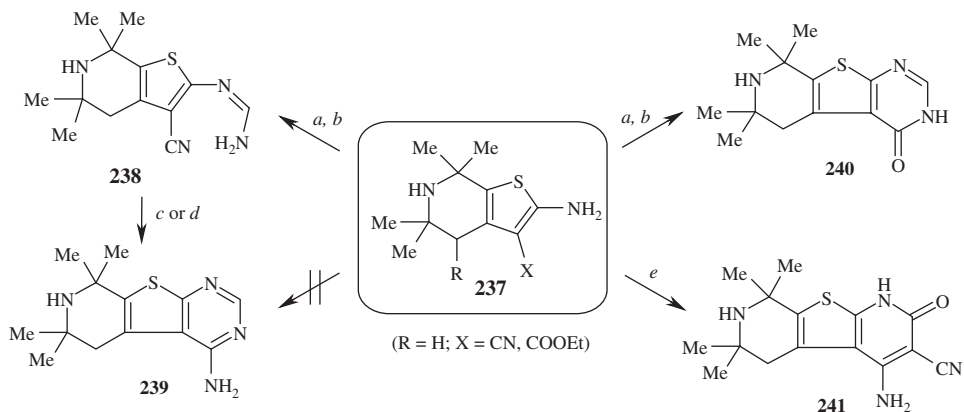
Ethyl 7*N*-[bis(methylthio)methylene]glycinate (**228**) and ethyl 2-*N*-(methylthiothiocarbonyl)glycinate (**229**) are convenient reagents for heteroannulation reactions. Heating these compounds with thienopyridines **211** affords tri and tetracyclic structures **232**, **233** and **235** (1995H851, 1996SPH647, 2001H1747). Compounds **232** and **233** were also prepared by an independent synthesis starting from ethyl isothiocyanoacetate **234** (1996MI2, 1997MI2).



R = Me, Bn, Bz.

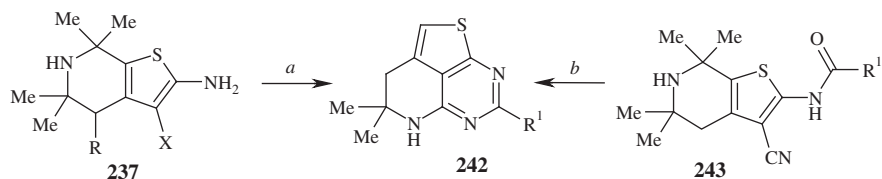
a) **230**, AcOH, reflux, 2–5 h; b) **231**, DMF, reflux, 8–10 h;
c) R = Me; **236**; d) **236**, pyridine, reflux; e) **231**, DMF, reflux, 8–10 h; f) EtONa.

Annulation of thienopyridines **237** with various electrophilic reagents gives rise to compounds **238–241** (1998HAC529, 2001H171).



a) HC(OEt)_3 , reflux, 6–7 h; b) NH_3 , $-20\text{ }^\circ\text{C}$;
c) EtONa, EtOH, reflux, 4 h; d) HC(O)NH_2 , t° ; e) XCH_2CN , EtONa

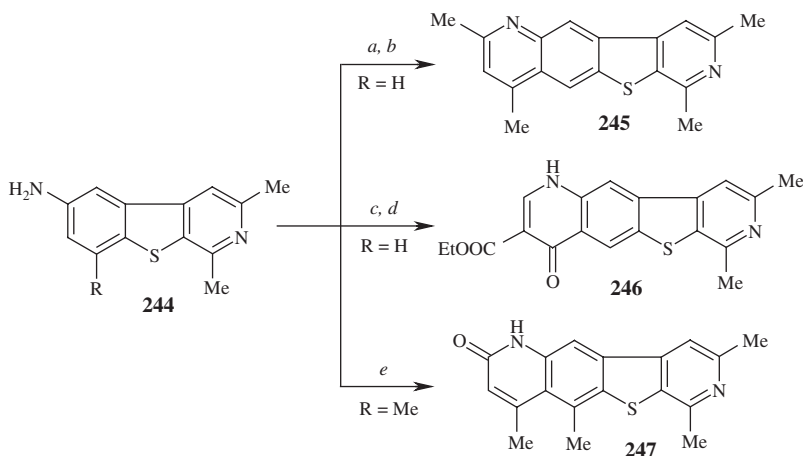
It should be noted that compound **239** cannot be prepared directly from thienopyridine **237** ($R = H$, $X = CN$). An attempt to perform this transformation by heating the latter in formamide unexpectedly led to the formation of *ortho-peri-fused* thienopyridopyrimidine **242** ($R' = H$) in 76% yield. Based on the results of an investigation of the mechanism of this unusual cascade reaction, a general procedure was developed for the synthesis of such thienopyridopyrimidines from amides **243** (2001H171).

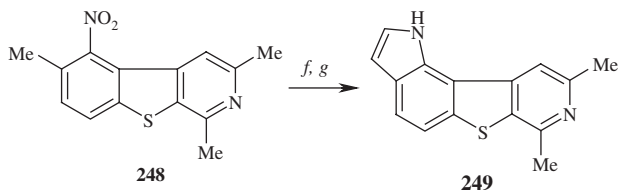


$R = H$; $R' = H, Me, Ph$; $X = CN$; NMA is N-methylacetamide.

a) $HC(O)NH_2$, 180 °C, 1 h; b) NH_4OAc , NMA, 140 or 185 °C, 1-4 h.

Selected properties of benzo[*b*]thieno[2,3-*c*]pyridines, associated predominantly with transformations of the benzene ring, were documented (1993KGS706, 1994KGS701, 1995KGS1124, 1997KGS406, 1997KGS1199). Among the results, interesting annulation reactions yielding tetranuclear fused heterocycles deserve notice (1997KGS1199). For example, dipyrindobenzothiophenes **245–247** were prepared from amine **244** according to methods based on pyridine ring construction in the Combes synthesis, the Gould–Jacobs reaction, and the Knorr synthesis, respectively. Pyridothienoindole derivative **249** was synthesized in good yield from **248** in two steps.

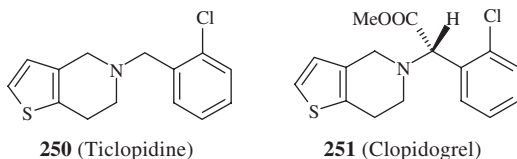




a) H_2CAC_2 , reflux, 1.5 h; b) H_2SO_4 , reflux, 0.5 h; c) $(\text{EtO})\text{CH}=\text{C}(\text{COOMe})_2$, toluene, reflux, 4 h; d) Ph_2O , t° , 2 h; e) $\text{AcCH}_2\text{COOEt}$, H_2SO_4 , reflux; f) $\text{Me}_2\text{NCH}(\text{OMe})_2$, DMF, reflux, 5 h; g) H_2 , Pd/C, MeOH.

D. THIENO[3,2-*c*]PYRIDINES

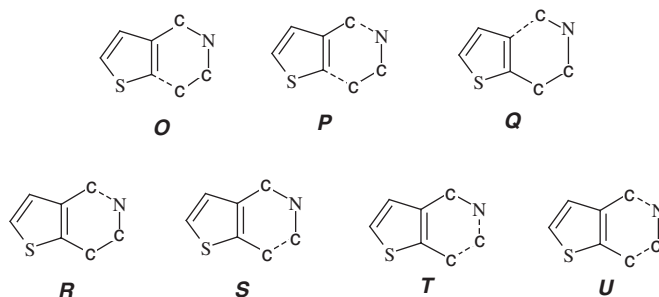
Methods for the preparation of [3,2-*c*]-annulated thienopyridine derivatives and the properties of these compounds are well known and were described in reviews (1977AHC65, 1987KFZ536, 1997THC37, 2000RCR218). The chemistry of this class of compounds has attracted interest because primarily of the high biological activities of many thieno[3,2-*c*]pyridine derivatives. Well-known drugs such as Ticlopidine **250** and Clopidogrel **251** possess antithrombotic activity.



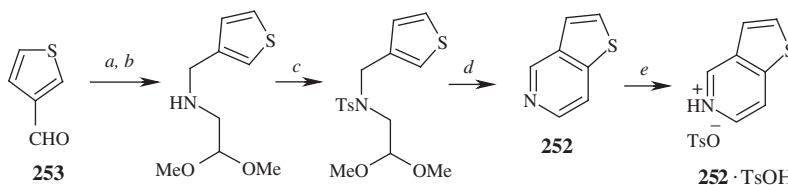
The antitumor activity of **250** and its salts was documented (1989USP4730049, 2001USP6043368). Methods for the synthesis of optically pure Clopidogrel **251**, its racemate, and the starting reagents were patented (1992EUP465358, 1992EUP466569, 1999PCT9851681, 1999PCT9851682, 1999PCT9851689, 1999PCT9918110, 2000PCT0027840). The synthesis of ^{13}C -labelled Clopidogrel was described (2000CRP891), and its metabolic oxidation with hepatic cytochrome P450 monooxygenase was studied (1992MI4). In addition to above **250** and **251**, some thieno[3,2-*c*]pyridine derivatives serve as structurally different platelet aggregation inhibitors, possess antibacterial, antimicrobial, psychotropic, analgetic, antitumor, anti-inflammatory, vasodilator, or hypotensive activities, and serve as 5-HT₃-receptor antagonists, anticonvulsive agents, drugs for the treatment of epilepsy, and inhibitors of fibrinogen binding. Compounds possessing strong antiviral activity, such as HIV-1 protease inhibitors, selective dopamine agonists, farnesyl transferase inhibitors, metalloprotease (metalloproteinase) inhibitors, serotonin antagonists, elastase inhibitors, nephrovascular dilators, antidepressants, and drugs for the treatment of hyperglycemia, diabetes, and ischemic and autoimmune diseases were documented. Some thieno[3,2-*c*]pyridines were proposed as cardio and cerebroprotectors and drugs for the treatment of neurologic and other diseases. Earlier data on biological activities were summarized in a review.

As in the case of the above-described isomeric structures, thieno[3,2-*c*]pyridines can be constructed by two radically different pathways, viz., either by pyridine ring

construction starting from a substituted thiophene or by annulation of the thiophene ring to the pyridine ring. The first method is more often used. For convenience, the types of the ring closure can be arbitrarily classified into the following main types, *O–Q*, and the modes *R–U* represented by a few examples.

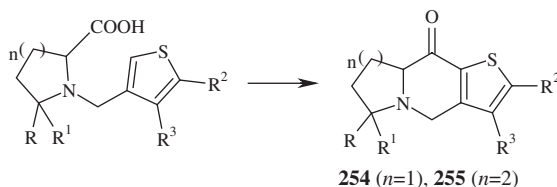


Strategy *O* assumes the C(7)–C(7a) ring formation in the key step of construction of a bicyclic system. The synthesis of the simplest thieno[3,2-*c*]pyridine **252** in low yield (<10%), described for the first time in 1953 (1953JA5122), provides an example. More recently, this procedure based on the Pomeranz–Fritsch reaction has been modified (1976JHC1347, 1993JHC289). The study (1993JHC289) demonstrated that thienopyridine **252** can be prepared in four steps from thiophene-3-carbaldehyde **253**; to facilitate the isolation and storage, the final product was transformed into the corresponding tosylate.



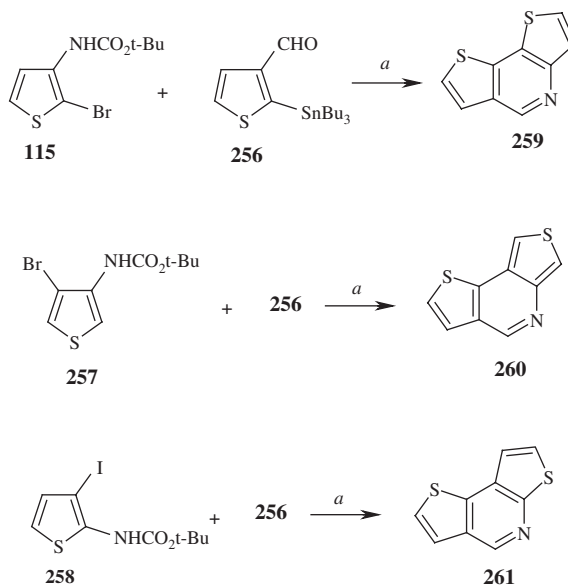
a) $\text{H}_2\text{NCH}_2\text{CH}(\text{OMe})_2$, $\sim 20^\circ\text{C}$, 16 h; *b*) H_2 , 5% Pd/C, EtOH, 12 h; *c*) TsCl, Et_3N , EtOAc, $\sim 20^\circ\text{C}$, 12 h; *d*) HCl, dioxane, reflux, 16 h; *e*) TsOH- H_2O , Me_2CO , $\sim 20^\circ\text{C}$, 2 h.

Methods were developed for the preparation of thienoindolizines **254** and thienoquinolizines **255** from derivatives of proline and pipercolinic acid (1993H2303, 1994JHC495, 1996JHC873, 1996PS169, 1999H445). Polyphosphoric acid (PPA) can be used as a cyclizing agent. The reaction can also be performed by the transformation of pipercolinic acids into acid chlorides followed by the intramolecular Friedel–Crafts reaction without isolation of the intermediate.



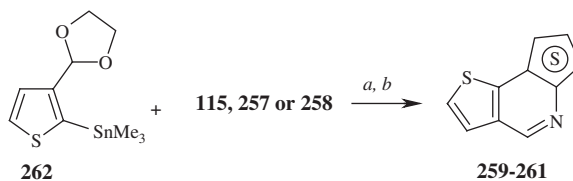
$\text{R}^1, \text{R}^2 = \text{H}$ or $\text{R}^1 + \text{R}^2 = \text{O}$, S; $\text{R}^3, \text{R}^4 = \text{H}$ or $\text{R}^3 + \text{R}^4 = \text{C}_4\text{H}_4$; $n = 1, 2$.

Pyridine ring construction according to strategy **P** is based on the one-step formation of the C(4)–N(5) and C(7)–C(7a) bonds. For example, this approach provides the basis for the synthesis of the simplest isomeric dithienopyridines (1988CS281). The Stille cross-coupling reaction of 2-tributylstannyl-3-thiophene-carbaldehyde (**256**) with thienylcarbamates **115**, **257**, and **258** affords the target compounds **259–261**, respectively, in different yields.



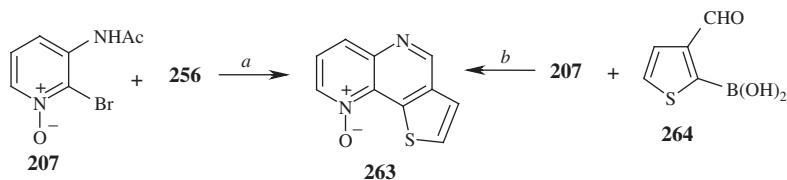
a) Pd(PPh)₃, DMF, 100 °C, 24 h.

In an alternative procedure for the preparation of dithienopyridines **259–261**, acetal **262** is used instead of aldehyde **256** and the reaction mixture is then treated with hydrochloric acid; however, this procedure affords the target products in lower yields (27–63%) (1989S130).



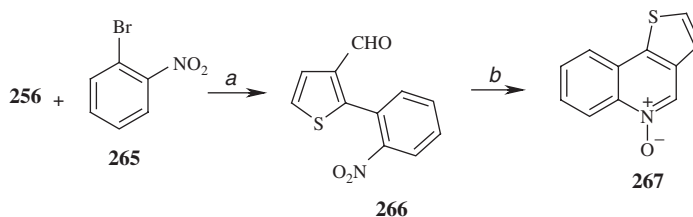
a) Pd(PPh)₃, DMF, 100–120 °C, 24 h; b) 2 N HCl, reflux, 1 h; **259** - 43%, **260** - 63%, **261** - 27%,

The tricyclic skeleton of thieno[3,2-*c*][1,5]naphthyridine 9-*N*-oxide (**263**) was constructed (1993H245) in two ways: by condensation of aldehyde **256** with pyridine *N*-oxide **207** or (in lower yield) by the modified Suzuki reaction of the latter with 3-formylthiophene-2-boronic acid (**264**).



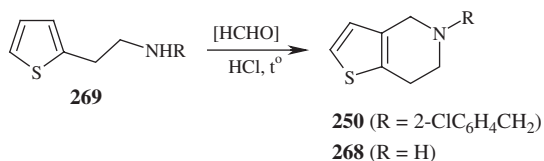
a) Pd(PPh)₃, CuO, DMF, 100 °C; *b)* Pd(PPh)₃, Na₂CO₃, (MeOCH₂)₂, reflux, 2 h,

The one-pot Stille cross-coupling reaction of compound **256** produced all four isomeric thieno[3,2-*c*]naphthyridines (1994JHC11). The stepwise formation of the C(7)–C(7a) and C(4)–N(5) bonds of the thieno[3,2-*c*]pyridine system can be considered as a modification of the above-described approaches. For example, aldehyde **256** reacts with arene **265** to give **266**; reduction of its nitro group is accompanied by cyclization to form thieno[3,2-*c*]isoquinoline *N*-oxide (**267**) (1990JHC1127).



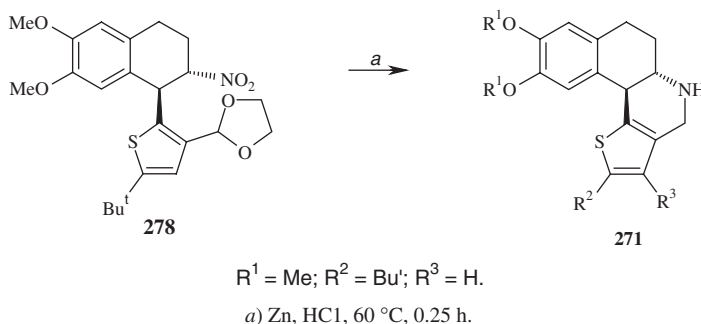
a) Pd⁰, DMF; *b)* FeSO₄, 2 *N* HCl, aqueous NH₃.

Method **Q** is based on C(3a)–C(4) bond formation in the direct pyridine ring closure and is most often used in the synthesis of the thieno[3,2-*c*]pyridine moiety. Of all the possible methods of this type, the Pictet–Spengler reaction has gained the most acceptance. This method provides a convenient and simple route to highly active drugs, including Ticlopidine **250** and Clopidogrel **251**. Ticlopidine or its precursor 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine **268**, can be synthesized by treating 2-(2-thienyl) ethylamine derivative **269** (or its acid chloride) in the presence of acid (generally, HCl) at high temperature with a HCHO solution (1997MI3) or its synthetic equivalents, such as 1,3-dithiane, 1,3-dioxane (1998EUP829482, 2001USP6043368), dimethoxymethane (1992EUP497695), or 1,3-dioxolane (1994CPB1676, 1995JAP426690, 1998EUP829482, 2001USP6043368), which can also serve as the solvent.

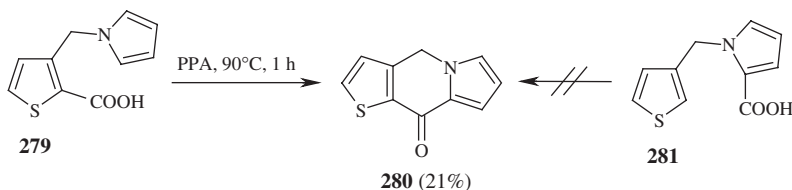


Approach **Q** was used to synthesize a series of selective dopamine agonists (1997JMC1585, 1998USP5597832). Amines **270** with paraformaldehyde in an alkaline medium and then in an acidic medium produced benzothieno[3,2-*c*]qumolines **271**, which were transformed into the target products **272** (as the corresponding salts) by deprotection under the action of boron halides. Compounds **272** possess the

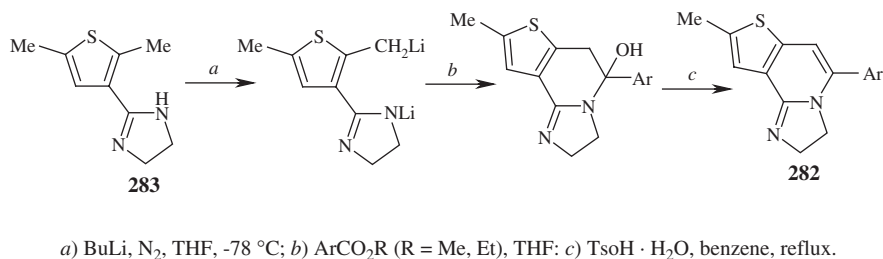
Method **R** involves C(4)–N(5) bond formation in the cyclization step. This approach was used to prepare **271** ($R^2 = \text{Bu}^t$, $R^3 = \text{H}$) starting from cyclic acetal **278** (1997JMC1585).



An alternative approach (1991JHC81) to the construction of the thieno[3,2-*c*]pyridine system is based on C(6)–C(7) bond formation (approach **S**). For example, heating carboxylic acid **279** in PPA resulted in its cyclization giving 9-oxo-4*H*, 9*H*-pyrrolo[1,2-*a*]thieno[2,3-*d*]pyridine (**280**) in low yield. An attempt to prepare this compound by an independent synthesis, viz., by cyclization of isomeric acid **281** under analogous conditions, failed.

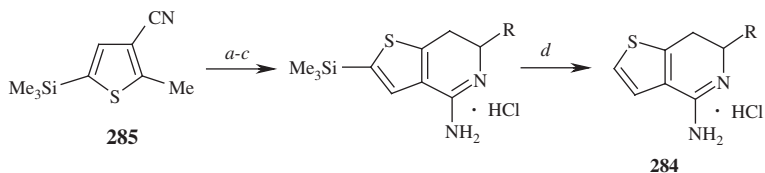


Approach **T** (the one-step formation of N(5)–C(6) and C(6)–C(7) bonds) was used only in the study (1996USP5141932) where imidazothienopyridines **282** possessing antitumor activity were synthesized from 2-(3-thienyl)imidazoline derivatives **283**.



Method **U** (pyridine ring construction through N(5)–C(4) and C(6)–C(7) bond formation) can be exemplified by the synthesis of 6,7-dihydrothieno[3,2-*c*]pyridines

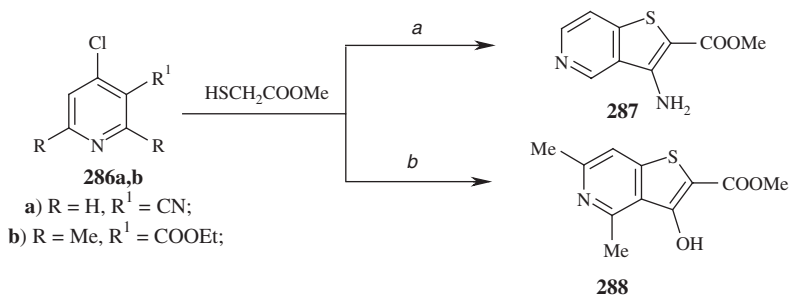
284. This method is based on the reaction of 2-methyl-5-trimethylsilylthiophene-3-carbonitrile (**285**) with aldimines generated *in situ* followed by desilylation of the intermediate.



R = Ph, Me₃SiC≡C, *cyclo*-Pr.

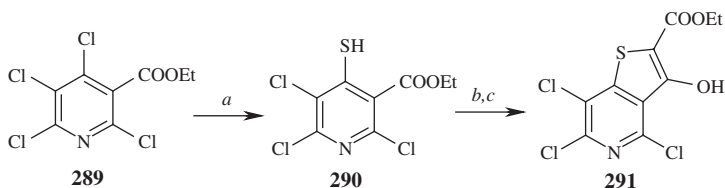
a) BuLi, PrⁱNH, DMPU, -78 °C; b) LiN(SiMe₃)₂, RCHO, -78 → 0 °C; c) 6 N HCl; d) Bu₄NF, THF.

Methods based on the pyridine to thieno[3,2-*c*]pyridine transformation are less well developed. Most of the above-described procedures are based on the nucleophilic displacement of the substituent at position 4 of the pyridine ring with a sulfur-containing fragment followed by cyclization of the resulting product. For example, the reaction of 4-chloropyridines **286** with methyl thioglycolate produced **287** and **288** in one step as a result of the replacement of the chlorine atom and Thorpe or Thorpe–Dieckmann cyclization (1987JHC85).



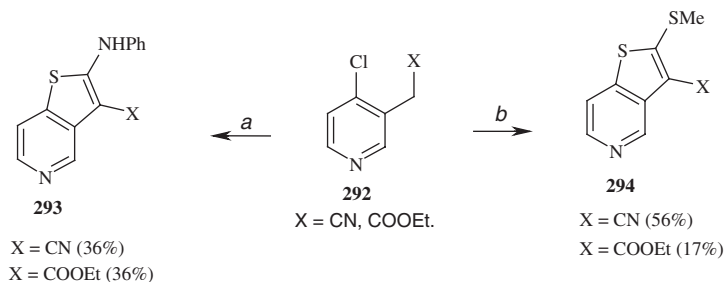
a) **286a**, MeONa, DMF, ~20 °C; b) **286b**, MeONa, DMF, t°, 20 min.

The reaction of tetrachloropyridine **289** with sodium hydrosulfide giving only 4-mercapto derivative **290**, which was transformed (1996KGS364) into compound **291** in 77% yield (with respect to mercaptopyridine **290**) by 5-alkylation and Dieckmann cyclization, is another example of the application of this approach.



a) NaSH, EtOH, ~20 °C, 0.5 h; b) BrCH₂COOEt, EtONa, EtOH, reflux, 3 h; c) NaH, THF, heating, 5 min.

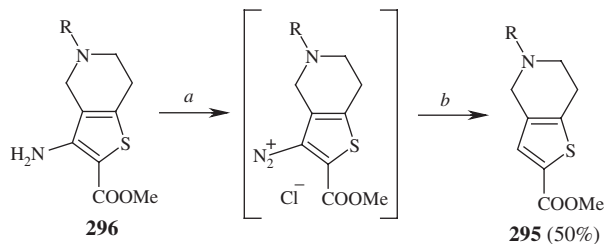
The thiophene ring can be constructed with the use of another sequence of reactions where nucleophilic displacement is the final step of cyclization (1992S528, 1997S949, 1998S1095). Pyridines **292** with heterocumulenes in the presence of a strong base produce thieno[3,2-*c*]pyridines **293** and **294** proceeding through the intermediate formation of disodium salts of ketene *S,N*-acetal or ketene *S,S*-acetal derivatives, respectively.



a) 1) PhNCS, N₂, NaH, DMSO, 70—80 °C; 2) MeI, ~20 °C;

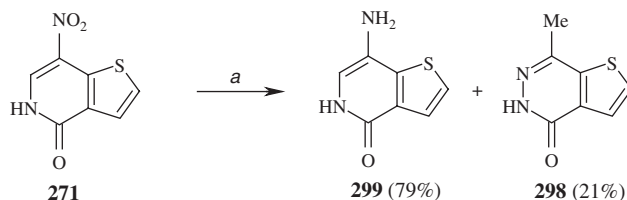
b) 1) CS₂, N₂, NaH, DMSO, 90 °C; 2) MeI, ~20 °C.

Numerous syntheses (1987JAP61-85391, 1987JAP61-271291, 1989USP4730049, 1992EUP465358, 1993FRP2664276, 1993USP5068360, 1994USP5334596, 1995JAP06298766, 1999PCT9918110, 1999PCT9927929) were based on *N*-alkylation of tetrahydrothieno[3,2-*c*]pyridine **268** and related compounds (see 1994EUP573955, 1994EUP573975, 1996CPB778). Many biologically active compounds, including Ticlopidine **250**, were synthesized. A number of precursors of this drug were prepared by deamination of 3-aminothieno[3,2-*c*]pyridine derivatives (1994EUP573954, 1994EUP573955, 1995JAP06271582, 1996USP5364941, 2000JAP273097). The synthesis of compound **295** from thienopyridine **296** (R = 2-ClC₆H₄CH₂) provides an example (1994EUP573975).



a) NaNO₂, H₂SO₄-H₂O, 0-5 °C, 0.5 h; *b*) PPA, ~20 °C, 1 h.

Other transformations of thieno[3,2-*c*]pyridines include reduction of both functional groups and endocyclic multiple bonds (1996CPB778, 1998SC949, 1999H445). An attempt to reduce thienopyridone **297** with hydrazine hydrate led to the formation of thienopyridazine derivative **298** along with the expected product **299** (1995ZOR304).



a) $N_2H_4 \cdot H_2O$, 135-140 °C, 3 h.

III. Conclusions

The development of new chemo-, regio-, stereo-, and enantioselective procedures for the synthesis of polyfunctional carbo- and heterocycles with practically useful properties is a fundamental problem of synthetic organic chemistry. Pyridine derivatives and its fused analogs are of special interest. Analysis of the data on the synthesis, chemical properties, and biological activities of the isomeric thienopyridines published over the last decade convincingly demonstrate that the chemistry of this heteroaromatic systems has attracted considerable interest. The design of new groups of biologically active compounds and a high pharmacological potential of thienopyridine derivatives gradually stimulate the elaboration of new ingenious methods, nonconventional approaches, and regio- and stereoselective procedures, which extend the synthetic scope of the chemistry of nitrogen heterocycles. The unexhausted potential of thienopyridine derivatives as synthons also attracts attention of organic chemists, because such compounds allow one to perform transformations, which have been previously inaccessible. In our opinion, methods for the synthesis, the chemical behavior, and biological activities of thienopyridines summarized in the present review provide an insight into the prospects of the comprehensive development of individual lines of investigation, as well as of this area of heterocyclic chemistry as a whole, and also focus attention to the most promising research in this field. Analysis of the generalized information gives promise that studies devoted to the elaboration of new synthetic methods and investigation of the properties of isomeric thienopyridines will be successfully continued.

This review was financially supported by the Russian Foundation for Basic Research (Project no. 05-03-32031).

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Organometallic Chemistry of Polypyridine Ligands I

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Abbreviations

AN	acetonitrile
bpy	2,2'-bipyridine
Bu	butyl
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
dbm	di- <i>n</i> -butyl maleate
DME	dimethoxyethane
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppm	1,2-bis(diphenylphosphino)methane
Et	ethyl
LF	ligand field
Me	methyl
MLCT	metal to ligand charge transfer
naph	1,8-naphthyridine
nbd	norbornadiene
OTf	triflate
Ph	phenyl
phen	1,10-phenanthroline
py	pyridine

solv	solvent
THF	tetrahydrofuran
THT	tetrahydrothiophene
Tol	tolyl
trpy	2,2':6,2''-terpyridine

I. Introduction

In 1998, we published our introductory chapter: "Five- and Six-Membered Heteroaromatic Compounds as σ - and π -Ligands" (98AHC1) in *Advances in Heterocyclic Chemistry*, where principles of coordination of heterocycles in their organometallic and coordination compounds were outlined. In the intervening period we have comprehensively reviewed the organometallic compounds of heterocycles in 10 subsequent chapters: (i) furan, thiophene and their benzannulated derivatives (01AHC(78)1), (ii) pyrrole, indole, carbazole, phospholes, and boroles (01AHC(79)115), (iii) pyrazoles (01AHC(80)158), (iv) pyrazolylborates and related ligands (01AHC(81)167), (v) polyheteroatom azoles other than pyrazole (02AHC117), (vi) chalcogenoazoles and their benzannulated derivatives (03AHC(84)192), (vii) boron, silicon, and phosphorus analogues of azoles (03AHC(85)1), (viii) pyridines and benzannulated pyridines (04AHC293), (ix) η^2 (N, C)-coordinated derivatives of pyridine (05AHC(88)112), and (x) B-, Si, (Ge-), and P- (As-, Sb-) analogues of pyridine (05AHC(89)126). The types of ligands now remaining to be reviewed are polypyridines, chelating pyridines, and azines (heterocycles containing two or more nitrogen heteroatoms in the six-membered ring), and analogues of these classes.

2,2'-Bipyridine, 1,10-phenanthroline and their derivatives and analogues are chemically stable π -acidic ligands that tend to form complexes with metals in their lower oxidation states. 2,2'-Bipyridine and its derivatives are the most widely used ligands (00CRV3553). In a great majority of cases, they act as classical chelating ligands (87MI2, 95MI1) and serve as electron reservoirs (96JOM(524)195). On reaction with alkali metals they tend to form radical anions and dianions (68ZC186), the radical anions sometimes act as ligands (89JA3329, 94JA2600, 96JOM(524)125, 97RCB1766, 99AGE952). 4,4'-Bipyridine as a rule forms bridges between two transition metal centers, which is attractive in coordination and supramolecular chemistry (94PIC67, 95CSR121, 96JCS(D)4257, 99CE27, 99JCS(D)183, 99JCS(D)2311, 99JCS(D)3121, 00CRV853). In the complexes of 2,3'-bipyridines (97TMC338), 3,3'-bipyridines (96IC760, 97IC6138, 98NJC287, 00ICC248, 00JCS(D)2255), and 2,4'-bipyridines (95ICA(234)5, 96JTA1763, 97JTA865, 97PJC513, 98IC5278, 98JTA103, 98PJC2218, 99ICA(288)215, 00JTA145), either monodentate coordination to one of the nitrogen donor centers, or bidentate bridging involving two different metal centers is possible. Among the popular ligands of the diimine group is 2,2':6',2''-terpyridine (87AICR69, 97CCR(160)1). Most often it coordinates in a terdentate manner (96JCR(S)386, 96NJC65, 98ICA(277)275, 98JCS(D)3479,

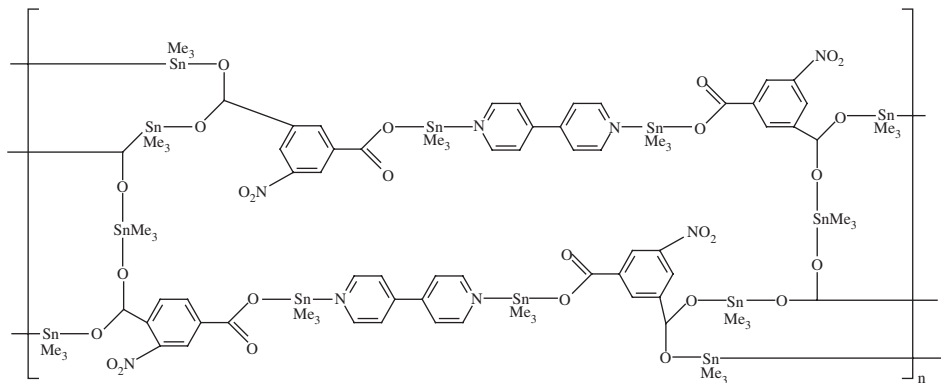
99EJ11409, 99OM573, 00JCS(D)445), although in some cases bidentate bonding excluding one of the pyridine heteroatoms becomes possible (84AJC929, 90AOC523, 90JCC119). At later stages the fluxionality of this ligand in its complexes in solutions was noted, allowing a switch between two coordination modes (92JCS(CC)303). Monodentate coordination is also possible (96IC4261). If the nitrogen heteroatom of the terminal pyridine ring is quarternized, along with N,N chelate formation, N,N,C-coordination becomes possible (96JCS(D)873).

Organometallic complexes of 2,2'-bipyridine are prominent catalysts of electrochemical (87CL597, 87OM181, 88CL2033, 90JCS(D)2155, 93CL955, 94IC2961, 94IC3415, 94JCS(CC)189) and photochemical (87CL1035, 90IC905, 90JOM(382)157, 93MI1, 96NJC759) reduction of carbon dioxide, as well as of the water gas shift reaction (80JCS(CC)1213, 82JCS(D)1885, 86OM724). Most recently, polypyridyl organometallic complexes attracted attention as building blocks in supramolecular structures, which in combination with their photochemical properties make them extremely attractive materials of modern electronics (95MI1).

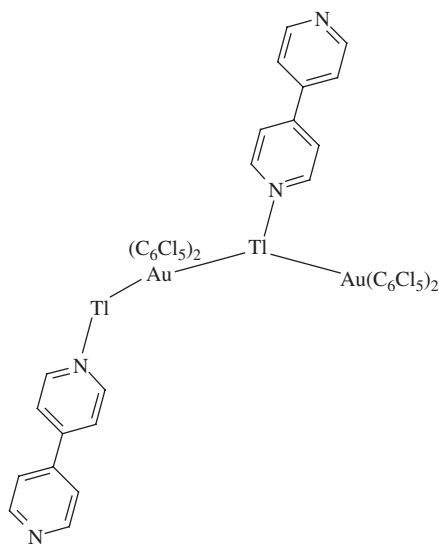
In the current chapter we consider organometallic complexes of non-transition metals and those of Groups IIIB–VIB. In the further three chapters on polypyridines we intend to consider the complexes of manganese group, then separately those of iron group, and finally complexes of the remaining groups and phosphorus analogues of polypyridines. The reason for such a subdivision is due to enormous popularity of polypyridine ligands, especially formed by rhenium(I) and ruthenium(II). The number of publications in these fields is growing in geometric progression and the number of topics, including the ones of applied interest is exciting.

II. Complexes with Non-Transition Metals

Such complexes are very scarce. Equimolar amounts of sodium and 2,2'-bipyridine in DME give [Na(bpy)] (62ZC208). 2,2'-Bipyridine reacts with phenylmagnesium bromide to afford [Mg(Ph)(bpy)] (83JOM(244)C1). [MgPh₂] or [PhMgBr] with 2,2'-bipyridine in THF give rise to [Mg(bpy)Ph(THF)_x] (81CB3789, 82JA3833). Metallocenes [(η⁵-Cp^{*})₂M] (M = Mg, Ca, Sr, Ba) yield complexes [(η⁵-Cp^{*})₂M(bpy)] (M = Mg, Ca, Sr, Ba) (87JOM(325)31). [Me₂B(bpy)]Br (78NMR381) is known. 4,4'-Bipyridine, 1,2-bis(4-pyridyl)ethane, and 1,2-bis(4-pyridyl)ethylene (LL) react with [AlMe₃] and [(*t*-Bu)₂Al(μ-OPh)₂] to yield dinuclear complexes of general composition [(Me₃Al)₂Al(μ-LL)] and [{*t*-Bu₂Al(OPh)₂}(μ-LL)] (04JCS(D)3689). The reaction between 4,4'-bipyridine, 5-nitroisophthalic acid, and trimethyltin chloride in the presence of sodium ethylate in methanol gives rise to the coordination polymer **1** where 4,4'-bipyridine performs a bridging function (06ICA2407). 4,4'-Bipyridine reacts with [AuTl(C₆Cl₅)₂]_n in toluene to yield the product **2** (04JCS(D)1801). [AuTl(C₆Cl₅)₂(4,4'-bipyridine)]_n was made either from 4,4'-bipyridine and [AuTl(C₆Cl₅)₂] in toluene or from 4,4'-bipyridine and complex **2**. 4,4'-Bipyridine and [AuTl(C₆Cl₅)₂]_n in THF afford [{Tl(bpy)}{Tl(bpy)_{0.5}(THF)}{Au(C₆Cl₅)₂}]_n (02IC1056).



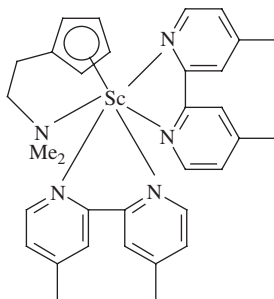
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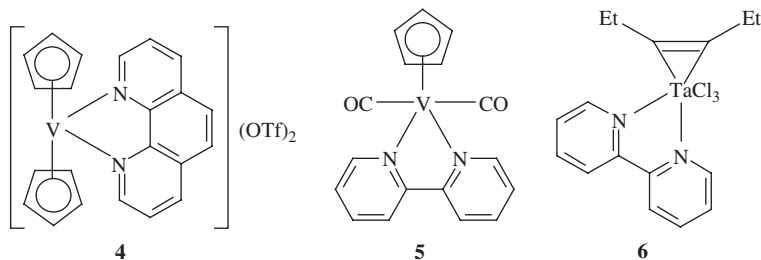
III. Complexes with Scandium, Titanium, and Vanadium Group Metals

The reaction of $[\{\eta^5, \eta^1\text{-C}_5\text{H}_4(\text{CH}_2)_2\text{NMe}_2\}\text{Sc}(\text{C}_6\text{H}_{10})]$ with 4,4'-dimethyl-2,2'-bipyridine in the ratio 1:2 gives **3** and 2,3-dimethyl-1,3-butadiene (03OM4372).

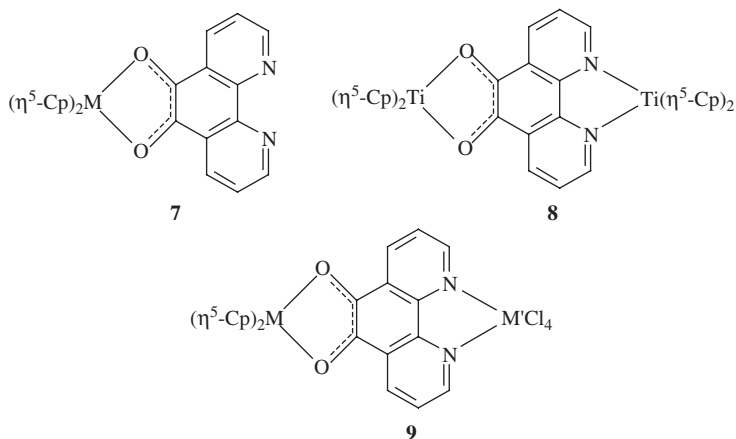


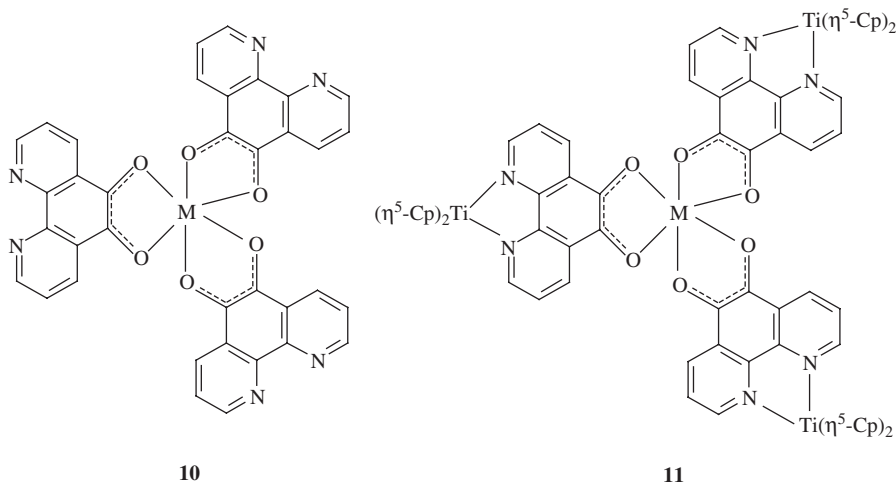
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The reaction of the dilithium salt of the 2,2'-bipyridine anion with $[(\eta^5\text{-Cp})_2\text{TiCl}_2]$ or 2,2'-bipyridine with $[(\eta^5\text{-Cp})_2\text{Ti}(\text{CO})_2]$ gives the relatively stable, weakly paramagnetic complex $[(\eta^5\text{-Cp})_2\text{Ti}(\text{bpy})]$ (79JA3425). $[(\eta^5\text{-MeC}_3\text{H}_4)_2\text{Ti}(\text{bpy})]$ was also prepared. One-electron oxidation of $[(\eta^5\text{-Cp})_2\text{Ti}(\text{bpy})]$ in the presence of ammonium hexafluorophosphate yields $[(\eta^5\text{-Cp})_2\text{Ti}(\text{bpy})](\text{PF}_6)$. Complexes $[(\eta^5\text{-Cp})_2\text{Ti}(\text{LL})](\text{OTf})_2$ (LL = bpy, phen) are known (86JOM(302)193). In a similar manner, 2,2'-bipyridine or 1,10-phenanthroline react with $[(\eta^5\text{-Cp})\text{VCl}_2]$ and silver triflate through the stage of $[(\eta^5\text{-Cp})_2\text{V}(\text{OTf})_2]$ to afford $[(\eta^5\text{-Cp})_2\text{V}(\text{LL})](\text{OTf})_2$ (LL = bpy, phen), e.g. **4** (99IC3730). Reaction of 2,2'-bipyridine with $[(\eta^5\text{-Cp})\text{V}(\text{CO})_3(\text{THT})]$ at room temperature in toluene gives **5** (88IC99). 2,2'-Bipyridine with the alkyl tantalum complex $[\text{TaCl}_3(\eta^2\text{-EtC}\equiv\text{CEt})(\text{DME})]$ affords the ligand-substitution product **6** (03OM464).

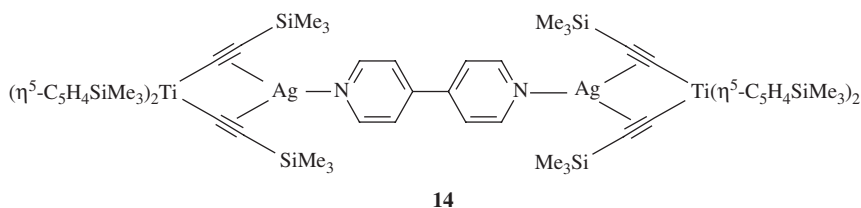
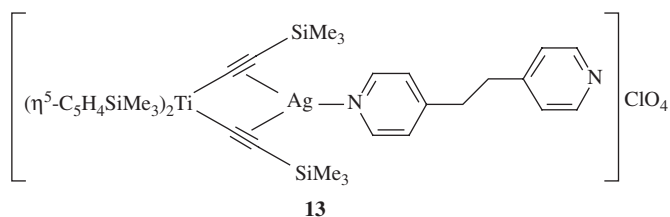
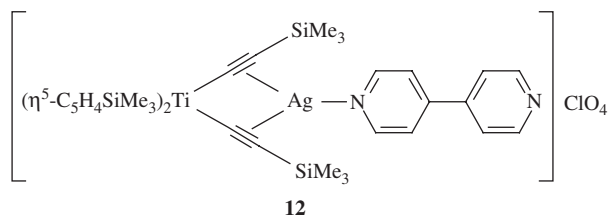


The reaction of 1,10-phenanthroline-5,6-dione with $[(\eta^5\text{-Cp})_2\text{M}(\text{CO})_2]$ (M = Ti, Zr) or $[(\eta^5\text{-Cp})_2\text{V}]$ at room temperature gives the mononuclear complexes **7** (M = Ti, Zr, V) with O,O-coordination (99JCS(D)4389). In the product, titanium is in the formal oxidation state of +III, while zirconium and vanadium are in the state of +IV. Species **7** (M = Ti) enters into further reaction with $[(\eta^5\text{-Cp})_2\text{Ti}(\text{CO})_2]$ under reflux to yield the dinuclear complex **8**. A series of complexes **9** (M = M' = Ti, M = Zr, M' = Ti; M = V, M' = Ti; M = Ti, M' = Hf; M = V, M' = Hf) follows from **7** (M = Ti, Zr, V) and titanium(IV), zirconium(IV), or hafnium(IV) chloride. 1,10-Phenanthroline-5,6-dione reacts with $[\text{Ti}(\eta^6\text{-toluene})_2]$ or $[\text{V}(\eta^6\text{-mesitylene})_2]$ to yield species **10** (M = Ti, V) (02ICA(330)136). Further reaction of **10** (M = Ti, V), which now functions as metal-containing polypyridine ligands with $[(\eta^5\text{-Cp})_2\text{Ti}(\text{CO})_2]$, affords homo- and heteropolynuclear complexes **11** (M = Ti, V).





4,4'-Bipyridine or 1,2-bis(4-pyridyl)ethylene reacts with $[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)_2\text{Ti}(\mu\text{-}\sigma, \pi\text{-C}\equiv\text{CSiMe}_3)_2]\text{AgClO}_4$ to give the heterodinuclear complexes **12** and **13**, respectively (05ICA50). In an excess of titanium-silver precursor, the heterotetranuclear species result, e.g. **14**. A similar reaction course is taken when CuPF_6 is applied instead of AgClO_4 .



IV. Complexes with Chromium Group Metals

A. COMPLEXES OF THE TYPE $[M(CO)_4(LL)]$

The mechanism of photosubstitution of $[M(CO)_6]$ ($M = Cr, Mo, W$) by a derivative of 2,2'-bipyridine or 1,10-phenanthroline to yield $[M(CO)_4(LL)]$ involves the formation of $[M(CO)_5LL]$ with subsequent decarbonylation and chelation (59JCS2323, 62JA4432, 62JCS4712, 64CB426, 67IC1582, 77IC2545, 80IC3015, 81JA6352, 82ICA(65)L1, 83JOM(249)165, 84IC2709, 84JOM(277)277, 86IC1354, 88IC81, 88MP1009, 88OM1237, 92JOM(426)187, 93IC2269). These complexes can be prepared by refluxing in toluene of an appropriate ligand with $[M(CO)_6]$ ($M = Cr, Mo, W$) and illustrations include complexes with 4,4',5,5'-tetramethyl-2,2'-bipyridine, 1,10-phenanthroline, and 3,4,7,8-tetramethyl-1,10-phenanthroline (95JCS(P2)2121, 96IC1235, 00JCS(D)4323, 01ICA(315)44, 01ICA(318)143). Complexes $[M(CO)_4(LL)]$ ($M = Cr, Mo, W$; $LL = bpy, 4,4'-Me_2bpy, phen, 4-Mephen, 5-Mephen, 5-Phphen, 5-Clphen, 5-NO_2phen$) may be listed (86IC1354, 90IC1158, 90JCR(S)271) as well as $[Mo(CO)_4(4,4'-X_2bpy)]$ ($X = OMe, t-Bu, Me, H, Cl, COOMe$) (85JOM(282)349) or $[W(CO)_4(6-p\text{-styryl}bpy)]$ (84JOM(272)385). The photochemical synthesis of $[M(CO)_4(phen)]$ (66AGE520, 72CB770) and other complexes, e.g. $[M(CO)_4(4,4'-R_2bpy)]$ ($M = Cr, Mo, W$; $R = Me, n-C_{19}H_{39}$) (82JA5784) is an alternative. $[W(CO)_4(phen)]$ can be prepared by refluxing of excess 1,10-phenanthroline with $[W(CO)_6]$ in acetonitrile in the presence of trimethylamine *N*-oxide (93IC2269). $[M(CO)_4(bpy)]$ ($M = Cr, Mo, W$) can be prepared by a microwave-assisted procedure (00OM2397). 2,2'-Bipyridine and 1,10-phenanthroline (LL) under microwave conditions readily produce $[Mo(CO)_4(LL)]$ (04JOM2429).

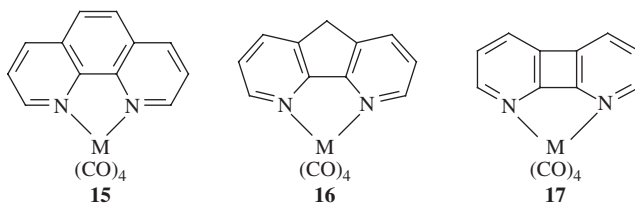
Kinetic characteristics of the process depend on the nature and steric bulk of the diamine ligand (83IC572, 84JCS(CC)506, 85IC2942, 86IC672, 86ICA(113)L3, 86OM2072, 87IC2254, 88JPC2219, 88OM2502, 90ICA(169)13, 90OM1418, 91IC355, 92JOM(440)113, 92OM2319, 94CCR(132)161, 94OM91, 96JCS(D)1629). Photochemical ligand substitution processes follow an associative mechanism when irradiation occurs to give the MLCT excited state (85IC4494, 85ICA(104)179, 85JOM(279)317, 88MP1009, 89JA541, 90CCR(104)39, 90OM1802) or a dissociative mechanism upon excitation of the LF band (90OM1802, 92JA10903, 00CCR(200)933). Irradiation producing the MLCT absorption band (98ICA(278)83) leads to the dissociation of CO from $[Cr(CO)_4(bpy)]$ and subsequent substitution by a solvent molecule (98CCR(177)181, 98CCR(177)219, 98IC661, 98IC1044, 99IC4771, 99JA5296, 00CCR(208)87, 02IC4318). Complexes were characterized by their multiple luminescence (89IC2154). Under electrochemical conditions, they undergo one-electron reduction (69JA4963, 87JOM(330)75). Electrochemical oxidation of $[Mo(CO)_4(bpy)]$ by one-electron loss is followed by the rapid substitution of one CO by a solvent molecule of AN or DMSO (92JEAC(331)831).

For $[Cr(CO)_4(phen)]$ and $[W(CO)_4(phen)]$, the crystal structures are known (85CJSC66, 85CJSC69, 90MK129). The ability of 1,10-phenanthroline to substitute 2,2'-bipyridine from $[Mo(CO)_4(bpy)]$ is ascribed to the more expressed π -acceptor function and rigidity of the 1,10-phenanthroline ligand (88IC81).

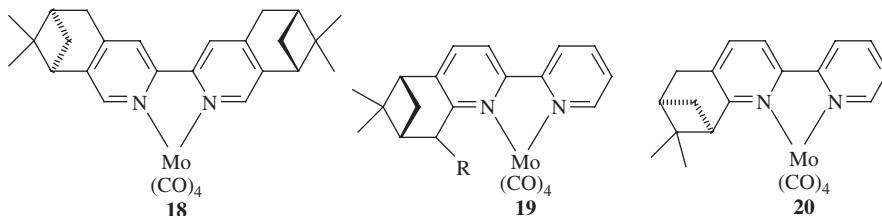
4,4'-Dimethyl-2,2'-bipyridine with $[\text{Cr}(\text{CO})_5(\eta^2\text{-Z-cyclooctene})]$ in pentane gives $[(\text{OC})_5\text{Cr}(\mu\text{-}4,4'\text{-Me}_2\text{bpy})\text{Cr}(\text{CO})_5]$. Upon standing in toluene, the product gradually transforms to $[\text{Cr}(\text{CO})_4(4,4'\text{-Me}_2\text{bpy})]$ (89IC2231). Another synthesis involves the reaction of ligand-substitution of $[\text{Mo}(\text{CO})_4(\text{py})_2]$ with 2,2'-bipyridine or 1,10-phenanthroline (LL); $[\text{Mo}(\text{CO})_4(\text{LL})]$ is the product (84IC4315).

A great many publications are devoted to the spectroscopic and photochemical properties of $[\text{M}(\text{CO})_4(\text{bpy})]$ and $[\text{M}(\text{CO})_4(\text{phen})]$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) (67CB228, 71SA(A)209, 75JOM(97)405, 77JOM(128)203, 78IC3385, 78ICA(26)255, 78ICA(28)133, 78JCS(CC)1016, 79CP365, 79ICA(34)267, 79ICA(36)97, 79JCS(CC)604, 80IC3015, 84MI1, 86ACS177, 86JOM(302)211, 90OM1235, 94CCR(132)167, 96ICA(251)341, 96OM4089, 97IC1684, 01JPC(A)1107, 02CCR(230)225). In the anion radical of $[\text{Cr}(\text{CO})_4(\text{bpy})]$, the unpaired electron is localized on the 2,2'-bipyridine ligand (68BCSJ359, 68BCSJ863, 70BCSJ2492, 72BCSJ470, 81CB3789, 98JCS(D)215, 99JCS(D)3081). On reduction, electronic redistribution within the $\text{Cr}(\text{CO})_4$ moiety occurs (98JCS(D)215). It includes delocalization of the spin density from 2,2'-bipyridine to axial carbon monoxide ligands and polarization of the π -electron density toward equatorial carbon monoxide ligands. Chemical reduction can be achieved by reacting of $[\text{M}(\text{CO})_4(\text{bpy})]$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) with the anion-radical of anthracene, the product being the anion-radical of a polypyridyl complex (85JOM(281)229).

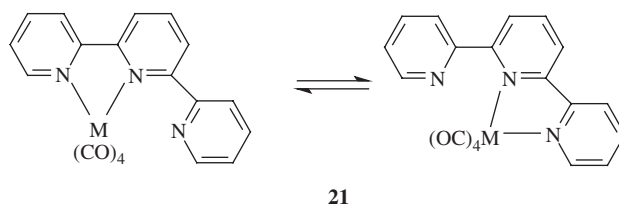
Photochemical irradiation of $[\text{M}(\text{CO})_6]$ in the presence of 1,10-phenanthroline and 4,5-diazafluorene gives complexes **15** and **16** ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$), and photochemical reaction of 1,8-diazabiphenylene with $[\text{M}(\text{CO})_5(\text{THF})]$ gives **17** ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) (87IC620). A photochemical synthetic approach applied to $[\text{M}(\text{CO})_5(\text{THF})]$ and 1,8-diazabiphenylene (LL) leads to complexes $[\text{M}(\text{CO})_5(\text{LL})]$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) with monodentate coordination of the ligand. Complexes $[\text{W}(\text{CO})_4(4\text{-Mephen})]$ are used to monitor the polymerization processes (96CM1540, 98CCR(177)3). A polystyrene attached complex of 2,2'-bipyridine follows from $[\text{W}(\text{CO})_6]$ and polystyrene-supported 2,2'-bipyridine ligand (78JA6635). It serves as an efficient catalyst for metathesis of internal olefins. The range of such complexes is described in ref. (78IC2345).



Several chiral 2,2'-bipyridine ligands when reacted with $[\text{Mo}(\text{CO})_6]$ give complexes **18**, **19** ($\text{R} = \text{H}, \text{Me}$), and **20** usable as catalysts in asymmetric allylic substitution, allylic oxidation, and cyclopropanation (01OM673).



Complexes $[M(CO)_5(\text{naph})]$ ($M = \text{Cr}, \text{Mo}, \text{W}$) contain the η^1 -coordinated fluxional 1,8-naphthyridine ligand (82IC4318). $[(\eta^4\text{-nbd})M(CO)_4]$ ($M = \text{Cr}, \text{Mo}, \text{W}$) with 2,2':6',2''-terpyridine form products **21** ($M = \text{Cr}, \text{Mo}, \text{W}$), where the ligand is coordinated in a bidentate manner but reveals the properties of fluxionality in solution, switching between two bidentate modes of coordination through the stage of the unstable species where all three pyridine nitrogens are involved in coordination (94JCS(D)111). 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine with $[Mo(CO)_4(\text{nbd})]$ gives complex of type **21** with the same fluxional behavior. 4'-Phenyl-2,2':6',2''-terpyridine (LL) with $[M(CO)_6]$ ($M = \text{Mo}, \text{W}$) in THF gives $[M(CO)_4(\text{LL})]$ ($M = \text{Mo}, \text{W}$) with bidentate coordination of the ligand and fluxionality of the coordination in solution (01ICA(312)7). However, in acetonitrile the same reagents ($M = \text{W}$) lead to $[W(CO)_3(\text{LL})]$ where the ligand is rigid and terdentate.



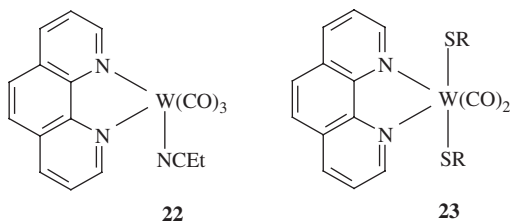
$[W(CO)_4(\text{phen})]$ enters substitution reactions with phosphine ligands to yield $[W(CO)_3(\text{phen})L]$ ($L = P(n\text{-Bu})_3, P(\text{OEt})_3, P(\text{OCH}_2)_3\text{CMe}, \text{PPh}_3$) (67IC992). Chromium analogues were also described (79JA5433, 86IC3212). Substitution reactions of $[\text{Cr}(CO)_4(\text{phen})]$ are the subject of publications (70IC966, 76IC1417). A similar reaction takes place between $[W(CO)_3(\text{CS})(\text{phen})]$ and phosphine ligands yielding $[W(CO)_2(\text{CS})(L)(\text{phen})]$ ($L = P(\text{OMe})_3, P(\text{OEt})_3, \text{PPh}_3, P(n\text{-Bu})_3$) (78IC2035). The starting complex is the result of the reaction of $(n\text{-Bu}_4\text{N})[W(CO)_4(\text{CS})\text{I}]$, silver tetrafluoroborate, and 1,10-phenanthroline. $[W(CO)_3(\text{CS})\text{bpy}]$ is also known (76IC1089). Combination of the MLCT and LF excited states of $[M(CO)_4(\text{phen})]$ ($M = \text{Cr}, \text{Mo}, \text{W}$) makes it possible to tune the substitution reactions with phosphines yielding $[M(CO)_3(\text{phen})(\text{PR}_3)]$ (74CRV401, 83IC3825, 89JCS(CC)367, 90CCR(97)155, 90JPC5865, 97OM572, 97OM3439). Irradiation giving the MLCT absorption band causes dissociation of an axial carbon monoxide ligand and its substitution by a solvent molecule or other ligand to yield $[M(CO)_3(\text{LL})(\text{S})]$. The anion-radical can be formally regarded as a chromium(0) $[(\text{Cr}(CO)_4(\text{bpy}))^-]$ and it is more prone to carbonyl substitution reactions than the parent complex (93CTIC1). Similar trends occur on MLCT substitution of $[\text{Cr}(CO)_4(\text{bpy})]$ when the state similar to that of a radical-anion is observed (94CCR(132)167, 97IC1684). Substitution products include $[\text{Cr}(CO)_3(\text{bpy})(\text{PBu-}n_3)]^-$ (75CB163). $[W(CO)_4(\text{phen})]$ exhibits dual luminescence and enters CO-substitution reactions by different mechanisms that are governed by the wavelength of photoexcitation. Excitation into the LF band causes dissociative substitution while the MLCT band provides an associative pathway (84ACR96). Chemically, $[W(CO)_4(\text{phen})]$ (87JOM(331)23) enters the substitution reaction with $n\text{-Bu}_3\text{P}$ to yield $[W(CO)_3(\text{phen})(n\text{-Bu}_3\text{P})]$ (88JOM(348)343). A photochemical analogous reaction proceeds promptly (99IC4771). The trimethylamine *N*-oxide-induced substitution of $[M(CO)_4(\text{bpy})]$ with bis(diphenylphosphino)methane

gives $[M(\text{CO})_3(\eta^2\text{-bpy})(\eta^1\text{-dppm})]$ ($M = \text{Cr, Mo, W}$) (87JOM(331)23). A synthetic procedure for the transformation of $[M(\text{CO})_4(\text{LL})]$ ($M = \text{Cr, Mo, W}$; $\text{LL} = \text{bpy, phen}$) to $[M(\text{CO})_3(\text{LL})(\text{P}(\text{OEt})_3)]$, originally under reflux in toluene, is simplified when the reaction is run in acetonitrile in the presence of trimethylamine *N*-oxide; room temperature is essential (88JOM(348)343). $[\text{Mo}(\text{CO})_4(\text{bpy})]$ with alkali metal xanthates and dialkyldithiocarbamates (SS) yields the products of substitution of 2,2'-bipyridine. Anionic six-coordinate complexes $(\text{PPh}_4)[\text{Mo}(\text{CO})_4(\text{SS})]$ were isolated (85JOM(296)367).

$[\text{Mo}(\text{CO})_4(\text{bpy})]$ oxidatively adds molecular bromine or iodine to afford $[\text{Mo}(\text{CO})_3(\text{bpy})\text{X}_2]$ ($\text{X} = \text{Br, I}$) (62JCS4712). $[\text{Mo}(\text{CO})_4(\text{LL})]$ ($\text{LL} = 4,4'\text{-di-tert-butyl-2,2'-bipyridine}$) is obtained from LL and $[\text{Mo}(\text{CO})_4(\text{nbd})]$ (83JOM(249)165). Refluxing LL with $[\text{Mo}(\text{CO})_6]$ (95JOM(505)109) with X_2 ($\text{X} = \text{Br, I}$) in toluene or methylene chloride gives $[\text{Mo}(\text{CO})_3(\text{LL})\text{X}_2]$ ($\text{X} = \text{Br, I}$) and with tin(IV) bromide it affords $[\text{Mo}(\text{CO})_3(\text{LL})(\text{SnBr}_3)(\text{Br})]$, all products of oxidative addition. The dibromo complex is more readily accessible from $[\text{Mo}(\text{CO})_4(\text{LL})]$ and copper(II) bromide in methylene chloride. $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ under these conditions gives $[\text{Mo}(\text{CO})_3(\text{LL})\text{Cl}_2]$. Complexes $[M(\text{CO})_4(\text{LL})]$ ($M = \text{Cr, Mo, W}$; $\text{LL} = \text{bpy, phen}$) react with mercuric halides or tin(IV) compounds by oxidative addition to give the M-Hg or M-Sn species (68JCS(A)2851, 71IC492). $[\text{W}(\text{CO})_4(\text{bpy})]$ reacts with $[\text{Cu}(\text{AN})_4]\text{X}$ ($\text{X} = \text{Cl, N}_3, \text{ClO}_4, \text{BF}_4$) and gives $[\text{W}(\text{CO})_4(\text{bpy})\text{CuX}]$ ($\text{X} = \text{Cl, N}_3, \text{ClO}_4, \text{BF}_4$) (97POL2193).

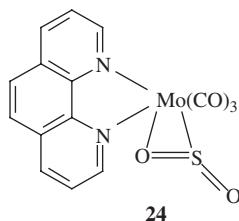
B. COMPLEXES WITH THREE, TWO AND ONE CARBONYL GROUPS

Reaction of 1,10-phenanthroline with $[M(\text{CO})_3(\text{cycloheptatriene})]$ ($M = \text{Cr, Mo, W}$) in donor solvents allows the preparation of $[M(\text{CO})_3(\text{phen})(\text{solv})]$ (70JOM(22)439). 1,10-Phenanthroline with $[\text{W}(\text{CO})_3(\text{EtCN})_3]$ gives complex **22**, but it is best prepared from 1,10-phenanthroline, $[\text{W}(\text{CO})_6]$, and propionitrile (94IC3899). Complex **22** oxidatively adds RSSR ($\text{R} = \text{Me, } t\text{-Bu, Ph, PhCH}_2$) to yield the tungsten(II) species **23** ($\text{R} = \text{Me, } t\text{-Bu, Ph, CH}_2\text{Ph}$). Interaction of $[\text{W}(\text{CO})_3(\text{phen})(\text{EtCN})]$ and $[\text{W}(\text{CO})_2(\text{phen})(\text{SPh})_2]$ gives $[\text{W}(\text{CO})_3(\text{phen})][\text{W}(\text{CO})_2(\text{phen})(\text{SPh})_2]$. Derivative **23** ($\text{R} = \text{Ph}$) reacts with phosphines to yield $[\text{W}(\text{CO})(\text{phen})(\text{PR}_3)(\text{SPh})_2]$ ($\text{R} = \text{Me, MeO}$). Complex $[\text{W}(\text{CO})_2(\text{SPh})_2(\text{phen})]$ reacts with NO to give $[\text{W}(\text{CO})_2(\text{SPh})(\text{NO})(\text{phen})]$ (99IC6212). With $[\text{W}(\text{CO})_2(\eta^2\text{-toluene } 3,4\text{-dithiolate})(\text{phen})]$, the reaction course is different, and the product is $[\text{W}(\text{NO})_2(\eta^2\text{-toluene } 3,4\text{-dithiolate})(\text{phen})]$.



$[\text{Mo}(\text{CO})_3(\text{phen})(\text{AN})]$ (66IC2119) reacts with sulfur dioxide under nitrogen to yield **24** where both 1,10-phenanthroline and sulfur dioxide are η^2 -coordinated

(80IC3003). A solution of $[\text{Mo}(\text{CO})_2(\text{bpy})(\text{py})(\pi\text{-allyl})](\text{BF}_4)$ (66JCS(A)317) in liquid SO_2 gradually yields $[\text{Mo}(\text{CO})_2(\text{bpy})(\eta^2\text{-SO}_2)_2]$ (68JCS(A)710, 80IC3003). The product with phosphines results from substitution of the sulfur dioxide ligand, and the products are $[\text{Mo}(\text{CO})_3(\text{bpy})(\text{PR}_3)]$ (95ICA(240)99).



The photochemical reaction of 2,2'-bipyridine with $[\text{W}(\text{CO})_6]$ in cyclohexane/carbon tetrachloride yields the tungsten(II) seven-coordinate product $[\text{W}(\text{CO})_3(\text{bpy})\text{Cl}_2]$ (88ICA(145)231, 89JOM(375)85). In the presence of tin(IV) tetrachloride as an oxidant, a mixture of products, $[\text{W}(\text{CO})_3(\text{bpy})\text{Cl}_2]$ and $[\text{W}(\text{CO})_3(\text{bpy})\text{Cl}(\text{SnCl}_3)]$, results (95JOM(492)241). Complexes $[\text{Mo}(\text{CO})_3(\text{LL})\text{X}_2]$ ($\text{X} = \text{Cl}, \text{Br}$; $\text{LL} = \text{bpy}, \text{phen}$) react with phosphines to give the seven-coordinate molybdenum(II) species $[\text{Mo}(\text{CO})_2(\text{LL})\text{X}_2(\text{phosphine})]$ ($\text{X} = \text{Cl}, \text{Br}$; $\text{LL} = \text{bpy}, \text{phen}$) (84AQ(B)533). The products of interaction of the same starting complexes with bis(diphenylphosphino)methane are also the molybdenum(II) seven-coordinate compounds, where the diphosphine is coordinated via only one phosphorus atom (87JCS(D)819). Under sunlight irradiation the 2,2'-bipyridine complex loses one carbonyl ligand and transforms to the seven-coordinate monocarbonyl $[\text{MoBr}_2(\text{CO})(\text{bpy})(\eta^2\text{-dppm})]$. $[\text{Mo}(\text{CO})_2(\text{bpy})(\eta^1\text{-dppm})\text{Br}]$ with sodium tetraphenylborate gives $[\text{Mo}(\text{CO})_2(\text{bpy})(\eta^2\text{-dppm})\text{Br}](\text{BPh}_4)$. The monocarbonyl complex on exposure to carbon monoxide gives $[\text{Mo}(\text{CO})_2(\text{bpy})(\eta^2\text{-dppm})\text{Br}]\text{Br}$, and on reaction with $\text{P}(\text{OCH}_2)_3\text{CMe}$ and NaBPh_4 affords $[\text{Mo}(\text{CO})(\text{bpy})(\text{dppm})\{\text{P}(\text{OCH}_2)_3\text{CMe}\}_2](\text{BPh}_4)_2$. $[\text{W}(\text{CO})(\text{AN})(\text{S}_2\text{CNC}_4\text{H}_8)(\eta^2\text{-MeC}_2\text{Me})_2](\text{BPh}_4)$ reacts with 2,2'-bipyridine and 1,10-phenanthroline (LL) to give $[\text{W}(\text{CO})(\text{S}_2\text{CNC}_4\text{H}_8)(\text{LL})(\eta^2\text{-MeC}_2\text{Me})](\text{BPh}_4)$ (90JCS(D)3169, 90JOM(391)C12, 93OM276).

$[\text{Mo}(\text{CO})_2(\text{bpy})_2]$ prepared from 2,2'-bipyridine and $[\text{Mo}(\text{CO})_4(\text{bpy})]$ (64CB426, 75IC274, 84IC2298) reacts with phosphines to yield $[\text{Mo}(\text{CO})_2(\text{bpy})(\text{PR}_3)_2]$ ($\text{R} = n\text{-Bu}, \text{Ph}, \text{OMe}$) (82JCS(D)2397). The same complexes are the products of interaction of $[\text{Mo}(\text{CO})_2(\text{PR}_3)_2(\text{AN})_2]$ ($\text{R} = n\text{-Bu}, \text{Ph}$) with 2,2'-bipyridine (71JOM(26)247, 75CB163). The complex with $\text{R} = \text{OMe}$ also follows from $[\text{Mo}(\text{CO})_4(\text{bpy})]$ and trimethylphosphite. On variation of the conditions with triphenylphosphine, $[\text{Mo}(\text{CO})_3(\text{PPh}_3)(\text{bpy})]$ may be prepared (82JCS(D)2397). With 1,2-bis(diphenylphosphino)ethane, the product is $[\text{Mo}(\text{CO})_2(\text{dppe})(\text{bpy})]$. A similar reaction occurs between $[\text{Mo}(\text{CO})_3(\text{LL})(\text{AN})]$ and polyfunctional cyclic P-P ligand (88POL489).

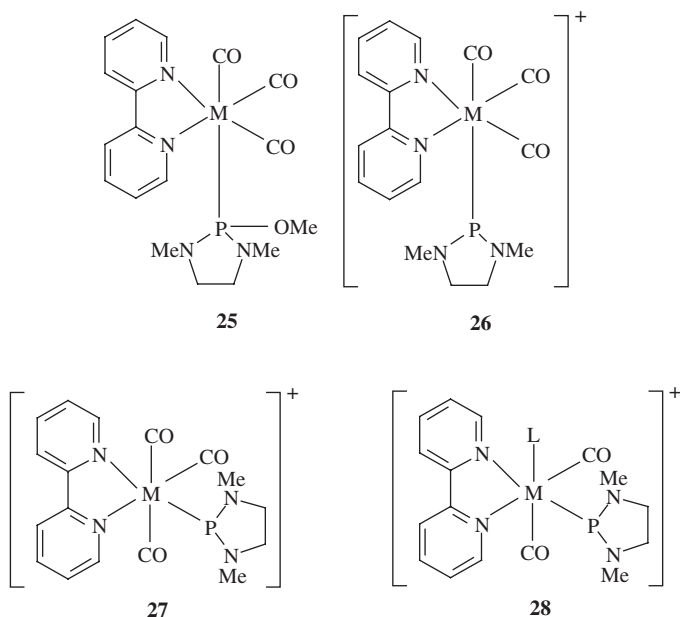
Reduction of $[\text{Mo}(\text{CO})_2(\text{bpy})_2]$ using sodium amalgam or sodium naphthalenide gives paramagnetic $[\text{Mo}(\text{CO})_2(\text{bpy})_2]^-$ in dimethoxyethane (81JOM(218)C31). Oxidation of $[\text{Mo}(\text{CO})_2(\text{bpy})_2]$ using silver tetrafluoroborate in acetonitrile or aluminum chloride in methylene chloride and followed by sodium tetrafluoroborate gives

diamagnetic dinuclear $[\text{Mo}(\text{CO})_2(\text{bpy})_2](\text{BF}_4)_2$. Heating an acetone solution of the product gives the paramagnetic mononuclear complex $[\text{Mo}(\text{CO})_2(\text{bpy})_2](\text{BF}_4)$. Both dinuclear and mononuclear cationic complexes in acetonitrile react with silver tetrafluoroborate to yield the seven-coordinated molybdenum(II) product $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{AN})](\text{BF}_4)_2$. In the presence of a neutral ligand, the oxidation leads to $[\text{Mo}(\text{CO})_2(\text{bpy})_2\text{L}](\text{BF}_4)_2$ ($\text{L} = \text{P}(\text{OMe})_3, \text{PhC}\equiv\text{CH}$) (85JOM(297)301).

The reaction between $[\text{Cr}(\text{CO})_4(\text{bpy})]$ and *p*-tolyl isocyanide or ethyl isocyanide produces $[\text{Cr}(\text{CO})_3(\text{CNR})(\text{bpy})]$ ($\text{R} = p\text{-Tol, Et}$). Similar reaction of *p*-tolyl isocyanide with $[\text{Mo}(\text{CO})_4(\text{bpy})]$ gives the product of complete substitution of the bipyridine ligand (66IC1837, 67JOM(8)139). In contrast, ethyl isocyanide leads to $[\text{Mo}(\text{CO})_3(\text{CNEt})(\text{bpy})]$ (82JCS(D)2397). A series of complexes $[\text{Mo}(\text{CO})_3(\text{bpy})(\text{P}(p\text{-C}_6\text{H}_4\text{X})_3)]$ ($\text{X} = \text{F, Cl, H, Me, OMe, NMe}_2$) is known (75JA6897). Reactions of $[\text{M}(\text{CO})_2(\text{bpy})_2]$ ($\text{M} = \text{Mo, W}$) with phosphines and isocyanides (L) lead to substitution of the 2,2'-bipyridine ligand to yield $[\text{M}(\text{CO})_2(\text{bpy})\text{L}_2]$ or $[\text{M}(\text{CO})_2\text{L}_4]$ depending on the nature of L and M , temperature and solvent (86JCS(D)511). The π -acceptor ligand, PF_3 , is capable of substituting the carbonyl ligands to give $[\text{M}(\text{bpy})_2(\text{PF}_3)_2]$ ($\text{M} = \text{Mo, W}$). $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{AN})](\text{BF}_4)_2$ with triphenylphosphine gives $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{PPh}_3)](\text{BF}_4)_2$. Tri-*n*-butylphosphine first substitutes the coordinated solvent molecule to yield $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{P}(n\text{-Bu})_3)](\text{BF}_4)_2$ and then enters the reductive substitution of a bipyridine ligand to yield the Mo(0) complex $[\text{Mo}(\text{CO})_2(\text{bpy})(\text{P}(n\text{-Bu})_3)_2]$. The main product of the reaction with triethylphosphine is $[\text{Mo}(\text{CO})(\text{bpy})_2(\text{PEt}_3)_2](\text{BF}_4)_2$. The molybdenum(0) and tungsten(0) complexes may be oxidized by a silver(I) in solution to give rather stable M(I) and M(II) complexes. In the +II oxidation state, molybdenum complexes are seven-coordinate and carry a solvent molecule in the coordination sphere, $[\text{Mo}(\text{CO})_2(\text{bpy})_2\text{S}]^{2+}$, while a tungsten complex remains six-coordinate, $[\text{W}(\text{CO})_2(\text{bpy})_2]^{2+}$. Oxidation of $[\text{Mo}(\text{CO})_2(\text{bpy})_2]$ using silver tetrafluoroborate and trimethoxyphosphine, gives $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{P}(\text{OMe})_3)](\text{BF}_4)_2$. In contrast, $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{AN})](\text{BF}_4)_2$ and trimethylphosphite in acetonitrile affords $[\text{Mo}(\text{CO})(\text{bpy})_2\{\text{P}(\text{OMe})_3\}_2](\text{BF}_4)_2$. The product of substitution with diphenylphosphinoethane has the composition $[\text{Mo}(\text{CO})(\text{bpy})_2(\text{dppe})](\text{BF}_4)_2$, as a result of substitution of one solvent molecule and one carbon monoxide ligand. Tungsten(II) complex $[\text{W}(\text{CO})_2(\text{bpy})_2](\text{BF}_4)_2$ behaves differently and with $\text{L} = \text{Ph}_3\text{P}$ and $\text{L} = (\text{MeO})_3\text{P}$ in acetone produces $[\text{W}(\text{CO})_2(\text{bpy})\text{L}_2](\text{BF}_4)_2$. With diphosphines, bis(diphenylphosphino)methane and bis(diphenylphosphino)ethane, the same complex yields the seven-coordinate tungsten(II) species $[\text{WF}(\text{CO})_2(\text{bpy})(\text{LL})](\text{BF}_4)$ ($\text{LL} = \text{dppm, dppe}$). $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{AN})](\text{BF}_4)_2$ gives on heating with 2,2'-bipyridine in acetonitrile $[\text{Mo}(\text{bpy})_3](\text{BF}_4)_2$ and $[\text{Mo}(\text{NO})_2(\text{bpy})_2](\text{BF}_4)_2$ with NO in acetonitrile. $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{AN})](\text{BF}_4)_2$ with isocyanides RNC gives first $[\text{Mo}(\text{bpy})_2(\text{CNR})_3](\text{BF}_4)_2$ and then $[\text{Mo}(\text{bpy})(\text{CNR})_5](\text{BF}_4)_2$ ($\text{R} = \text{Et, C}_6\text{H}_4\text{Me-}p$). Other substitution products are $[\text{M}(\text{CO})_3(\text{bpy})(\text{L})]$ ($\text{M} = \text{Mo, W}$) where L is pyridine (71JCMS75) or the monodentately coordinated di-2-pyridylamine (86JCS(D)759). $[\text{Mo}(\text{CO})_2(\text{bpy})_2](\text{BF}_4)_2$ with 2,2'-bipyridine in acetonitrile gives $[\text{Mo}(\text{bpy})_3](\text{BF}_4)_2$ (87JOM(325)181). The reaction between $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{AN})](\text{BF}_4)_2$ and 4,4'- X_2 -2,2'-bipyridine ($\text{X} = \text{NMe}_2, t\text{-Bu, Cl}$) in acetonitrile gives $[\text{Mo}(\text{bpy})_2(4,4'\text{-X}_2\text{bpy})](\text{BF}_4)_2$. Under air, $[\text{Mo}(\text{CO})(\text{bpy})_2(4,4'\text{-X}_2\text{bpy})](\text{BF}_4)_2$ is formed, but on heating $[\text{Mo}(\text{bpy})_2(4,4'\text{-X}_2\text{bpy})](\text{BF}_4)_2$ is the

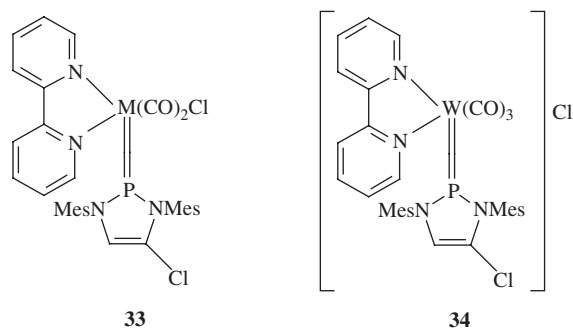
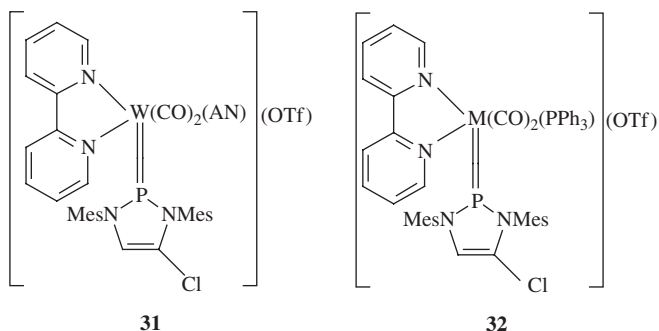
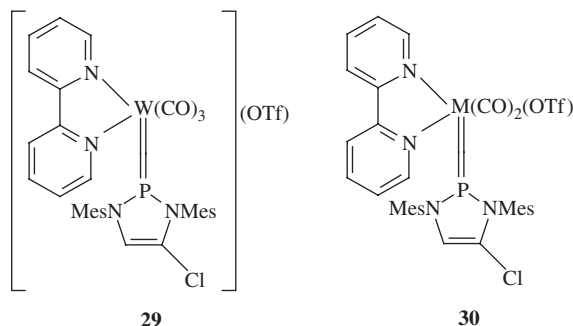
product. $[\text{Mo}(\text{CO})_2(\text{bpy})_2(\text{AN})](\text{BF}_4)_2$ with pyridine in acetonitrile gives $[\text{Mo}(\text{CO})(\text{bpy})_2(\text{py})_2](\text{BF}_4)_2$, but under thermolysis $[\text{Mo}(\text{bpy})_2(\text{py})_2](\text{BF}_4)_2$ is formed.

$[\text{Mo}(\text{CO})_2(\text{phen})(\text{dbm})_2]$ with C_{60} forms $(\text{C}_{60})[\text{Mo}(\text{CO})_2(\text{phen})(\text{dbm})]_n$ ($n = 2, 3$) and with C_{70} - $[(\eta^2\text{-C}_{70})\text{Mo}(\text{CO})_2(\text{phen})(\text{dbm})]$ (97JCS(D)3585, 99JCS(D)965, 00EJI1345). 2,2'-Bipyridine reacts with $[\text{Wl}_2(\text{CO})(\text{AN})(\eta^2\text{-MeC}_2\text{Me})_2]$ to yield $[\text{Wl}_2(\text{CO})(\text{bpy})(\eta^2\text{-MeC}_2\text{Me})_2]$ with monodentate coordination of the bipyridine ligand (88IC2287) and after some time the cationic complex $[\text{Wl}(\text{CO})(\text{bpy})(\eta^2\text{-MeC}_2\text{Me})_2]^+$, where bipyridine has a normal bidentate mode. The same starting precursor with excess 2,2'-bipyridine followed by NaBPh_4 forms the dicationic species $[\text{W}(\text{CO})(\text{bpy})_2(\eta^2\text{-MeC}_2\text{Me})](\text{BPh}_4)_2$. 5,6-Dimethyl-1,10-phenanthroline and 2,2'-bipyridine (LL) react with $[\text{MoI}_2(\text{CO})(\text{AN})(\eta^2\text{-RC}_2\text{Ph})_2]$ to give $[\text{MoI}_2(\text{CO})(\text{LL})(\eta^2\text{-RC}_2\text{Ph})]$ ($\text{R} = \text{Ph}$, $\text{LL} = 5, 6\text{-Me}_2\text{phen}$; $\text{R} = \text{Me}$, $\text{LL} = \text{bpy}$) (98POL3455). $[\text{W}(\text{C}\equiv\text{CPh})\text{Cl}(\text{CO})_2(\text{bpy})]$ is known (85IC3976). Complexes $[\text{MI}_2(\text{CO})_3(\text{AN})(\text{PPh}_3)]$ ($\text{M} = \text{Mo}, \text{W}$) with 2,2'-bipyridine or 1,10-phenanthroline (LL) give $[\text{MI}(\text{CO})_3(\text{PPh}_3)(\text{LL})]^+$ ($\text{M} = \text{Mo}, \text{W}$; $\text{LL} = \text{bpy}, \text{phen}$) (89JOM(367)101). Complex $[\text{WCl}(\text{CO})(\text{bpy})(\eta^2\text{-MeC}_2\text{Me})_2]^+$ is known (98JCR(S)379). Complexes **25** ($\text{M} = \text{Mo}, \text{W}$) on interaction with $\text{BF}_3 \cdot \text{OEt}_2$ or BCl_3 experience extraction of an OMe group from the diaminophosphite ligand and give the cationic phosphonium species **26** in a facial geometry (88IC973, 89OM638, 94JOM(465)193, 95OM773, 95OM4173, 96BCSJ983, 96OM2517, 96OM4383, 00OM3323). The products isomerize to the meridional **27**. Complexes react with phosphite ligands (L) by a carbonyl ligand substitution route to give **28** ($\text{M} = \text{Mo}, \text{W}$). $[\text{Mo}(\text{CO})_3(\text{bpy})\{\text{P}(\text{OR})_3\}]$ ($\text{R} = \text{Me}, \text{Et}, i\text{-Pr}$) with $\text{BF}_3 \cdot \text{OEt}_2$ gives the product of OR/F substitution within the phosphite ligand, $[\text{Mo}(\text{CO})_3(\text{bpy})\{\text{P}(\text{OR})_2\text{F}\}]$ (00JOM(611)349).



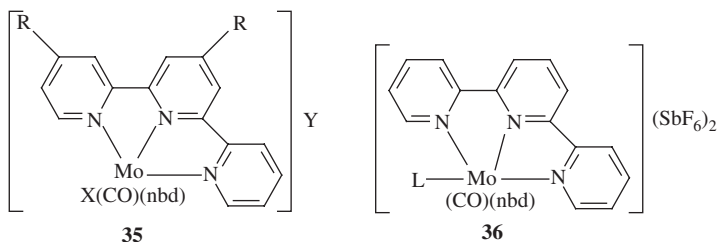
A series of carbene complexes is based on $[\text{M}(\text{CO})_4(\text{bpy})]$ ($\text{M} = \text{Mo}, \text{W}$) and $[\text{W}(\text{CO})_3(\text{bpy})\text{L}]$ ($\text{L} = \text{CO}, \text{AN}$) (01JOM(617)383). $[\text{M}(\text{CO})_3(\text{bpy})\text{L}]$ react with

diazaphospholenium salts and *p*-chlorodiazaphospholenes, provided these carbene-like compounds contain aryl substituents at the nitrogen atoms. *N*-*t*-butyl derivatives failed to react (00CEJ3414). 1,3-Dimesityl-4-chloro-1,3,2-diazaphospholenium triflate with $[W(CO)_3(bpy)L]$ ($L = AN, CO$) forms tricarbonyl complex **29** (01JOM (617)383). The product enters a variety of reactions including decarbonylation on heating to yield the neutral species **30** ($M = W$) and carbonyl substitution in acetonitrile to give **31**. 1,3-Dimesityl-4-chloro-1,3,2-diazaphospholenium triflate also reacts with $[M(CO)_4(bpy)]$ ($M = Mo, W$) to give the neutral **30** ($M = Mo, W$), which on reaction with triphenylphosphine transforms to cationic complexes **32** ($M = Mo, W$). *p*-Chlorodiazaphospholene with $[M(CO)_4(bpy)]$ ($M = Mo, W$) gives the neutral complexes **33** ($M = Mo, W$), which on reaction with trimethylsilyl triflate transform into **30** ($M = Mo, W$). With $[W(CO)_3(bpy)(AN)]$, however, the cationic complex **34** results; on decarbonylation it gives **33** ($M = W$).



2,2'-Bipyridine and 4,4'-di-*t*-butyl-2,2'-bipyridine with $[(\eta^4\text{-nbd})\text{Mo}(\text{CO})_4]$ and X_2 ($\text{X} = \text{Br}, \text{I}$) give $[(\eta^4\text{-nbd})\text{Mo}(\text{CO})(\text{LL})\text{X}_2]$ along with $[\text{Mo}(\text{CO})_3(\text{LL})\text{X}_2]$ ($\text{LL} = \text{bpy}, 4,4'\text{-}t\text{-Bu}_2\text{bpy}$; $\text{X} = \text{Br}, \text{I}$) (95JOM(505)109). Similar complexes are $[\text{Mo}(\text{CO})_3(\text{bpy})(\text{SnX}_3)\text{X}]$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) (68IC310, 72IC1, 93JOM(455)121, 93JOM(463)121), $[\text{Mo}(\text{CO})_3(\text{bpy})(\text{SnMeCl}_2)\text{Cl}]$ (69IC1268), $[\text{Mo}(\text{EtNC})_3(\text{bpy})_2](\text{BF}_4)_2$ (85AX(C)184), $[\text{Mo}(\text{CO})_3(\text{bpy})(\text{HgCl})\text{Cl}]$ (74AJC2667), and other seven-coordinate species (94JOM(466)139).

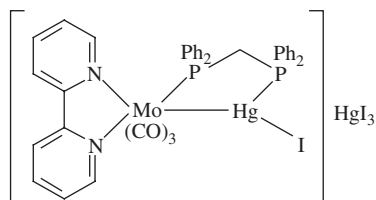
2,2':6'',2''-terpyridine and 4,4',4''-tri-*t*-butyl-2,2':6'',2''-terpyridine react with $[(\eta^4\text{-nbd})\text{Mo}(\text{CO})_4\text{I}_2]_n$ to yield **35** ($\text{R} = \text{H}, t\text{-Bu}$; $\text{X} = \text{Y} = \text{I}$) (96JOM(509)225). The ligands in these and similar complexes lack flexibility and are tridentately coordinated. Metathesis reactions with potassium or ammonium hexafluorophosphate, or silver hexafluoroantimonate allowed the preparation of **35** ($\text{R} = \text{H}, t\text{-Bu}$; $\text{X} = \text{I}$; $\text{Y} = \text{PF}_6, \text{SbF}_6$). Addition of 2,2':6'',2''-terpyridine to the product of interaction of $[\text{Mo}(\text{CO})_4(\text{nbd})]$ and CuBr_2 gives **35** ($\text{R} = \text{H}, \text{X} = \text{Y} = \text{Br}$) from which ($\text{R} = \text{H}, \text{X} = \text{Br}$; $\text{Y} = \text{PF}_6, \text{SbF}_6$) were obtained in a similar manner to the iodo-complexes. Species **35** ($\text{R} = \text{H}$; $\text{X} = \text{Br}, \text{I}$) with two equivalents of silver hexafluoroantimonate produce $[\{\text{Mo}(\text{CO})(\text{nbd})(\text{trpy})\}_2(\text{acetone})](\text{SbF}_6)_4$, whose structure is not completely clear. With trimethylphosphine, this dinuclear complex forms the dicationic species **36** ($\text{L} = \text{PMe}_3$) and with excess propionitrile it gives **36** ($\text{L} = \text{NCeT}$). The same dinuclear complex with sodium azide or sodium chloride gives the monocationic complexes **35** ($\text{R} = \text{H}$; $\text{X} = \text{N}_3, \text{Cl}$; $\text{Y} = \text{SbF}_6$).



2,2':6'',2''-Terpyridine with $[\text{MI}_2(\text{CO})_3(\text{AN})_2]$ ($\text{M} = \text{Mo}, \text{W}$) in methylene chloride gives the cationic complexes $[\text{M}(\text{CO})_3(\eta^3\text{-trpy})\text{I}]\text{I}$ ($\text{M} = \text{Mo}, \text{W}$) (00JOM(604)191). With $[\text{MoCl}(\text{GeCl}_3)(\text{CO})_3(\text{AN})(\text{PPh}_3)]$, the product is $[\text{Mo}(\text{GeCl}_3)(\text{CO})_2(\text{PPh}_3)(\eta^3\text{-trpy})]\text{Cl}$. 2,2':6'',6''-Terpyridine reacts with $[\text{MI}_2(\text{CO})(\text{AN})(\eta^2\text{-RC}_2\text{R})_2]$ ($\text{M} = \text{Mo}, \text{W}$; $\text{R} = \text{Ph}$; $\text{M} = \text{W}, \text{R} = \text{Me}$) to produce the cationic complexes $[\text{MI}(\text{CO})(\text{trpy})(\eta^2\text{-RC}_2\text{R})\text{I}]$ ($\text{M} = \text{Mo}, \text{R} = \text{Ph}$; $\text{M} = \text{W}, \text{R} = \text{Me}$) and $[\text{WI}(\text{trpy})(\eta^2\text{-PhC}_2\text{Ph})_2]\text{I}$. Complex $[\text{WI}(\text{CO})(\text{trpy})(\eta^2\text{-MeC}_2\text{Me})]\text{I}$ reacts with sodium tetraphenylborate to yield $[\text{WI}(\text{CO})(\text{trpy})(\eta^2\text{-MeC}_2\text{Me})](\text{BPh}_4)$.

Complex $[\text{Mo}(\text{CO})_3(\text{bpy})(\eta^1\text{-dppm})]$ (87JOM(331)23) with mercury(II) chloride gives the heterotrinnuclear derivative $[\text{Mo}(\text{CO})_3(\text{bpy})\text{Cl}]_2\text{Hg}$ (87POL1781, 90ICA(170)139). $[\text{Mo}(\text{CO})_3(\text{LL})(\eta^1\text{-dppm})]$ ($\text{LL} = \text{bpy}, \text{phen}$) (90JOM(382)397) react with HgX_2 ($\text{X} = \text{Cl}, \text{Br}, \text{CN}, \text{SCN}$) to yield $[\text{Mo}(\text{CO})_3(\text{LL})\text{X}]_2\text{Hg}$ ($\text{LL} = \text{bpy}, \text{phen}$; $\text{X} = \text{Cl}, \text{Br}, \text{CN}, \text{SCN}$) (91POL2611). Similar complexes follow from $[\text{Mo}(\text{CO})_3(\text{LL})(\text{L})]$ ($\text{LL} = \text{bpy}, \text{phen}$; $\text{L} = \text{N-}, \text{P-}, \text{or S-donor ligands}$) with HgX_2 ($\text{X} = \text{Cl}, \text{Br}$) (83JOM(247)293, 83JOM(254)325, 84JOM(266)247, 84JOM(270)311, 86JOM(311)145, 87POL1781). In contrast, with HgI_2 , the products are the dinuclear cationic complexes of composition $[\text{Mo}(\text{CO})_3(\text{LL})(\mu\text{-dppm})\text{HgI}]\text{HgI}_3$ ($\text{LL} = \text{bpy},$

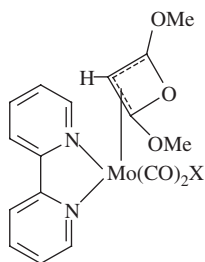
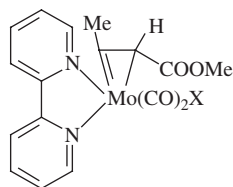
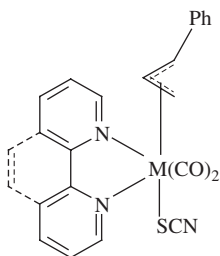
phen), and the 2,2'-bipyridine derivative is illustrated as **37** (91POL2611). $[\text{Mo}(\text{CO})_3(\text{LL})(\eta^1\text{-dppm})]$ (LL = 2,9-dimethyl-1,10-phenanthroline) reacts with HgX_2 (X = Cl, Br, CN, SCN) differently and affords $[\text{Mo}(\text{CO})_3(\text{LL})(\text{HgX})\text{X}]$ (LL = 2,9-dimethyl-1,10-phenanthroline; X = Cl, Br, CN, SCN). $[\text{Mo}(\text{CO})_3(\text{bpy})(\eta^2\text{-SO}_2)]$ (62GCI343, 83JA1883) enters substitution reactions with phosphines to yield $[\text{Mo}(\text{CO})_3(\text{bpy})(\text{PR}_3)]$ (R = OMe, *n*-Bu) (95ICA(240)99).

**37**

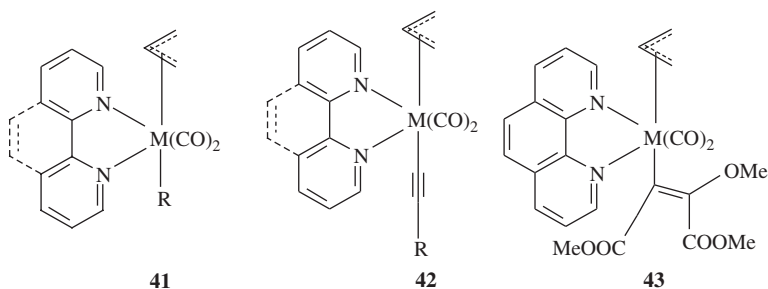
In $[(\text{OC})_5\text{Cr}(\mu\text{-}4,4'\text{-Me}_2\text{bpy})\text{Cr}(\text{CO})_5]$ the bipyridine ligand performs a very rare bridging function with violation of planarity (89ICA(157)151).

C. COMPLEXES CONTAINING ALLYL OR DIENE LIGANDS

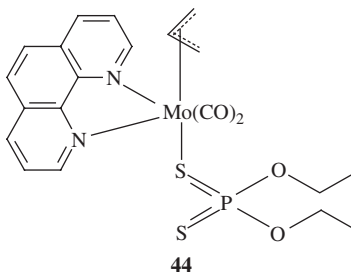
$[\text{Mo}(\text{CO})_4(\text{bpy})]$ enters an exchange reaction with halide ions to yield $[\text{Mo}(\text{CO})_3(\text{bpy})\text{X}]^-$ (X = Cl, Br) (86JCS(D)2405). The resulting anionic complexes $(\text{PPh}_4)[\text{Mo}(\text{CO})_3(\text{bpy})\text{X}]$ (X = Cl, Br) react with propargyl halides $\text{CH}\equiv\text{CCH}_2\text{Hal}$ to yield $[\text{Mo}(\text{CO})_2(\text{bpy})(\text{C}_5\text{H}_7\text{O}_2)\text{X}]$ (X = Cl, Br) proven to have structure **38** (X = Cl, Br) in solution equilibrium with **39**. $[\text{Mo}(\text{CO})_4(\text{bpy})]$ and $[\text{Mo}(\text{CO})_4(\text{phen})]$ react with 1-phenylallyl chloride to yield $[(\eta^3\text{-}1\text{-PhC}_3\text{H}_4)\text{Mo}(\text{CO})_2(\text{bpy})\text{Cl}]$ (86JOM(301)109). The product enters the ligand substitution reaction with potassium thiocyanate to form **40**.

**38****39****40**

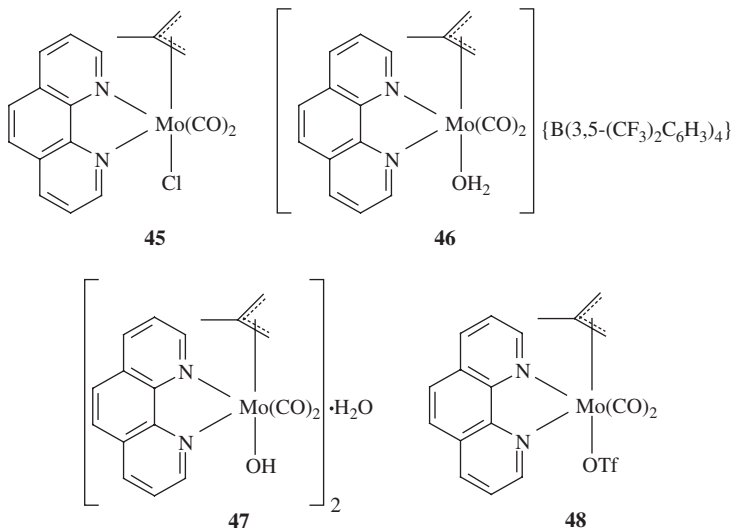
Complexes $[(\eta^3\text{-allyl})\text{Mo}(\text{CO})_2(\text{LL})\text{X}]$ (LL is a polypyridine ligand) are stable (84JOM(277)85, 95ADOC45, 02JCS(CC)384). The list of complexes for which comprehensive structural studies were fulfilled includes $[(\eta^3\text{-C}_3\text{H}_5)\text{W}(\text{CO})_2(\text{bpy})\text{Cl}]$, $[(\eta^3\text{-2-Me-C}_3\text{H}_4)\text{W}(\text{CO})_2(\text{bpy})\text{Cl}]$, $[(\eta^3\text{-C}_3\text{H}_5)\text{W}(\text{CO})_2(\text{bpy})(\text{OOCMe})]$, $[(\eta^3\text{-C}_3\text{H}_5)\text{W}(\text{CO})_2(\text{bpy})\text{Br}]$, $[(\eta^3\text{-C}_3\text{H}_5)\text{W}(\text{CO})_2(\text{phen})\text{Cl}]$, $[(\eta^3\text{-2-Me-C}_3\text{H}_4)\text{W}(\text{CO})_2(\text{phen})\text{Cl}]$, and $[(\eta^3\text{-C}_3\text{H}_5)\text{W}(\text{CO})_2(\text{phen})\text{Br}]$ (81JOM(219)53). A series of complexes $[(\eta^3\text{-C}_3\text{H}_4\text{R})\text{Mo}(\text{CO})_2(\text{bpy})\text{L}](\text{BF}_4)$ (R = H, Me; L = NH_3 , py, PPh_3 , AsPh_3 , $(\text{PhO})_3\text{P}$) was prepared (77JOM(129)175). Other similar complexes are $[(\eta^3\text{-C}_3\text{H}_4\text{R})\text{Mo}(\text{CO})_2(\text{bpy})(\text{py})]^+$ (R = H, Me) (67JOM(9)519) and $[\text{Mo}(\text{CO})_2(\text{phen})(\eta^3\text{-allyl})](\text{OTf})$ (96AX(C)77). $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{LL})\text{Cl}]$ (LL = bpy, phen) (67JOM(9)519, 68JOM(14)375, 77JOM(125)225) react with R_2Mg (R = Me, Et, PhCH_2) in THF to yield $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{LL})\text{R}]$ (LL = bpy, phen; R = Me, Et, PhCH_2) (01JA7469, 02OM1622). A complete series of complexes may be illustrated as **41** (R = Me, Et, CH_2Ph ; M = Mo, LL = bpy, phen; R = Me, Et, CH_2Ph ; M = W; LL = phen). Complexes $[(\eta^3\text{-C}_3\text{H}_5)\text{M}(\text{CO})_2(\text{LL})\text{Cl}]$ (M = Mo, LL = bpy, phen; M = W, LL = phen) react with $\text{M}'\text{C}\equiv\text{CR}$ (M' = Li, Na; R = Ph, SiMe_3 , H) giving rise to the alkynyl products **42** (M = Mo, LL = bpy, R = Ph, SiMe_3 , H; M = W, LL = phen, R = Ph, SiMe_3 , H). $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{LL})\text{Cl}]$ (LL = bpy, phen) react with carbanionic nucleophiles to yield stable alkyls (01JA7469). Reaction of $[(\eta^3\text{-C}_3\text{H}_5)\text{M}(\text{CO})_2(\text{phen})\text{Cl}]$ (M = Mo, W) with sodium methoxide gives $[(\eta^3\text{-C}_3\text{H}_5)\text{M}(\text{CO})_2(\text{phen})(\text{OMe})]$ (M = Mo, W) (02OM1750). Further reaction with dimethylacetylene dicarboxylate gives the insertion products **43** (M = Mo, W).

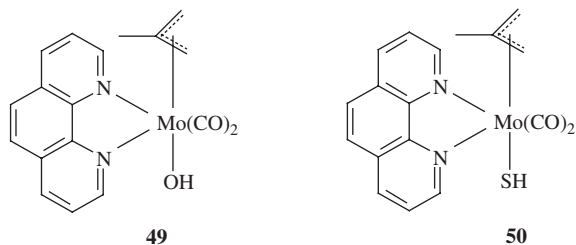


$[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{bpy})\text{Br}]$ with thallium hexafluorophosphate in acetonitrile gives $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{bpy})(\text{AN})](\text{PF}_6)$ (01JOM(632)197). $[(\eta^3\text{-C}_3\text{H}_5)\text{M}(\text{CO})_2(\text{bpy})\text{Br}]$ (M = Mo, W) reacts with *S,S*-donor ligands (*O*-alkyldithiocarbamates or xanthates, *N,N*-dialkyldithiocarbamates, and *N,N*-dialkyldithiocarbamates) by the bromide/*S,S*-ligand substitution route to yield the six-coordinate products $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{bpy})(\eta^1\text{-S,S})]$ where the *S,S*-ligands are η^1 -coordinated (81JOM(221)63). 1,10-Phenanthroline reacts with $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{AN})\text{P}\{\eta^2\text{-S}_2\text{P}(\text{OEt}_2)\}]$ to yield **44** (02JOM(658)191). Other molybdenum allyl complexes are $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{phen})(\eta^1\text{-OTf})]$ (97OM942) and $[(\eta^3\text{-C}_5\text{H}_7)\text{Mo}(\text{CO})_2(\text{phen})(\text{AN})](\text{BF}_4)$ (90OM1862).

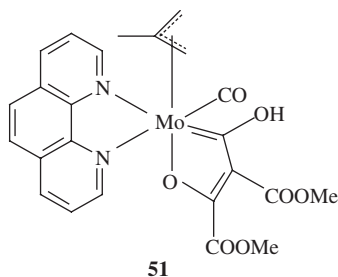


The reaction of $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{phen})(\text{OTf})]$ with $\text{NaB}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4$ gives cationic complexes $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{H}_2\text{O})(\text{CO})_2(\text{phen})](\text{B}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4)$ (**02OM1540**). Complex **45** (**77JOM(129)175**) reacts with water and $\text{NaB}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4$ in ether/hexane medium to yield **46** (**02OM4934**). The water ligand is labile and easily replaceable by acetonitrile to yield $[(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})\text{Mo}(\text{CO})_2(\text{phen})(\text{AN})](\text{B}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4)$. The aqueous complex **46** also reacts with strong bases (*n*-BuLi, $\text{K}\{\text{N}(\text{SiMe}_3)_2\}$) to give the neutral hydroxo complex **47** in the form of a hydrate. Another route to complex **47** is the interaction of **45** with potassium hydroxide in methylene chloride/water. Treatment of **47** with triflic acid affords the neutral complex **48** when the water ligand formed on protonation is released and substituted by the triflate anion of the acid. The reaction of $[(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})\text{Mo}(\text{H}_2\text{O})(\text{CO})_2(\text{phen})](\text{B}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4) \cdot \text{Et}_2\text{O}$ with $[(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})\text{Mo}(\text{OH})(\text{CO})_2(\text{phen})]_2(\mu\text{-H}_2\text{O})$ gives $[(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})\text{Mo}(\text{CO})_2(\text{phen})]_2(\mu\text{-OH})](\text{B}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4)$. $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{bpy})\text{Cl}]$ reacts with various nucleophilic ligands in the presence of silver tetrafluoroborate to yield the seven-coordinate complexes $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{bpy})\text{L}](\text{BF}_4)$. In the absence of the nucleophilic ligand, the product is the dinuclear complex $[(\eta^3\text{-C}_3\text{H}_5)(\text{OC})_2(\text{bpy})\text{Mo}(\mu\text{-Cl})\text{Mo}(\text{bpy})(\text{CO})_2(\eta^3\text{-C}_3\text{H}_5)](\text{BF}_4)$ containing the bridging chloride ligand (**84JOM(272)43**). Neutral complex **49** on reaction with carbon disulfide gives **50** (**03JCS(CC)328**).

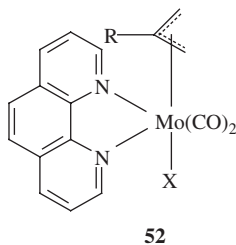


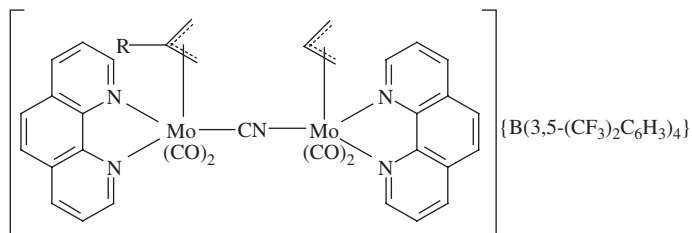


$[(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})(\text{CO})_2(\text{phen})]$ reacts with *p*-tolyl isocyanide to afford an adduct of the carbonato-bridged complex $[(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})(\text{OC})_2(\text{phen})\text{Mo}(\mu\text{-}\eta^1(\text{O}), \eta^1(\text{O})\text{-CO}_3)\text{Mo}(\text{phen})(\text{CO})_2(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})]$ and *N,N'*-di-*p*-tolylurea (04CEJ1765). The reaction of $[(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})(\text{CO})_2(\text{phen})(\text{OH})]$ with *p*-tolyl isothiocyanate results in the insertion of *p*-TolNCS into the Mo–O bond, and the product is $[(\eta^3\text{-C}_3\text{H}_4\text{-Me-2})(\text{CO})_2(\text{phen})\{\text{SC}(\text{O})\text{NH}(\textit{p}\text{-Tol})\}]$. The starting hydroxo-complex also reacts with dimethyl acetylenedicarboxylate to yield the metallacyclic product **51** where coupling embraces the entering acetylene derivative as well as the carbon monoxide and hydroxo ligands.

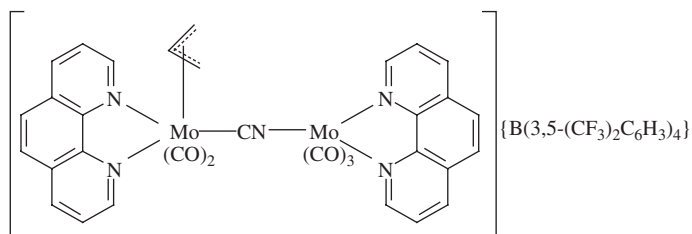


Complexes **52** ($\text{R} = \text{H, Me; X} = \text{Cl}$) (75JCS(D)1999) with sodium cyanide in methylene chloride form **52** ($\text{R} = \text{H, Me; X} = \text{CN}$) (03EJI1113). Interaction of **52** ($\text{R} = \text{H, X} = \text{OTf}$) with **52** ($\text{R} = \text{H, Me; X} = \text{CN}$) in the presence of $\text{NaB}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4$ gives the dinuclear cationic complexes **53** ($\text{R} = \text{H, Me}$) bearing the bridging cyano group, which is stable with respect to $\text{CN} \rightleftharpoons \text{NC}$ isomerization. The starting cyano molybdenum complex **52** ($\text{R} = \text{H, X} = \text{CN}$) also reacts with $[\text{M}(\text{CO})_3(\text{bpy})(\text{OTf})]$ ($\text{M} = \text{Mn, Re}$) and $\text{NaB}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4$ to afford the heterodinuclear complexes **54** ($\text{M} = \text{Mn, Re}$). Complex $[\text{Re}(\text{CO})_3(\text{bpy})(\text{OTf})]$ with tetraethylammonium cyanide gives $[\text{Re}(\text{CO})_3(\text{bpy})(\text{CN})]$ (91IC3722), and then with **52** ($\text{R} = \text{H, X} = \text{OTf}$) in the presence of $\text{NaB}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4$ it yields the heterodinuclear complex **54** ($\text{M} = \text{Re}$).





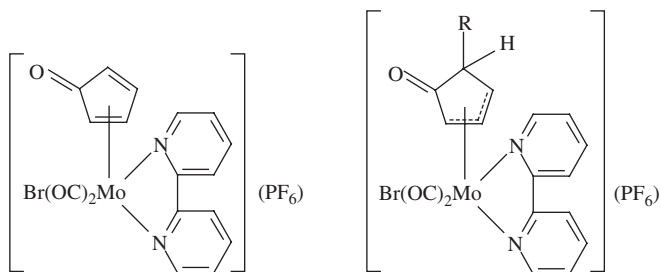
53



54

Reaction of $(\text{Ph}_4\text{P})[\text{Mo}(\text{CO})_3(\text{bpy})\text{Cl}]$ with $\text{ClCH}_2\text{C}\equiv\text{CCH}_2\text{Cl}$ in methanol gives $[\text{Mo}(\text{CO})_2(\text{bpy})\text{Cl}(\eta^3\text{-CH}_2\text{C}(\text{COOMe})\text{C}=\text{CH}_2)]$ containing a butadienyl ligand (88JOM(344)C8). $(\text{Ph}_4\text{P})[\text{Mo}(\text{CO})_3(\text{bpy})\text{Cl}]$ in methanol/THF reacts with excess amine $\text{RR}'\text{NH}$ ($\text{R} = \text{Me}, \text{Et}, n\text{-Pr}, \text{CH}_2\text{CH}=\text{CH}_2, \text{CH}_2\text{C}\equiv\text{CH}, \text{R} = \text{H}; \text{R} = \text{R}' = \text{Me}, \text{Et}, n\text{-Pr}$) and then 1,4-dichlorobut-2-yne to give $[\text{Mo}(\text{CO})_2(\text{bpy})\text{Cl}(\eta^3\text{-CH}_2\text{C}(\text{CONRR}')\text{C}=\text{CH}_2)]$. $[\text{Mo}(\text{CO})_2(\text{bpy})\text{Cl}(\eta^3\text{-CH}_2\text{C}(\text{CONHMe})\text{C}=\text{CH}_2)]$ with sodium hexafluorobutyrate and silver tetrafluoroborate in acetone gives $[\text{Mo}(\text{CO})_2(\text{bpy})(\text{OOC}_3\text{F}_7)(\eta^3\text{-CH}_2\text{C}(\text{CONRR}')\text{C}=\text{CH}_2)]$.

Complex **55** (96OM181) reacts with a range of phosphines (trimethyl-, tricyclohexyl-, and triphenylphosphine) to yield **56** ($\text{R} = \text{PMe}_3, \text{PCy}_3, \text{PPh}_3; z = 1$) (96OM2954). With $\text{PPh}_2\text{C}_2\text{H}_4\text{NMe}_2$ the product is **56** ($\text{R} = \text{PPh}_2\text{C}_2\text{H}_4\text{NMe}_2, z = 1$) and with $\text{LiSMe}, \text{LiSPh}, \text{LiHC}(\text{COOMe})_2$ it is **56** ($\text{R} = \text{SMe}, \text{SPh}, \text{CH}(\text{COOMe})_2; z = 0$).

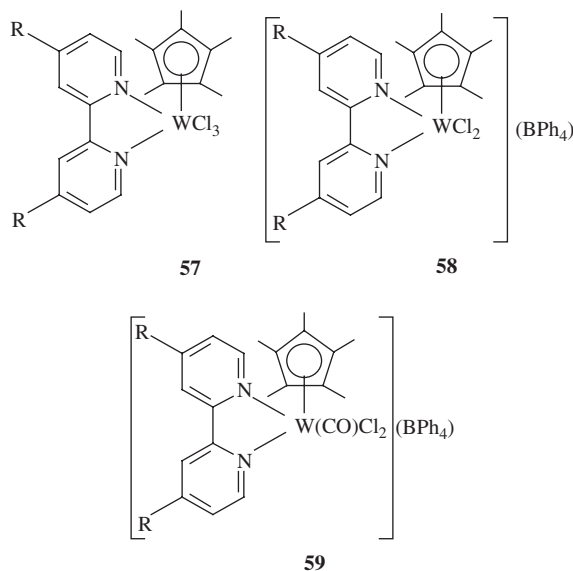


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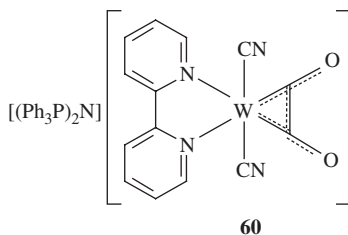
2,2'-Bipyridine with $[(\eta^5\text{-Cp})\text{Mo}(\text{CO})_2\text{Br}_3]$ gives $[(\eta^5\text{-Cp})\text{Mo}(\text{bpy})\text{Br}_3]$ (66JCS(A) 1606). In a similar fashion, 4,4'-disubstituted 2,2'-bipyridines react with $[(\eta^5\text{-Cp}^*)\text{W}(\text{CO})_2\text{Cl}_3]$ to yield tungsten(IV) complexes **57** ($\text{R} = \text{Me}, t\text{-Bu}, \text{NMe}_2$) (97C650, 99JCS(D)1967). An alternative way to these products starts with $[(\eta^5\text{-Cp}^*)\text{WCl}_4]$,

which with $(\text{Me}_2\text{N})_2\text{C}=\text{C}(\text{NMe}_2)_2$ gives $[\eta^5\text{-Cp}^*)\text{WCl}_3]_2$ and subsequent reaction with bipyridines gives **57** ($\text{R} = \text{Me}, t\text{-Bu}, \text{NMe}_2$). Complexes **57** ($\text{R} = \text{Me}, \text{NMe}_2$) react with sodium tetraphenylborate in THF to produce the cationic complexes **58** ($\text{R} = \text{Me}, \text{NMe}_2$) (99JCS(D)1967). The complex with $\text{R} = \text{Me}$ is very water-sensitive and even under special precautions tends to form the dimer $[\{(\eta^5\text{-Cp}^*)\text{W}(4,4'\text{-Me}_2\text{bpy})\}_2(\mu\text{-O})(\mu\text{-Cl})_2]^{2+}$. Complexes **58** ($\text{R} = \text{Me}, \text{NMe}_2$) readily add carbon monoxide in methylene chloride. Partial carbonylation occurs to yield **59** ($\text{R} = \text{Me}, \text{NMe}_2$).



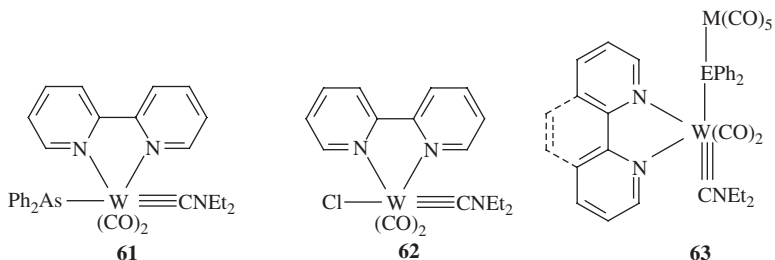
D. CARBYNE COMPLEXES

$[\text{W}(\text{CO})_2(\text{LL})(\equiv\text{CR})\text{Br}]$ ($\text{LL} = \text{bpy}, \text{phen}; \text{R} = \text{Me}, \text{Ph}$) react with potassium cyanide to yield the η^2 -ketenyl complexes **60** isolated as the $(\text{Ph}_3\text{P})_2\text{N}^+$ -salts (83JOM(254)C1, 84JOM(276)377).

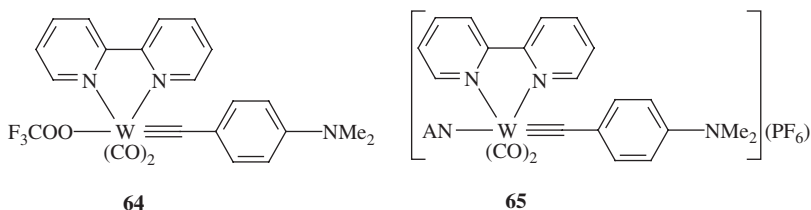


$[\text{W}(\text{CO})_2(\text{LL})(\equiv\text{CNEt}_2)\text{Br}]$ ($\text{LL} = \text{bpy}, \text{phen}$) with potassium cyanide give the cyanide/bromide substitution product to yield $[\text{W}(\text{CO})_2(\text{LL})(\equiv\text{CNEt}_2)(\text{CN})]$ (85JOM(296)69). $[\text{W}(\text{CO})_2(\text{bpy})(\equiv\text{CNEt}_2)\text{Br}]$ reacts with NaAsPh_2 to yield the product of substitution of the halide ligand, the carbyne complex **61** (86JOM(308)11).

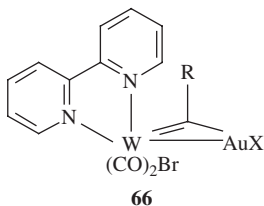
Nucleophilic attack of methylene chloride on the product at low temperatures leads to **62**. $[\text{W}(\text{CO})_2(\text{LL})(\equiv\text{CNEt}_2)\text{Br}]$ (LL = bpy, phen) reacts with $[\text{M}(\text{CO})_5(\text{EPh}_2)]^-$ (M = Cr, Mo, W; E = P, As, Sb) followed by substitution of the bromide ligand and formation of **63** (M = Cr, Mo, W; E = P, As, Sb; LL = bpy, phen) where the P, As, and Sb heteroatoms form bridges between two metals (87JOM(326)59). $[\text{W}(\text{CO})_2(\text{LL})(\equiv\text{CNEt}_2)\text{I}]$ (LL = bpy, phen) with $\text{Na}_2\text{S}_2\text{C}_2(\text{CN})_2$ results in substitution of the iodide ligand and elimination of the chelating polypyridine ligand LL. The product is the five-coordinated anionic carbyne complex $[\text{W}(\text{CO})_2\{\text{S}_2\text{C}_2(\text{CN})_2\}(\equiv\text{CNEt}_2)]^-$ (87JOM(330)C1). $[\text{W}(\text{CO})_2(\text{LL})(\equiv\text{CNEt}_2)\text{I}]$ (LL = bpy, phen) also reacts with phosphines, PR_3 (R = Me, Et) to give the cationic complexes $[\text{W}(\text{CO})_2(\text{LL})(\equiv\text{CNEt}_2)(\text{PR}_3)]\text{I}$ (LL = bpy, phen; R = Me, Et) (88JOM (340)331).



$[\text{W}(\text{CO})_2(\text{OOCFCF}_3)(\text{NC}_5\text{H}_4\text{Me-4})_2(\equiv\text{CC}_6\text{H}_4\text{NMe}_2-4)]$ with 2,2'-bipyridine in methylene chloride gives the ligand substitution product **64** (05OM707). In acetonitrile, in the presence of thallium hexafluorophosphate, the displacement of the F_3COO ligand occurs, and the cationic complex **65** results.

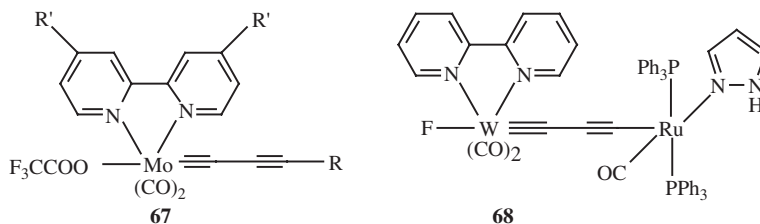


Alkylidyne complex $[\text{W}(\equiv\text{CC}_6\text{H}_4\text{Me-4})(\text{CO})_2(\text{bpy})\text{Br}]$ reacts with $[\text{Au}(\text{C}_6\text{F}_5)$ (THT)] or $[\text{AuCl}(\text{THT})]$ to yield the heterodinuclear complexes with a tungsten-gold bond, **66** (X = C_6F_5 , Cl) (88JCS(D)1957).



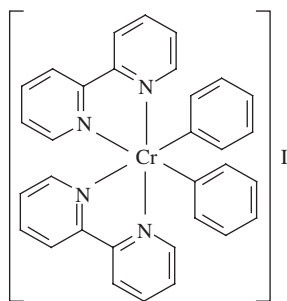
2,2'-Bipyridine and 4,4'-dimethyl-2,2'-bipyridine (LL) react with alkynylcarbyne complexes $[\text{M}(\text{CO})_4(\text{OTf})(\equiv\text{CC}\equiv\text{CR})]$ (M = Mo, W; R = SiMe_3 , Ph, *p*-Tol, *t*-Bu) to yield **67** (M = W, Mo; R = SiMe_3 , Ph, *p*-Tol, *t*-Bu; R' = H, Me) (03JOM(667)16).

$[\text{W}(\text{CO})_2(\text{bpy})(\equiv\text{CC}\equiv\text{CSiMe}_3)\text{F}]$ with tetra-*n*-butylammonium fluoride followed by $[\text{RuHCl}(\text{CO})(\text{HPz}^*)(\text{PPh}_3)_2]$ gives the heterodinuclear complex **68** (04AGE476).

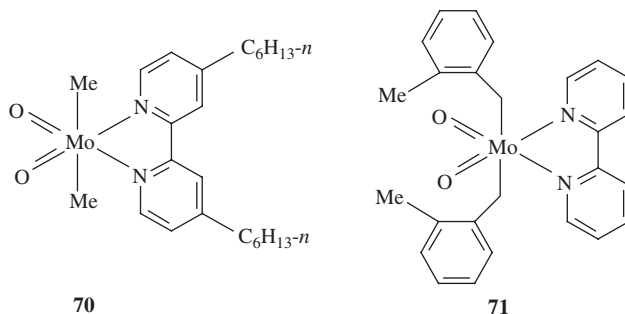


E. COMPLEXES WITH ALKYL AND ARYL LIGANDS

Complexes *cis*- $[(\text{Ar})_2\text{Cr}(\text{bpy})_2]\text{I}$ (Ar = Ph, 2-, 3-, and 4-MeOC₆H₄, 4-MeC₆H₄, Ph), *cis*- $[(2\text{-MeOC}_6\text{H}_4)_2\text{Cr}(\text{bpy})_2]\text{I} \cdot \text{H}_2\text{O}$, and $[(\text{Me}_3\text{SiCH}_2)_2\text{Cr}(\text{bpy})_2]\text{I}$ are stable (72JCS(D)2584, 73HCA503, 73JCS(D)73, 73JCS(D)1497, 73JOM(47)125, 02OM2800). One representative of this group is illustrated, **69**.

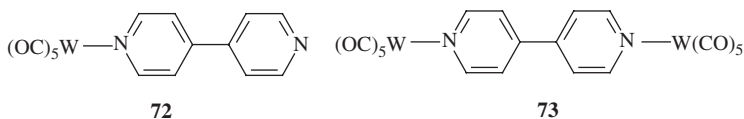


$[\text{MoO}_2\text{Cl}_2(4,4'\text{-bis-}n\text{-hexyl-2,2'\text{-bipyridine})]$ in ether at -25°C reacts with methylmagnesium chloride to yield **70** (02JOM(649)108). $[\text{MoO}_2\text{Br}_2(\text{bpy})]$ reacts with *p*-methyl or *p*-ethylbenzyl magnesium bromide to give the molybdenum(VI) dioxo complexes $[\text{MoO}_2(p\text{-RC}_6\text{H}_4\text{CH}_2)_2(\text{bpy})]$ (R = Me, Et) (95TMC426). *o*-MeC₆H₄CH₂Li · Et₃N gives complex **71**. Other $[\text{MoO}_2\text{R}_2(\text{bpy})]$ complexes include those with R = Me (82OM44), Et (86OM2452), *t*-Bu (85OM481), and CH₂Ph (83OM1163).



F. COMPLEXES WITH 4,4'-BIPYRIDINE LIGANDS

1,2-Bis(4-pyridyl)ethane or 4,4'-bipyridine with $[\text{W}(\text{CO})_6]$ in hexane on UV irradiation gives both mononuclear, **72**, and binuclear, **73**, complexes illustrated for 4,4'-bipyridine (00POL1621).



Anion-radicals of 4,4'-bipyridine and 1,2-bis(4-pyridyl)ethylene (LL) react with $[\text{M}(\text{CO})_6]$ ($\text{M} = \text{Mo}, \text{W}$) in THF and DME to give the dinuclear anion-radical complexes $[(\text{OC})_5\text{M}(\mu\text{-LL})\text{M}(\text{CO})_5]^-$ (81ICA(53)L151, 82CB910, 90IC2909). 4,4'-Bipyridine with $[\text{Mo}(\text{CO})_6]$ forms the polymeric complex $[\text{Mo}(\text{CO})_4(4,4'\text{-bpy})]_n$ (85POL69). Equimolar amounts of $[\text{Mo}(\text{CO})_5(\text{THF})]$ and 4,4'-bipyridine in methylene chloride give $[\text{Mo}(\text{CO})_4(4,4'\text{-bpy})]$, but using an excess of $[\text{Mo}(\text{CO})_5(\text{THF})]$ gives $[\text{Mo}(\text{CO})_4(\text{bpy})]_n$. Bis(4-pyridyl)ethylene (LL) on reaction with $[\text{Mo}(\text{CO})_4(\text{nbd})]$, however, gives the dinuclear complex $[(\text{OC})_4\text{Mo}(\mu\text{-LL})\text{Mo}(\text{CO})_4]$, but with 4,4'-bipyridine the product is again the polymeric complex stated above. $[\text{Mo}(\text{CO})_4(\text{bpy})]$ with both 4,4'-bipyridine and bis(4-pyridyl)ethylene (LL) yields dinuclear complexes of composition $[(\text{OC})_3(\text{bpy})\text{Mo}(\mu\text{-LL})\text{Mo}(\text{CO})_3(\text{bpy})]$. The list of known dinuclear complexes includes $[(\text{OC})_5\text{W}(\mu\text{-}4,4'\text{-bpy})\text{W}(\text{CO})_5]$ (89IC85, 94JCS(D)2217, 95JCS(D)2711) $[(\text{OC})_5\text{W}\{\mu\text{-}1,2\text{-bis}(4\text{-pyridyl})\text{ethylene}\}\text{W}(\text{CO})_5]$, $[(\text{OC})_5\text{W}\{\mu\text{-}1,2\text{-bis}(4\text{-pyridyl})\text{ethane}\}\text{W}(\text{CO})_5]$ (89IC85), $[(\text{OC})_5\text{M}(\mu\text{-LL})\text{M}(\text{CO})_5]$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$; $\text{LL} = 4,4'\text{-bipyridine}, 1,2\text{-bis}(4\text{-pyridyl})\text{ethylene}, 1,2\text{-bis}(4\text{-pyridyl})\text{ethane}$) (88IC1139), $[(\text{OC})_n\text{M}(\mu\text{-LL})\text{M}(\text{CO})_n]$ ($n = 4, 5$; $\text{M} = \text{Cr}, \text{Mo}, \text{W}$) (82POL53, 83POL279, 86IC3306, 86JA3578, 87IC210, 87POL1673, 88IC200), tungsten carbonyls containing 4,4'-dipyridylbutadiyne, and 1,4-bis(4'-pyridylethynyl)benzene (95IC2323).

V. Conclusion

Polypyridine ligands stabilize complexes of metals of Groups VB and VIB in their low oxidation states forming stable species with interesting photochemical and electrochemical properties. They nearly always form chelates with η^2 -coordination, and all the chemical changes occur in the rest of the complex. However, the coordination situations may vary and the structure of the polypyridine ligand may be modified, which opens new areas of application.

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