Thienopyridines: synthesis, properties, and biological activity*

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The current state and prospects of development of the chemistry of isomeric thienopyridines (synthesis, chemical transformations, and biological activities) are analyzed. Particular attention is given to studies published in the last 10—15 years.

Key words: isomeric thienopyridines, synthesis, pyridine and thiophene ring closure, chemical transformations, biological activity.

Introduction

In organic chemistry, derivatives of pyridine and its fused analogs attract considerable interest because of their great practical usefulness, primarily, due to their various biological activities. In the paper devoted to the 150th anniversary of the pyridine chemistry,[1] E. Lukevics noted that compounds containing the pyridine or piperidine ring accounted for more than 10% out of 1500 medicines most regularly used at the end of the 20th century. Among these medicines are vitamins (B_3, B_6, and PP), analgetics, analeptics, antiarrhythmics, antiseptics, antidepressants, spasmolytics, neuroleptics, tranquilizing agents, and drugs having other pharmacological activities. In the recent monograph on the chemistry of pyridine bases,[2] the authors stated that pyridine and its homologs are among the most important reagents for the fine and industrial organic synthesis, which are widely used in chemical and petrochemical industry, as well as in production of dyes, pharmaceuticals, agents for chemical plant protection, surfactants, acid corrosion inhibitors, ion-exchange resins, selective sorbents, and extractants. Among pyridine derivatives, its fused analogs are often of much greater interest from the standpoint of biological activity than the corresponding constituent monocyclic compounds. Qualitatively new properties of annelated molecules, greater possibilities of varying pharmacophoric groups in different positions of the molecules, and the ability of such molecules to react with a wider range of receptors adopting different conformations play a decisive role. In addition, these factors are supplemented with variations in the molecular structure due to annelation at different positions of the heterocyclic fragments. Among these heterocyclic systems, thienopyridines occupy a special place and have attracted considerable attention, which was reflected in the reviews,[1—43] monographs,[44—46] and other publications.[47,48]

This notwithstanding, the data in this field of chemistry have been summarized only within narrow-subject areas. However, recent years have witnessed a tremendous growth of 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,[49] who used the Skraup reaction starting from 2-aminothiophene, up to the publication of the most comprehensive review[3] on these heterocyclic systems by Barker (in 1977), whereas more than 800 publications, including patents, appeared in the literature during the last 10 years. The importance of this field of heterocyclic chemistry and the lack of a summary analysis of its current state in the world literature gave impetus to the present review, where data on the synthesis, reactivity, and biological activities of isomeric thienopyridines (which have been published primarily in the last 10—15 years) are systematized and analyzed for the first time. Emphasis is given to studies, in which the most general and promising approaches to the synthesis of the target structures were considered and data on the properties and biological activities were published. The scope of our review does not include all publications on the chemistry of thienopyridines and complete bibliography, and only the most interesting studies in narrow-subject areas are considered.

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* Dedicated to Academician V. I. Minkin on the occasion of his 70th birthday.

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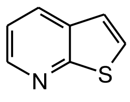
Thienopyridines

Six isomeric thienopyridine structures characterized by different annelation 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 most detail. Data on the "isostructural" isomers **5** and **6** are scarce and disembodied and they are beyond the scope of the present review.



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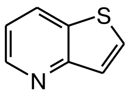

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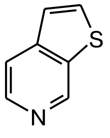

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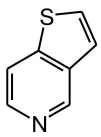

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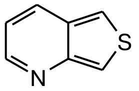

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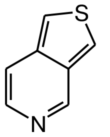


6

1. Thieno[2,3-*b*]pyridines

As remarked above, thieno[2,3-*b*]pyridines (and thienopyridines, as such) were mentioned for the first time in 1913.[49] Nowadays, after a lapse of ninety 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 rather broad and includes antiinflammatory, antidepressant, antibacterial, antimicrobial, antiviral, and antitumor activities. In addition, certain derivatives of thienopyridine **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, anticonvulsants and mutagens, drugs for the treatment of dysmnesia, 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.

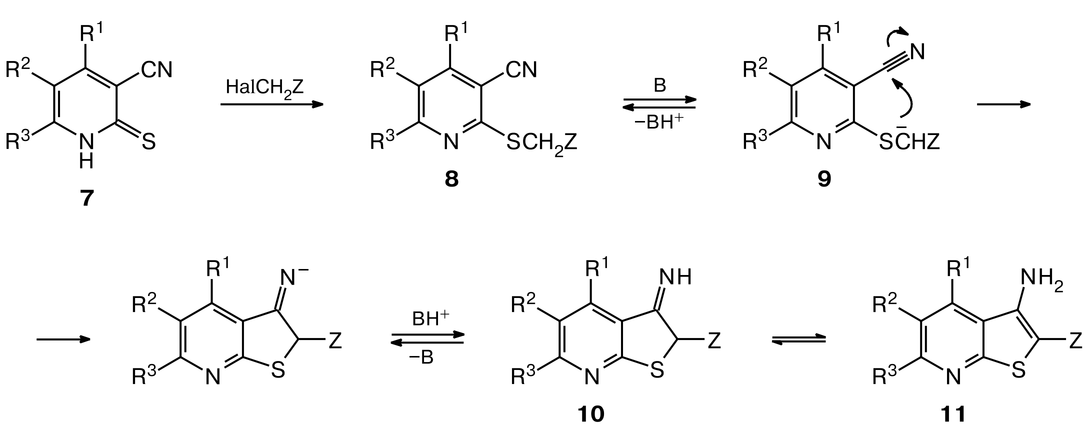
The available elegant and preparatively convenient methods for the synthesis of thieno[2,3-*b*]pyridine (**1**) and its analogs **2**—**4** have played a considerable role in the development of chemistry of these compounds. These approaches include the thiophene ring closure based on pyridine derivatives and the pyridine ring closure based on thiophene derivatives.

1.1. 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(1*H*)-thiones (**7**) are readily accessible, diverse 3-cyanopyridine-2(1*H*)-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 Scheme 1.[39,45]

The electron-withdrawing effect of the substituent Z, which is responsible for stability and the concentration of

Scheme 1



Z is an electron-withdrawing group, B is a base.

carbanion **9**, is the main factor determining the cyclization rate. The tautomeric equilibrium **10** $\rightleftharpoons$ **11** is completely shifted to amino form **11**. It was empirically established that the activity of the electron-withdrawing substituents Z decreases in the following series:[4,39]

$NO_2 > ArC(O) > CN > COOR > C(O)NH_2 > H$.

Some general preparative aspects of cyclization, such as the choice of catalysts, solvents, *etc.*, have been described earlier.[4,39] 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 in a wide range. 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 the reagents of choice. The Na_2CO_3/EtOH,[50] K_2CO_3/acetone,[51] 7% MeONa/EtOH,[52] KOH/EtOH/H_2O,[53] AcONa/anhydrous EtOH,[54] Et_3N/dioxane,[55] Et_3N/EtOH,[55,56] and Et_3N/DMSO[57] systems are used more rarely. In these reactions both excess and catalytic amounts of bases are used. Sometimes, the ring closure occurs spontaneously already 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 already at room temperature, although heating is required in certain reactions. Examples of cyclization in refluxing pyridine[51a,58] and under phase-transfer catalysis conditions[59] with the use of $Bu_4N^+Br^-$ are known.

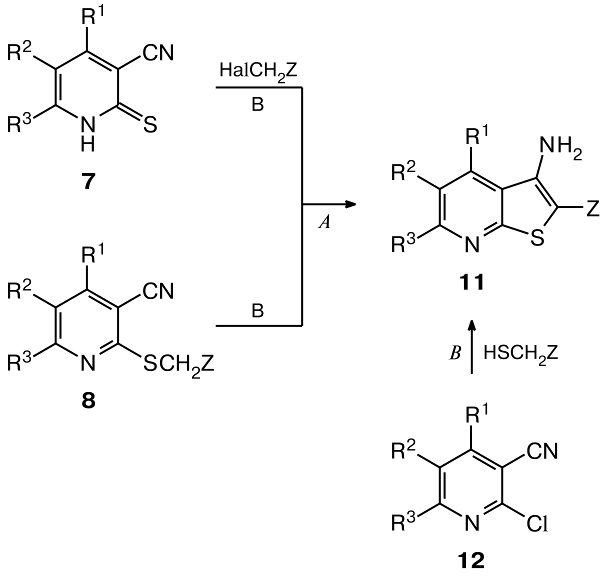
Based on the structures of the starting reagents, several main pathways of formation (*A—C*) of the thiophene ring by the Thorpe reaction can be proposed (Scheme 2).

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 of this method is based on cyclization without intermediate isolation of 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 the nucleophilic substitution followed by the 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.

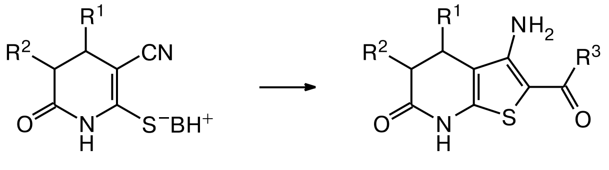
Scheme 2



The method *A* has a very wide application and was used to prepare various derivatives of thieno[2,3-*b*]pyridine (**1**) and related systems, such as quinoline, isoquinoline, cyclopentano[*b*]pyridine (pyrindine), *etc.*

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 essential complications to give lactams **14** as the final products.[60]

Scheme 3



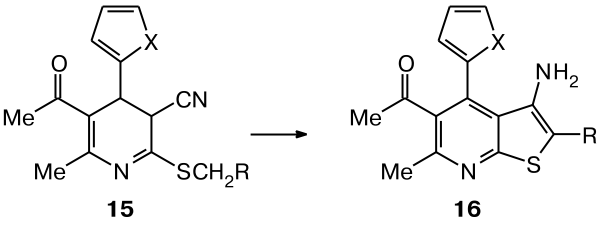
R^1 = H, Ar, Het; R^2 = H, CN, COOEt; R^3 = NH_2, Ar, Het.

Reagents: $HalCH_2C(O)R^3$, KOH, Et_3N, or EtONa.

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** (Scheme 4).[61] However, numerous data on the synthesis of partially hydrogenated pyridine-2(1*H*)-thiones and their derivatives summarized in the reviews[16,18,39] 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.

Scheme 4

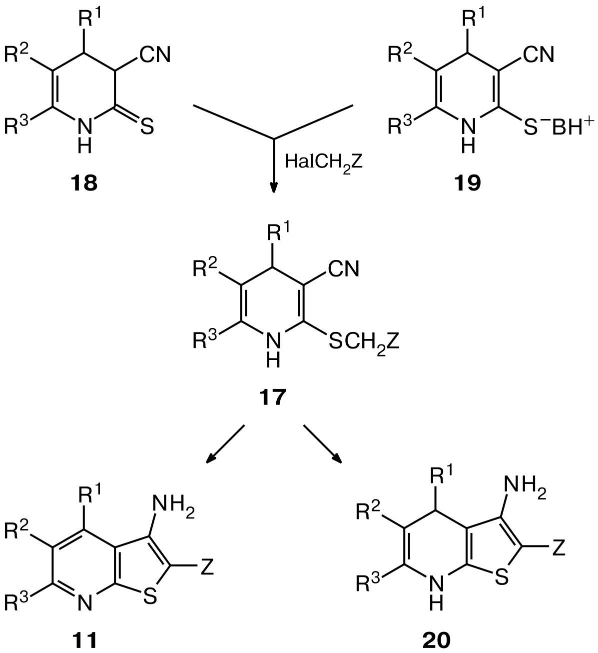


X = O, S; R = Ac, Bz, OH.

Reagents: KOH, MeOH, or EtOH.

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 finally both 4,7-dihydrothieno[2,3-*b*]pyridines **20**[62] and their aromatic analogs **11**,[63] which are generated, evidently, due to oxidation of the hydrogenated pyridine system with atmospheric oxygen (Scheme 5). The conditions, under which the reaction produces compounds **11**, were not reliably determined. Most likely, 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, and the solution of this problem requires additional investigation.

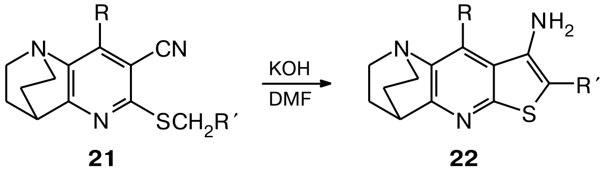
Scheme 5



R^1 = Me, Ar, Het; R^2 = C(O)NHAr, COOEt; R^3 = Me, NH_2; $R^2 + R^3$ = $C(O)CH_2CMe_2CH_2$; Z = CN, COOEt, $CONH_2$, $C(NCN)NH_2$, C(O)Ar, C(O)NHAr.

The Thorpe reaction of 2-alkylthiopyridoquinuclidines **21** resulting in its isomerization to form the corresponding thienopyridoquinuclidines **22** (Scheme 6)[64] is another example of the construction of the thieno[2,3-*b*]pyridine system according to the method *A*.

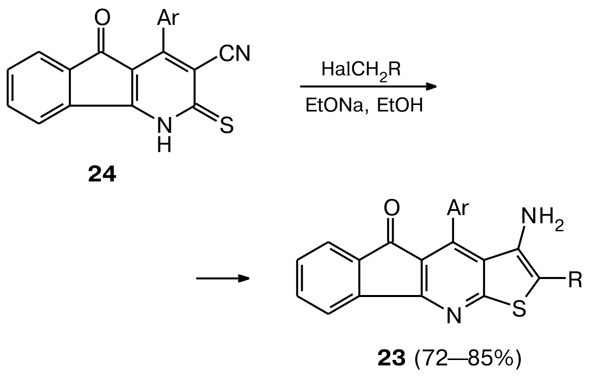
Scheme 6



R = H, Ar; R′ = CN, $C(NH_2)$=N(CN).

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** (Scheme 7).[65] It should be noted that compounds **23** have been synthesized according to the same procedure three years earlier.[66] However, the latter study is not an original work as well, because this transformation was described[67] as early as 1990.

Scheme 7



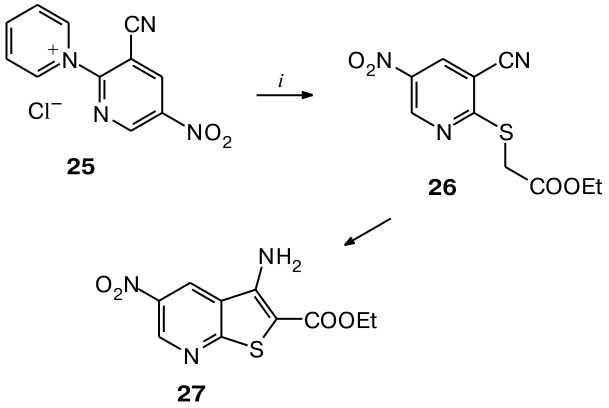
R = COOEt, Bz, $CONH_2$.

The method *B*, which involves the replacement of the halogen atom by a sulfur-containing nucleophile in

2-chloro-3-cyanopyridines **12** followed by Thorpe cyclization, is used more rarely (see, for example. Refs 50 and 68). Evidently, the reason is that *S*-nucleophiles, *viz*., thioglycolic acid derivatives, are less accessible compared to diverse alkylating agents used in the 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, the 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, ester) in alcoholic medium (EtOH or MeOH) in the presence of an excess of a base over a long period of time. In this reaction, MeONa,[68b] EtONa,[68c,68d] Na_2CO_3,[60,68a] or K_2CO_3 [68e] can be used as a base. A decrease in the heating time,[68e] the use of the AcONa—EtOH system at room temperature,[68i,68j] or the reaction in DMF in the presence of KOH [68f] or K_2CO_3 [68g] allow isolation of linear intermediates **8**, which undergo cyclization under the action of EtONa in hot ethanol. Nevertheless, it was demonstrated[68k] that, in some cases, spontaneous cyclization occurs even under rather mild conditions (K_2CO_3, 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 (Scheme 8).[68m]

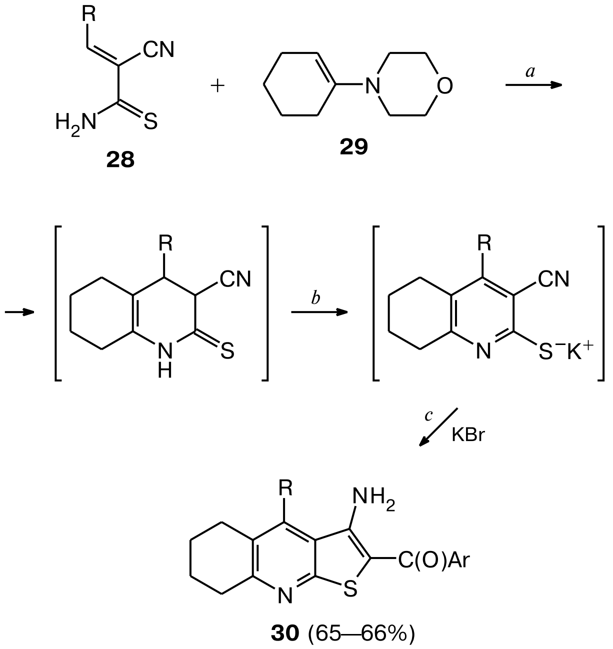
Scheme 8



i. $HSCH_2COOEt$, Et_3N, or AcONa.

Examples of the synthesis of thieno[2,3-*b*]pyridines according to the 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 of the reaction mixture with a twofold excess of KOH and then with α-bromo ketones produced thienoquinolines **30** (Scheme 9).[69]

Scheme 9



R = 2-(5-Ph-furyl), 2-thienyl; Ar = 4-ClC_6H_4, 4-MeC_6H_4.

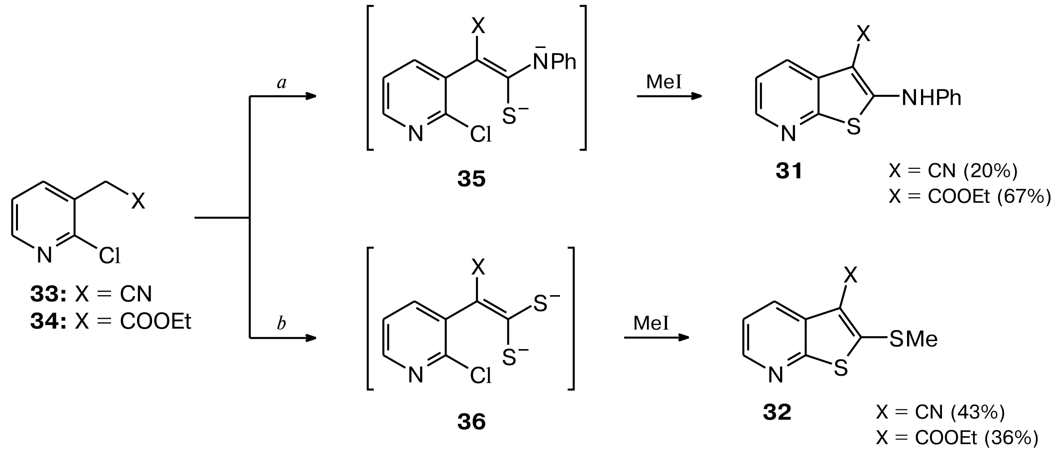
Reagents and conditions: *a*) EtOH, 20 °C, 4 h; *b*) 10% KOH (2 equiv.), EtOH; *c*) $ArC(O)CH_2Br$, EtOH.

A method, which was used to prepare four of six possible thienopyridines,[70] 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, *viz*., carbon disulfide and phenyl isothiocyanate (Scheme 10). The reaction proceeds through the formation of the corresponding dianions **35** and **36** followed by cyclization through the intramolecular nucleophilic substitution of the chlorine atom.

1.2. Pyridine ring closure in thiophene derivatives

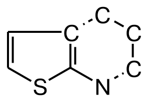
The most widely employed methods for the construction of the pyridine ring are based on the use of

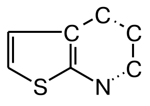
Scheme 10



Reagents and conditions: *a*) PhNCS, N_2, NaH, DMSO, 100 °C; *b*) CS_2, N_2, NaH, DMSO, Δ.

2-aminothiophene derivatives. Some examples of the construction of the thieno[2,3-*b*]pyridine system were given in the reviews.[13,14,38] 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.


A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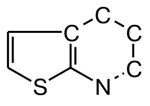
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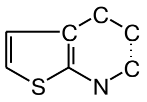
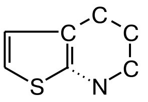

D

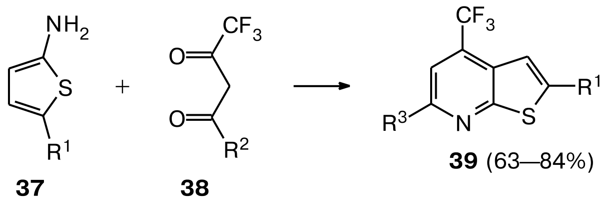

E

The method *A* is based on the use of 3-unsubstituted 2-aminothiophenes or their precursors. For example, heating of 2-aminothiophenes **37** and dicarbonyl compounds **38** led to their regioselective cyclocondensation to form 4-trifluoromethylthieno[2,3-*b*]pyridines **39** (Scheme 11).[71]

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** (Scheme 12).[72] The latter was transformed in three steps into acid **44**, which is a potential bactericide.

The method *B* assumes the 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 a 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[31,73a,b] (Scheme 13).

Scheme 11

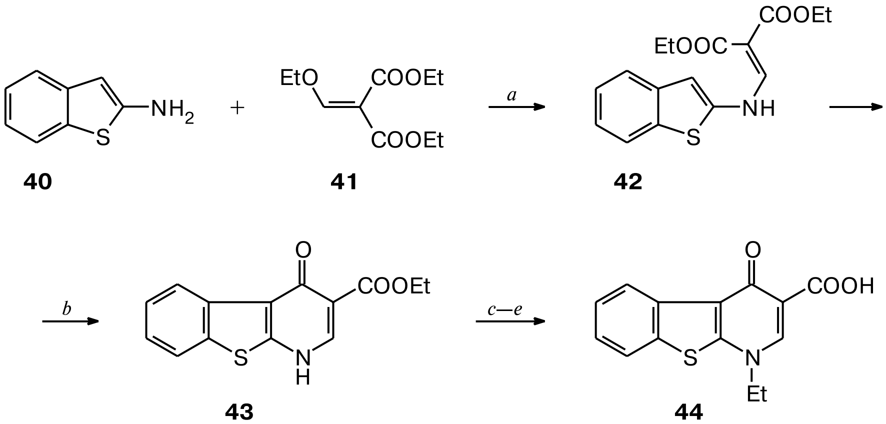


Reagents and conditions: AcOH, Δ, 2—4 h.

The 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 **48**) can be prepared by multicomponent cascade heterocyclization of phenyl isothiocyanate, CH-acids, and alkylating agents.[74] Cyclization of compounds **48** affords 6-oxo(imino)-6,7-dihydrothieno[2,3-*b*]pyridines **49** as the final products (Scheme 14).

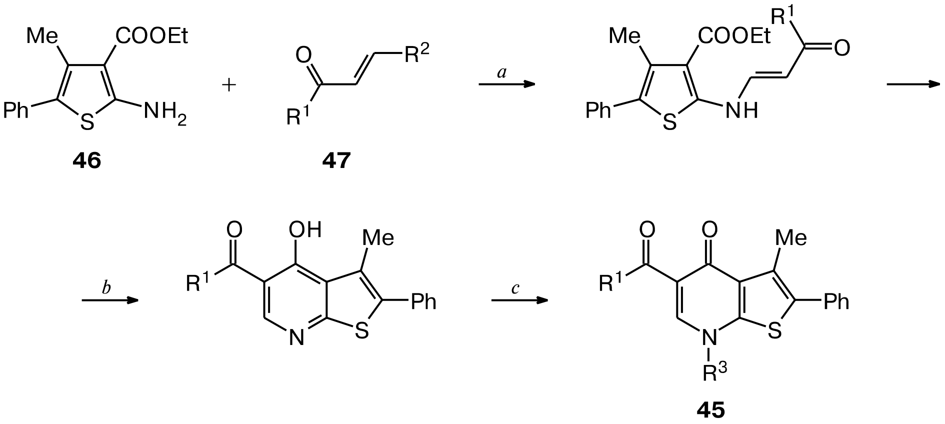
Among the studies published in the last 10 years, we found only one example[75] of the synthesis of thieno[2,3-*b*]pyridines according to the method *D*. The pyri-

Scheme 12



Reagents, conditions, and yields: *a*) 140 °C, 0.5 h, 93%; *b*) $(BuOCH_2CH_2)_2O$, Ar, 245 °C, 10 min, 67%; *c*) EtI, K_2CO_3, DMF, 100—110 °C, 5 h, 49%; *d*) 10% NaOH, EtOH, 2 h; *e*) 10% H_2SO_4, pH 2, 84%.

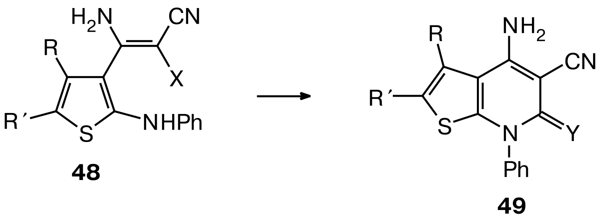
Scheme 13



$R^1 = Pr^i$; R^2 = MeO; R^3 = 2,6-$F_2C_6H_3CH_2$.

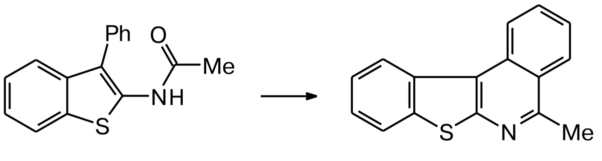
Reagents, conditions, and yields: *a*) $TsOH \cdot H_2O$, PhMe, 20 °C, 2.5 h, 92.4%; *b*) Ph_2O, reflux, 4 h, 80.6%; *c*) R^3Br, DMF, K_2CO_3, 20 °C, 4 h, 97.1%.

Scheme 14



X = CN, COOEt; Y = NH, O; R = Ph; R′ = OH, NH_2.

Scheme 15

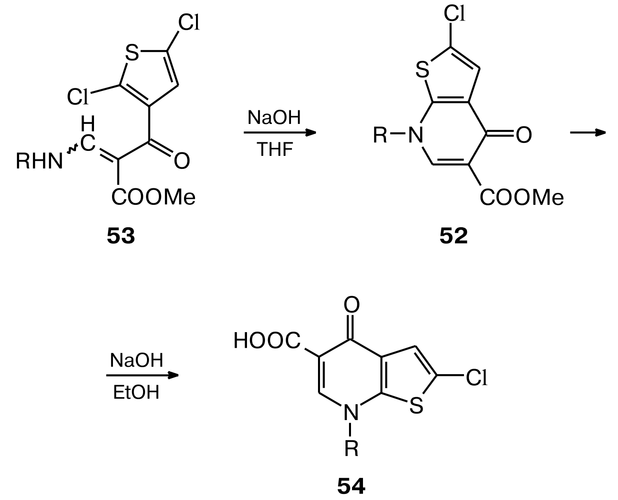


Reagents and conditions: $POCl_3$—P_2O_5 (2 : 1), $PhCH_3$, reflux.

dine fragment was constructed by intramolecular Bischler—Napieralski cyclization of 2-(acetamido)benzothiophene **50** (Scheme 15). The maximum yield of the target isoquinoline derivative **51** (54%) was achieved with the use of the P_2O_5—$POCl_3$ system as a condensing agent.

The method *E*, which assumes the N(7)—C(7a) bond formation in the cyclization step, is also rather rarely used in the synthesis of thienopyridines. For example, the method[76] for the preparation of 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid esters **52** is based on intramolecular *N*-nucleophilic substitution of (*E*/*Z*)-aminomethylene derivatives of (2,5-dichloro-3-thenoyl)acetic acid esters **53** in the presence of a strong base (Scheme 16). Esters **52** and products of their alkaline hydrolysis **54** have an antibacterial action; the influence of the substituents on the biological activity of the resulting compounds was studied.

Scheme 16



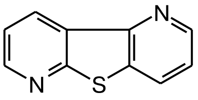
R = Et, Pr^i, Pr, *cyclo*-Pr, Bu^t, Ar.

1.3. Syntheses of tri- and polycyclic systems based on thieno[2,3-*b*]pyridines

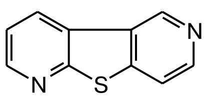
We restrict our consideration of the reactivities of thieno[2,3-*b*]pyridines to the annelation reactions giving rise to three- and polycyclic heterocycles. Information on such transformations has been systematized for the first time in the late 1980s.[14,39] Data on this problem have also been published more recently.[4,5,13,16,18,25,44,47k] Since the synthesis and properties of annelated thienopyridines have been particularly extensively studied in the last years, the need arose for a tentative generalization of the available data on this problem.

1.3.1. Pyridothienopyridines

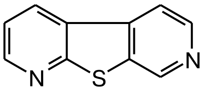
Methods were developed only for the preparation of pyrido[3´,2´:4,5]thieno[3,2-*b*]pyridines **55a** derived from one of four isomeric dipyridothiophene structures (**55a—d**), which are possible annelation products of thieno[2,3-*b*]pyridines, and their properties were documented. Evidently, this is 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 monocylcic or acyclic precursors.



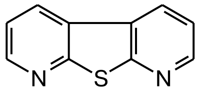
55a



55b



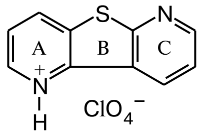
55c



55d

Data on the biological actions of dipyridothiophenes are scarce. Information on this problem is lacking in the review,[14] 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.[77]

The structures of the simplest thieno[2,3-*b*:4,5-*b*´]dipyridine (**55a**) and its monohydroperchlorate **56** were studied.[78] Only the N atom of the ring A in compound **55a** is subjected to protonation.

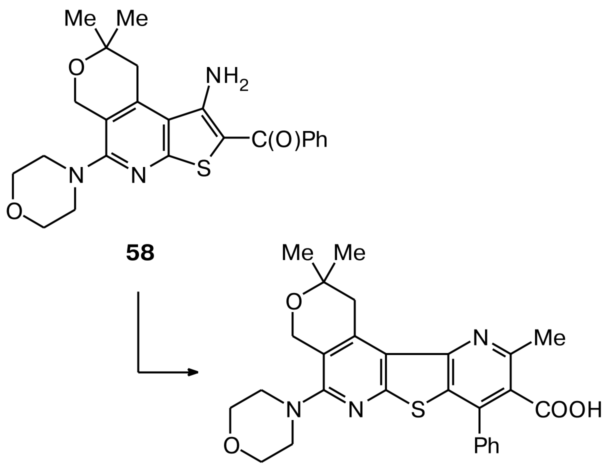


56

As mentioned above, amines of the thienopyridine series synthesized by the Thorpe reaction always contain an electron-withdrawing substituent (acyl, alkoxycarbonyl, *etc.*) at position 2. The presence of the *o*-aminocarbonyl fragment in these compounds makes these compounds useful as synthons for the pyridine ring construction in the Friedlaender synthesis. Generally, condensation of this type occurs in the presence of a basic catalyst. The acid-promoted synthesis can be exemplified by the preparation of tetracyclic structure **57** from pyranothienopyridine **58** (Scheme 17).[77]

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.[79] On the whole, this type of heterocyclization has the following advantages over the conventional method of annelation 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 the 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 **59** (67—75%) (Scheme 18). At the same time,

Scheme 17

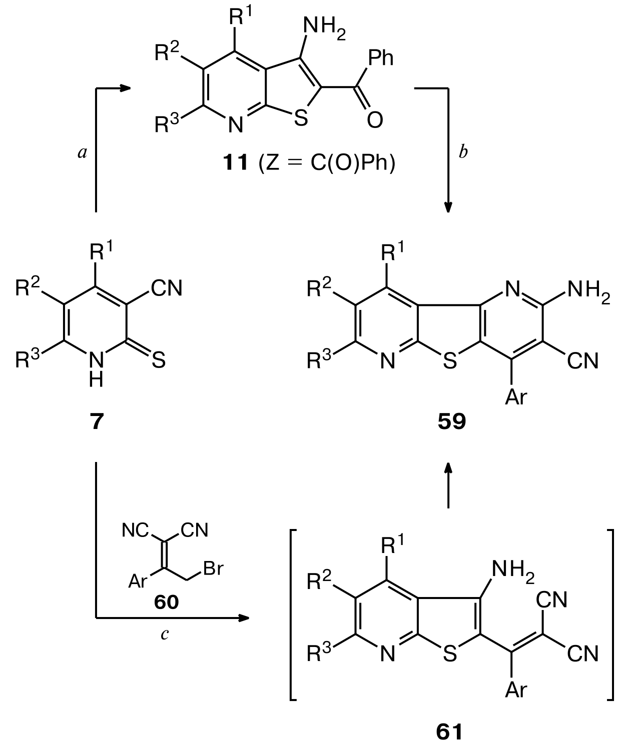


58

57 (82.2%)

Reagents and conditions: $AcCH_2COOEt$, $ZnCl_2$, *m*-xylene, reflux.

Scheme 18



11 (Z = C(O)Ph)

7

59

60

61

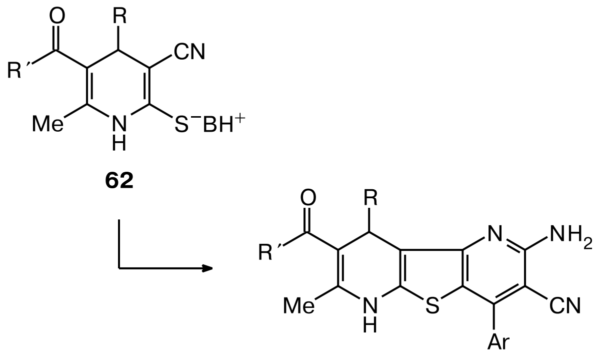
Ar = Ph, 4-BrC_6H_4; R^1 = H, Me, Ph; R^2 = H, R^3 = Me, Ph or $R^2 + R^3 = (CH_2)_n$; *n* = 3, 4.

Reagents and conditions: *a*) $BrCH_2C(O)Ph$, 10% KOH, DMF; *b*) 3 equiv. of $CH_2(CN)_2$, Py, 105—110 °C, 12 h; *c*) EtOH, Pip, 50 °C, 2 min.

compounds **59** can be successfully prepared within two minutes from the same thiones **7** and 2-aryl-3-bromo-1,1-dicyanopropenes **60** in 57—95% yields; the intermediate, *viz.*, thienopyridine **61**, underwent cyclization *in situ* and cannot be isolated.[79]

More recently, an approach based on the use of bromides **60** was employed in the synthesis of other dipyridothiophenes.[62a,80] In particular, 6,9-dihydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines **63** were prepared for the first time from thiolates **62** (Scheme 19). It should be emphasized that cascade heterocyclization occurs spontaneously in the absence of a basic catalyst.[62a]

Scheme 19



62

63 (41—82%)

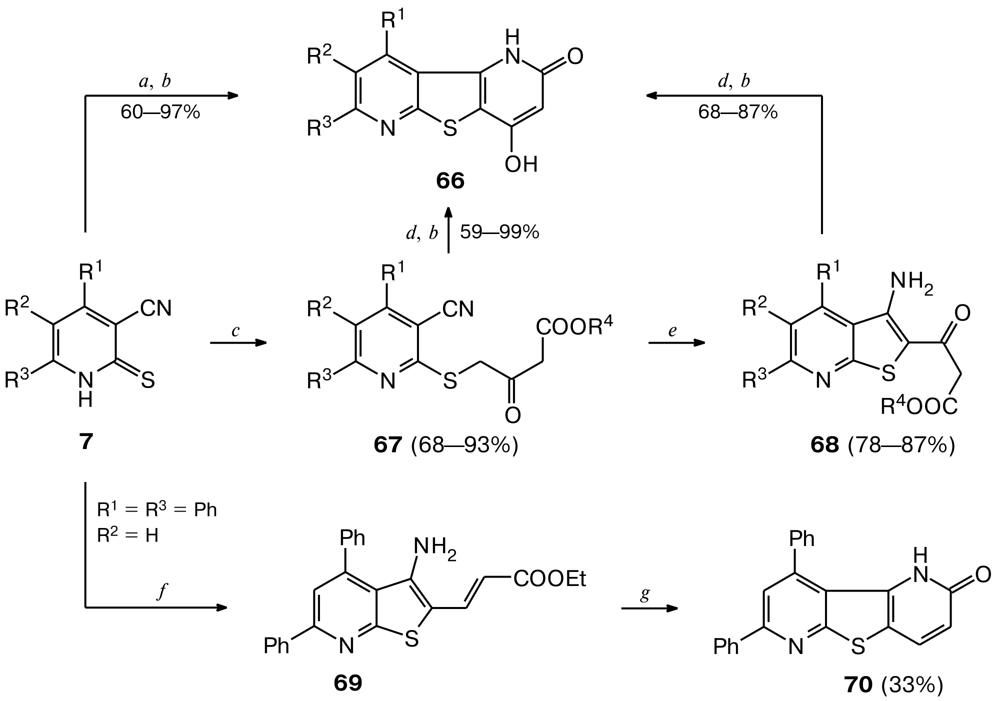
R = 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 2-thienyl; R′ = EtO, Me; Ar = 4-BrC_6H_4; B — piperidine.

Reagents and conditions: **60**, EtOH, 40 °C, 10 min; ~20 °C, 16 h.

In addition to dicyanobromopropenes **60**, γ-chloroacetoacetic acid esters ($ClCH_2C(O)CH_2COOR$) (**64**)[56c,81] and ethyl 4-bromocrotonate ($BrCH_2CH=CHCOOEt$) (**65**)[82] can also be 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 **64** in refluxing ethanol in the presence of KOH or EtONa is a method of choice for the preparation of dipyridothiophenes **66**. If the reaction is performed under milder conditions, intermediates, *viz.*, pyridine **67** and thieno[2,3-*b*]pyridine **68**, can be isolated, and the latter are readily subjected to heterocyclization under the action of bases to form the target products **66**.[56b] Analogously, thienopyridine **69** prepared by the reaction of thione **7** ($R^1 = R^3$ = Ph, R^2 = H) with crotonate **65** can be transformed into dipyridothiophene **70** (Scheme 20).[82]

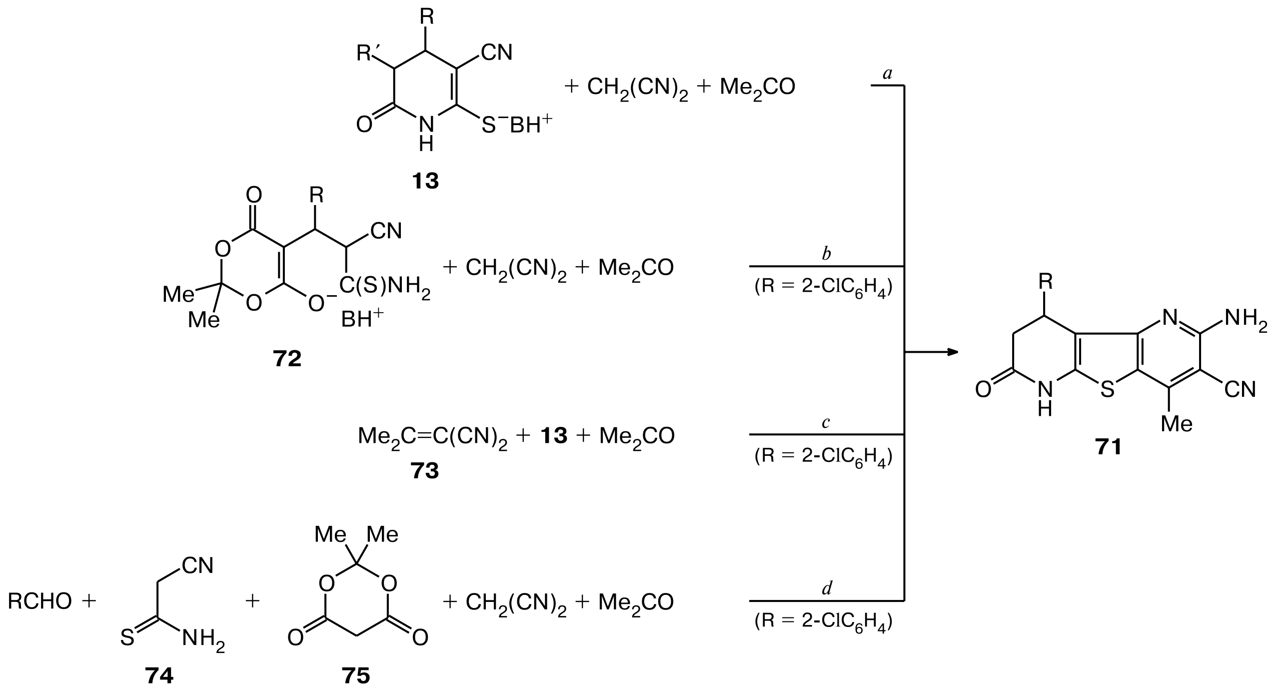
Let us mention the multicomponent approach to the synthesis of substituted 6,7,8,9-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines **71** based on the reaction of pyridinetiolates **13**, malononitrile, and acetone

Scheme 20



Reagents and conditions: *a*) **64** (R = Et, Pr^i), KOH or EtONa, EtOH, reflux; *b*) 10% HCl; *c*) **64**, 10% KOH, DMF; *d*) KOH or EtONa, EtOH, reflux; *e*) Et_3N, EtOH, reflux; *f*) **65**, KOH or EtONa, EtOH; *g*) HCl, MeOH, reflux, 8 h.

Scheme 21



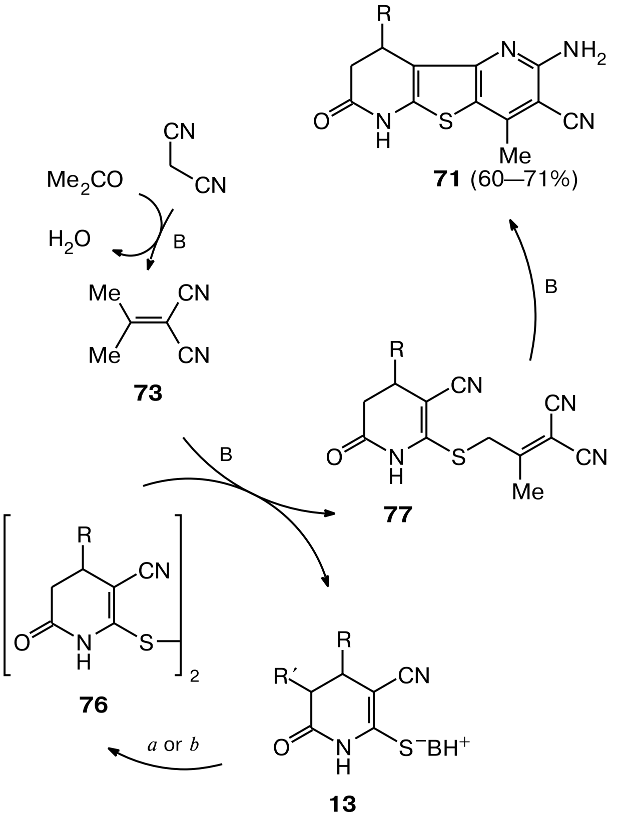
R = Ar, Het; R′ = H; B is *N*-methylmorpholine.

Reagents, conditions, and yields: *a*) Method *A*: EtOH, reflux, 15—25 h, 27—51%; *b*) Method *B*: EtOH, reflux, 35 h, 18.5%; *c*) Method *C*: EtOH, reflux, 20 h, 33%; *d*) Method *D*: EtOH, B, reflux, 10 days, 7%.

(method *A*).[83] Attempts to modify this method by performing the reaction with precursors of thiolates **13**, *viz.*, Michael adducts **72**, instead of thiolates by themselves (method *B*), using isopropylidenemalononitrile **73** instead of malononitrile (method *C*), or performing multicomponent cyclocondensation of 2-chlorobenzaldehyde, cyanothioacetamide **74**, Meldrum's acid **75**, acetone, and malononitrile (method *D*) resulted in a decrease in the yields of the above-mentioned target products with a simultaneous increase in the reaction time (Scheme 21).[83a]

The above-described reaction (method *A*) occurs only in the presence of atmospheric oxygen.[84] These data suggest the following reaction mechanism. Under the reaction conditions, pyridinethiolate **13** is oxidized to the corresponding bis(2-pyridyl) disulfide (**76**), which reacts with the isopropylidenemalononitrile anion **73** (derived *in situ* from malononitrile and acetone) resulting in the S—S bond cleavage and the formation of dicyanoallyl sulfide **77** and thiolate **13** (Scheme 22). The latter is again oxidized to disulfide, and compound **77** is involved in cascade heterocyclization giving rise to the dipyridothiophene system. The possibility of this reaction pathway was confirmed by the independent synthesis of compounds **71** from disulfides **76** (method *E*), which were prepared in virtually 100% yield by mild oxidation of thiolates **13**; the target products were isolated in the maximum yields (60—75%).

Scheme 22



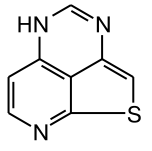
B is *N*-methylmorpholine; R = Ar, Het; R´ = H.

Reagents, conditions, and yields: *a*) O_2, EtOH (*in situ*); *b*) I_2, EtOH—H_2O, 24 h, 90—100%.

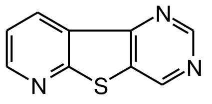
1.3.2. Pyridothienopyrimidines

Of all fused thienoazines derived from thieno[2,3-*b*]pyridines, pyridothienopyrimidine derivatives have received the most study. Certain 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 the chemical and pharmaceutical industries. Selected data on biological activities of pyridothienopyrimidine derivatives were given in the review.[26] In the present review, we analyze information on the chemistry of pyridothienopyrimidines considering them as a special class of compounds, *viz.*, thienopyridine derivatives.

It should be noted that all pyridothienopyrimidines prepared by annelation of thieno[2,3-*b*]pyridines are derivatives of two regioisomeric structures, *viz.*, 5*H*-thieno[2,3,4-*e*,*d*]pyrido[4,3-*d*]pyrimidine (**78**) or pyrido[3´,2´:4,5]thieno[3,2-*d*]pyrimidine (**79**).



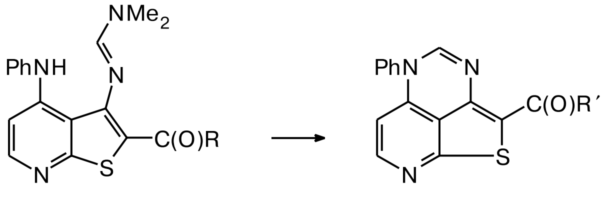
78



79

Compounds with a structure of isomer **78** can be synthesized by intra- or intermolecular cyclization of substituted 3,4-diaminothieno[2,3-*b*]pyridines. For example, heating of (*N*,*N*-dimethylaminomethylene)amines **80** affords tricyclic pyrimidine derivatives **81** *via* intramolecular cyclocondensation (Scheme 23).[85]

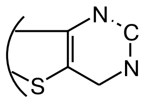
Scheme 23



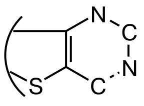
R = OEt, N=CH(NMe₂); R´ = OEt (87%), NHC(O)H (94%).

Reagents and conditions: 70% AcOH, 100 °C, 0.5 h.

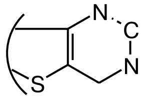
There is a large body of data on the synthesis and properties of pyrido[3´,2´:4,5]thieno[3,2-*d*]pyrimidine derivatives (**79**). All methods used in practice for the construction of the pyrimidine ring in these compounds can be classified into several types (*F—I*).



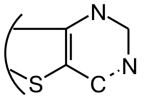
F



G



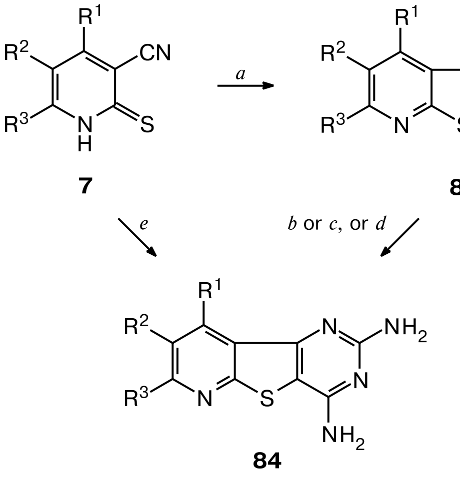
H



I

The 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 of the use of this approach were given in the studies.[62a,64b,86] For instance, thienopyridines **82** derived from 3-cyanopyridine-2(1*H*)-thione derivatives **7** and *N*-cyanochloroacetamidine (**83**) are subjected to both base- and acid-catalyzed cyclization giving rise to tricyclic 2,4-diaminopyridine derivatives **84** (the yields are, on the average, 60—90%) (Scheme 24). The latter can also be synthesized directly from thiones **7** and chloride **83** by one-pot cascade heterocyclization.

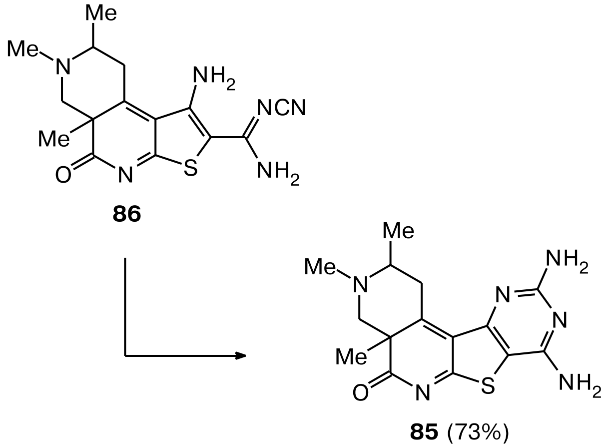
Scheme 24



Reagents and conditions: *a*) $ClCH_2C(NCN)NH_2$ (**83**), KOH, DMF; *b*) EtONa, EtOH, reflux, 6 h; *c*) 35% HCl, MeOH, 0.5—12 h; *d*) Ac_2O, reflux, 6 h; *e*) 1) EtOH, KOH, ~20 °C; 2) **83**, ~20 °C; 3) EtONa, EtOH, reflux, 2 h.

Transformations of compounds **84** were studied.[64b] 6,9-Dihydropyrido[3´,2´:4,5]thieno[3,2-*d*]pyrimidines were successfully prepared by the reaction with the use of the corresponding 1,4-dihydropyridine-2-thiolates **19** instead of thiones **7**.[62a,86a] This approach made it possible to synthesize pyrimidothieno[2,7]naphthyridine derivative **85** starting from tricyclic structure **86** (Scheme 25).[87]

Scheme 25



Reagents and conditions: 1) 35% HCl, MeOH, reflux, 1 h; 2) Na_2CO_3, H_2O.

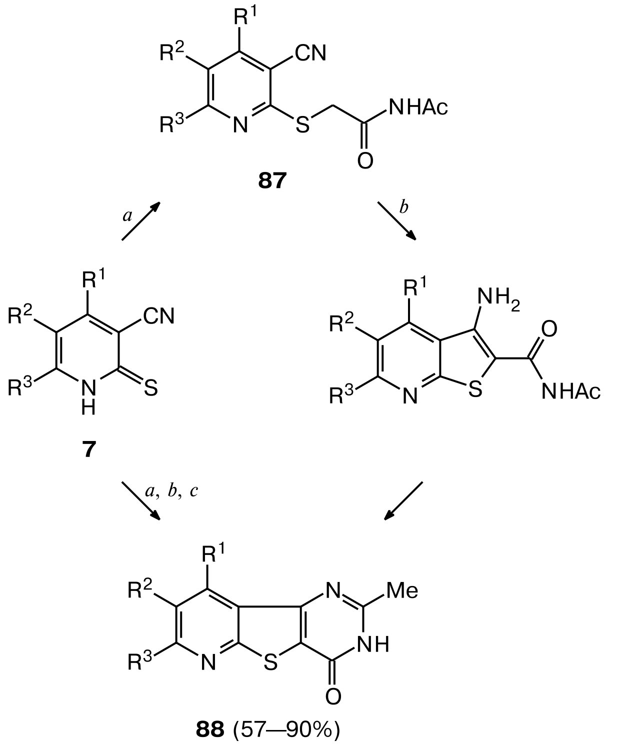
In a basic medium, pyridines **87** are involved in cascade heterocyclization giving rise to fused pyrimidines **88**. The starting compounds **87** can be generated *in situ* from 3-cyanopyridine-2(1*H*)-thiones **7** (Scheme 26).[88]

Analogously, pyrido[3´,2´:4,5]thieno[3,2-*d*]pyrimidine **90** is derived from *N*-cyanoamide **89** in moderate yield under mild conditions (Scheme 27).[81a] The treatment of pyridinethiones **7** (R^1, R^3 = Ar, R^2 = H) with *N*-(ethoxycarbonyl)chloroacetamide **91** provides a convenient one-pot method for the synthesis of tricyclic thienoazines **92**.[81b]

The 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 **93** with primary amines or hydrazine giving rise to fused pyrimidin-4(3*H*)-ones **94** (Scheme 28).[89a,b] In the case of R^4 = EtO, the reaction yields pyrimidine-2,4-dione derivatives **95** as the final products.[90]

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 of this approach involves intramolecular condensation of 3-(acyl-

Scheme 26



R^1 = H, Me, Ph, CF_3; R^2 = H; R^3 = Me, Ph, or $R^2 + R^3 = (CH_2)_n$, *n* = 3, 6.

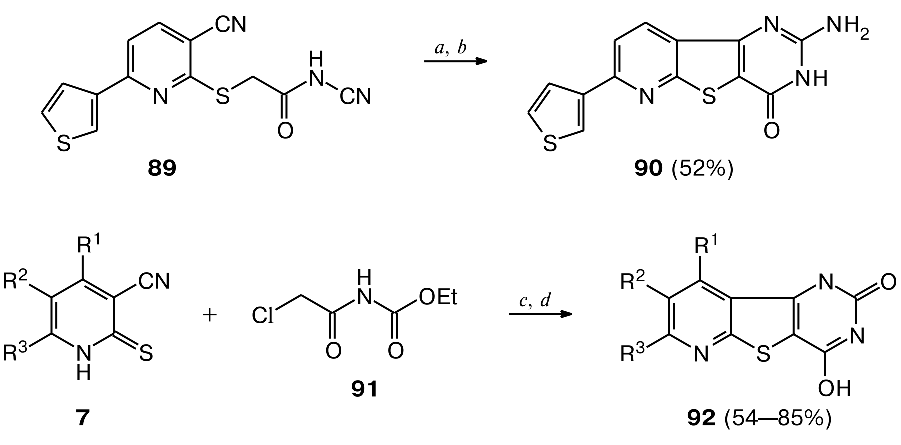
Reagents and conditions: *a*) $ClCH_2C(O)NHAc$, 10% KOH, EtOH, 50 °C, 30 min; *b*) 10% KOH, EtOH, reflux for 1.5 h; *c*) HCl, pH 7.

amino)thienopyridines produced by acylation of 3-amino-2-carbamoylthieno[2,3-*b*]pyridines or their structural analogs.[91] An example is the synthesis of pyrimidothienobenzoquinoline **96** from chloroacetamide **97** (Scheme 29).[91]

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 **98** are subjected to the reactions (usually, under drastic conditions, *e.g.*, reflux or fusion) with various monocarbon 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 annelated structures **99—101** containing different substituents in the pyrimidine ring. These approaches are also suitable for the preparation of polyfused systems containing the partially hydrogenated pyridine fragment.[60e] It was demonstrated[92] that pyrimidinones **99** can exist in part as the 4-hydroxy tautomers. Refluxing of certain 3-amino-2-cyanothieno[2,3-*b*]pyridines with CS_2 in pyridine leads to the transformation of the CN group into the thiocarbamoyl group to give tetrahydropyrimidine derivatives **100** (X = Y = S, R^4 = H) (Scheme 30).[93] Compounds **101** (R^4 = H, R^6 = Ar, Alk, R^7 = H) were oxidized to annelated pyrimidin-4(3*H*)-ones **99** (67—98% yields).[94]

The method *I* is based on the reactions giving rise to the pyrimidine ring *via* the 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, it was demonstrated[68j] that the reaction of formamidine **102** with $MeNH_2$ provides a convenient approach to the synthesis of pyridothienopyrimidine **103** (Scheme 31).

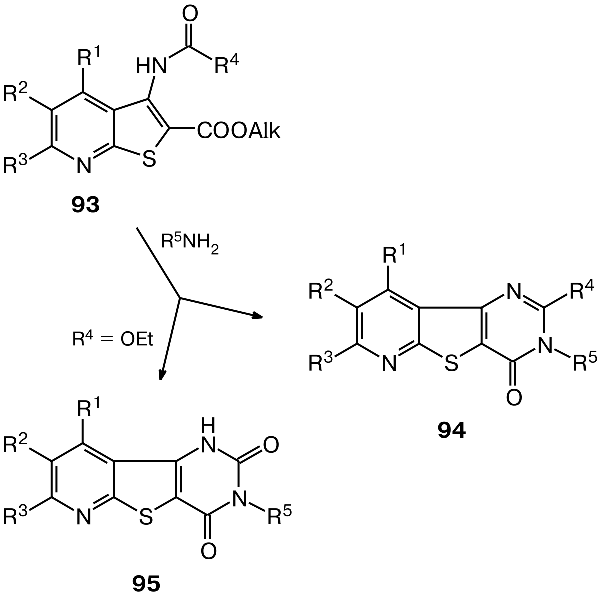
Scheme 27



R^1 = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$; R^2 = H; R^3 = Ph, 2-thienyl.

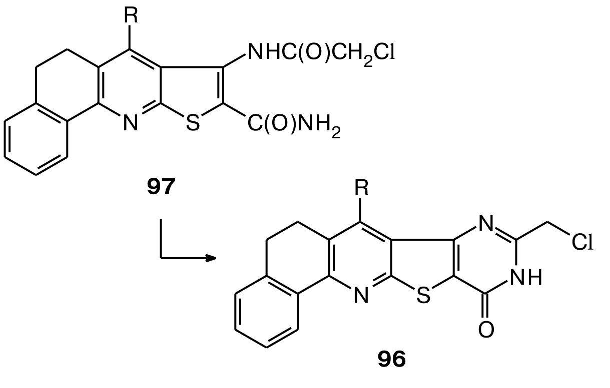
Reagents and conditions: *a*) EtOH, HCl, 5 °C, 24 h; *b*) 10% Na_2CO_3; *c*) EtONa, EtOH—DMF (1 : 1), reflux, 2 h; *d*) 10% HCl, 20 °C.

Scheme 28



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

Scheme 29



R is 2-furyl.

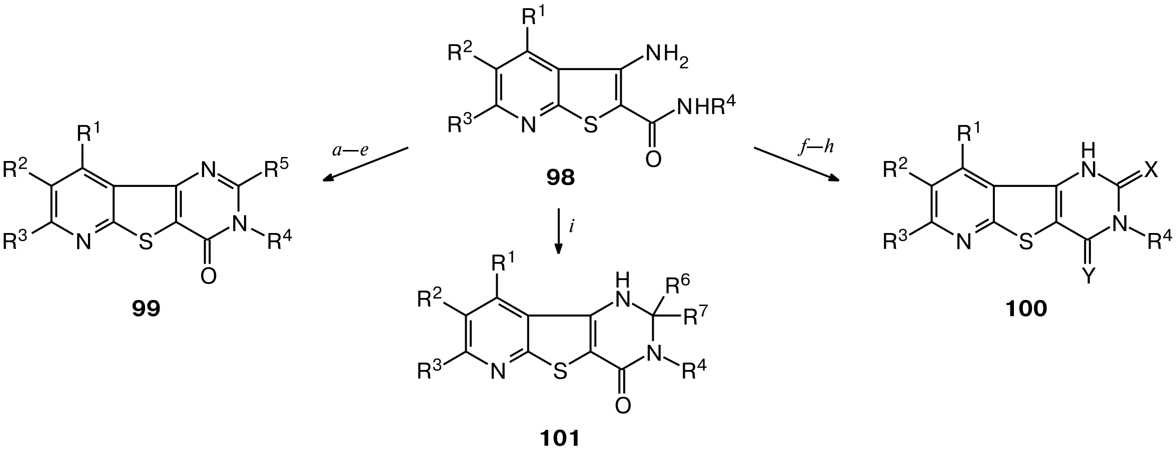
Reagents and conditions: Ac$_2$O, reflux.

The one-step reactions resulting in the 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 in such transformations. Formamide acts also as the solvent; the final products can be prepared in high yields by refluxing compounds **11** in formamide for several hours. This method for the preparation of pyridothienopyrimidine derivatives was included in the synthetic arsenal from the early 1970s.[39] In recent years, this method has been used to prepare a series of polyfused azines with general formulas **94** and **104** (Scheme 32).[65,92a,95]

1.3.3. Pyridothienotriazines

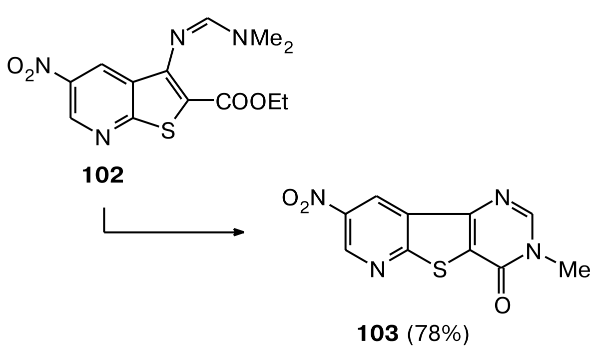
Scarce data on the synthesis of this class of compounds were reported in the reviews[16,39] in connection with an investigation of the properties of their precursors, *viz.*, 3-cyanopyridine-2(1*H*)-thiones. Investigation of the properties of pyridothienotriazines and the development of procedures for their preparation hold promise taking

Scheme 30



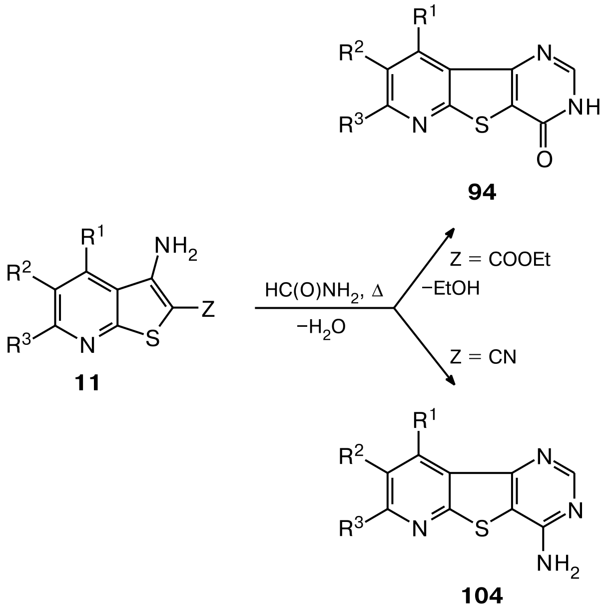
Reagents and conditions: *a*) Ac$_2$O, reflux, R^5 = Me; *b*) R^{5}C(O)Cl, AcOH or fusion, R^5 = Me, ClCH$_2$, Ar; *c*) POCl$_3$—DMF, R^1 = H; *d*) HCOOH, reflux, R^1 = H; *e*) HC(OMe)$_3$ or HC(OEt)$_3$, Ac$_2$O, reflux, R^1 = H; *f*) CS$_2$, pyridine, 100 °C, or dioxane, X = S, Y = S, O; *g*) (NH$_2$)$_2$C(O), fusion, X = Y = O; *h*) ClCOOEt, X = Y = O; *i*) R^{6}C(O)R^7, reflux in AcOH or PhMe—TsOH (cat.), R^6 = Ar, Alk; R^7 = H, or R^6 + R^7 = (CH$_2$)$_n$, n = 5, 6.

Scheme 31

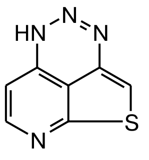


Reagents and conditions: 15% $MeNH_2$/MeOH, 120 °C, 15 h.

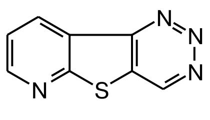
Scheme 32



into account that some compounds belonging to this class possess analgetic, anticonvulsive, antimicrobial, antifungal, antitumor, antianaphylactic, or antiallergic activities. In spite of a considerable body of data on the synthesis of pyridothienotriazines, there are a few synthetic approaches to the triazine ring construction in the thieno[2,3-*b*]pyridine series. Only derivatives of the 1,2,3-triazine system represented by two isomers, **105** and **106**, were documented.



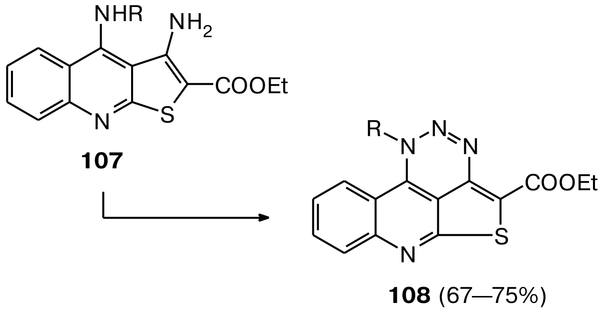
105



106

Under the diazotization conditions, 3,4-diaminothienoquinolines **107** are transformed into derivatives of a new heterocyclic system, *viz.*, 1*H*-5-thia-1,2,3,6-tetraazaacephenanthrylene **108**, in high yields (Scheme 33).[68c,68d]

Scheme 33

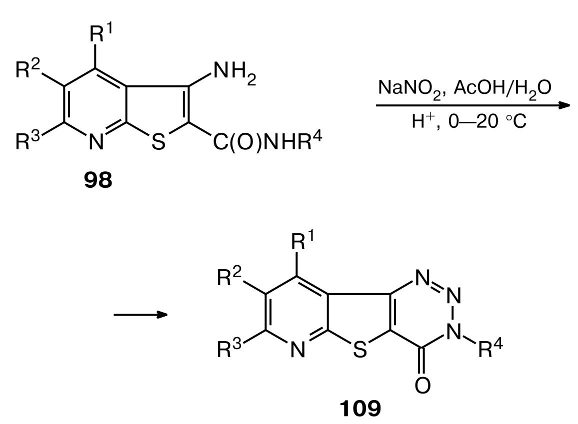


R = Me, Et, Pr^i, Bu^i, C_6H_{11}.

Reagents and conditions: $NaNO_2$, 70% H_2SO_4, −5 °C, 1 h.

The same approach to the construction of 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 **106**. Nitrous acid generally serves as a source of the N(2) atom. This acid is generated *in situ* from $NaNO_2$ and AcOH, often in the presence of HCl or H_2SO_4; the reaction proceeds under mild conditions and gives the final products in good yields (on the average, 60—80%). Isoamyl nitrite was used as the source of the nitrogen atom in the only study.[96] However, it should be noted that diazotization with the $NaNO_2$—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

Scheme 34



R^4 = H, Ar, Het.

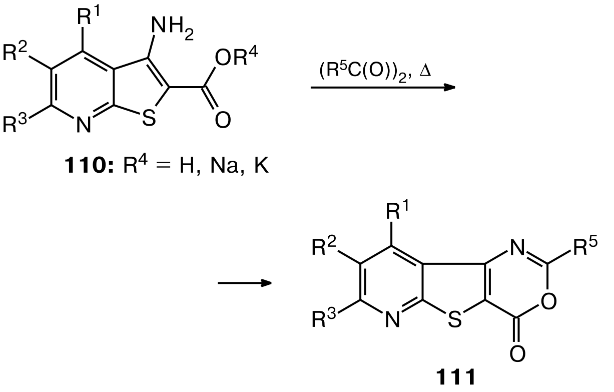
1,2,3-triazin-4(3*H*)-ones **109** from 3-amino-2-carbamoylthieno[2,3-*b*]pyridine derivatives **98** (Scheme 34) has been studied most extensively.[96,97]

1.3.4. Pyridothienooxazines

Some aspects of the synthesis and reactions of pyridothienooxazines were covered in the reviews.[16,39] 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 annelated analogs.[14] More recently, the antibacterial[98] and possible antitumor and radioprotecting[99] actions of these compounds 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 **110** (or the corresponding salts **110**) with carboxylic acid anhydrides (usually, Ac_2O) by refluxing (Scheme 35).[61b,92a,97d,98,99b,100] The yields of products **111** are, on the average, 60—75%.

Scheme 35



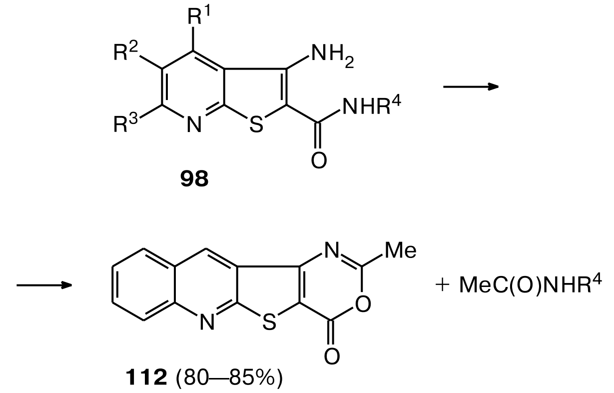
110: R^4 = H, Na, K

111

R^5 = Me, Et, Pr, Ph.

In another modification of this approach,[101] the corresponding anilides **98** (R^1 = H, $R^2 + R^3 = C_4H_4$) are used instead of acids **110**. This method was employed to prepare oxazinothienoquinoline **112** (Scheme 36). However, it should be noted that numerous data suggest that (see Section 2.1.3.2) pyrimidine derivatives **94**, rather than 1,3-oxazine derivatives, would be expected to be produced under these conditions. Apparently, to resolve this contradiction, additional investigations are required.

Scheme 36



98

112 (80—85%)

R^1 = H; $R^2 + R^3 = C_4H_4$; R^4 = Ph, 4-MeC_6H_4, 4-ClC_6H_4.

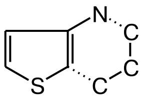
Reagents and conditions: Ac_2O, reflux, 4 h.

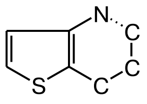
2. Thieno[3,2-*b*]pyridines

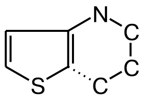
Methods for the preparation of thieno[3,2-*b*]pyridine derivatives (**2**) and their properties are less well described in the literature compared to [2,3-*b*]-isomer **1**. Scarce data on the synthesis of thienopyridine **2** and its fused analogs were included in the reviews.[5—7,14,18,42,45,46] The transformations of the [3,2-*b*]-isomer were discussed in more detail in the review.[3]

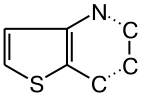
The biological actions of compounds containing the thieno[3,2-*b*]pyridine structural fragment are well known. Certain representatives of this class of compounds serve as endothelin receptor antagonists, ligands of γ-aminobutyric acid receptors, immunoregulators, calcium channel blockers, α-1-adrenoreceptor 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 of this class 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.[14,102] 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.

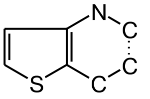
Most of the known methods for the synthesis of these compounds are based on the use of readily accessible 3-aminothiophenes or their *N*-derivatives. The following main ways of the pyridine ring construction (*J—N*) are possible:


J


K

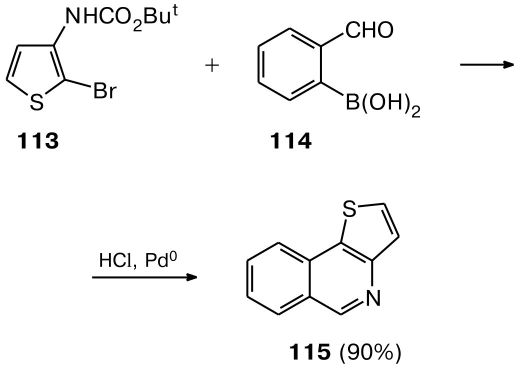

L


M


N

The approach *J* is rather 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 the methods developed for the preparation of some simplest [3,2-*b*]-fused thienoazines. For example, the modified Suzuki reaction of carbamate **113** with *o*-formylphenylboronic acid **114** produces unsubstituted thieno[3,2-*c*]quinoline **115** (Scheme 37).[103]

Scheme 37

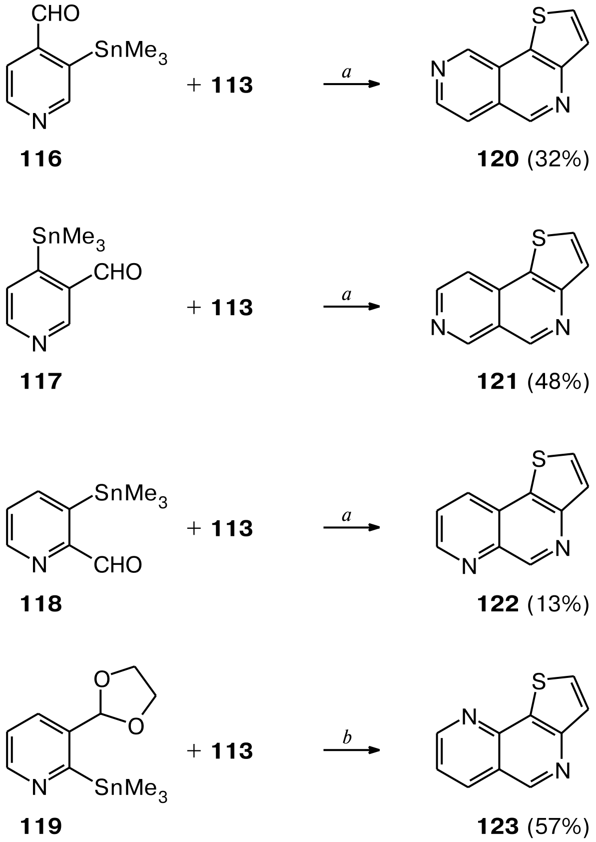


The Stille cross-coupling reactions of 3-thienylcarbamate **113** with *o*-formyl(trimethylstannyl)pyridines **116—118** [104] or acetal **119** [104,105] afford a series of isomeric thienonaphthyridines **120—123** (Scheme 38). The addition of CuO to the reaction mixture leads to an increase in the reaction rate.[105b]

An alternative cross-coupling process based on the reaction of 2-(trimethylstannyl)-3-thienylcarbamate **124** with *o*-halopyridinecarbaldehydes **125—128** afforded the same products in higher yields (Scheme 39).[106]

It was also demonstrated[107] that the reactions can be performed under analogous conditions not only with pyridine **128** but also with 2-chloro-3-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.

Scheme 38



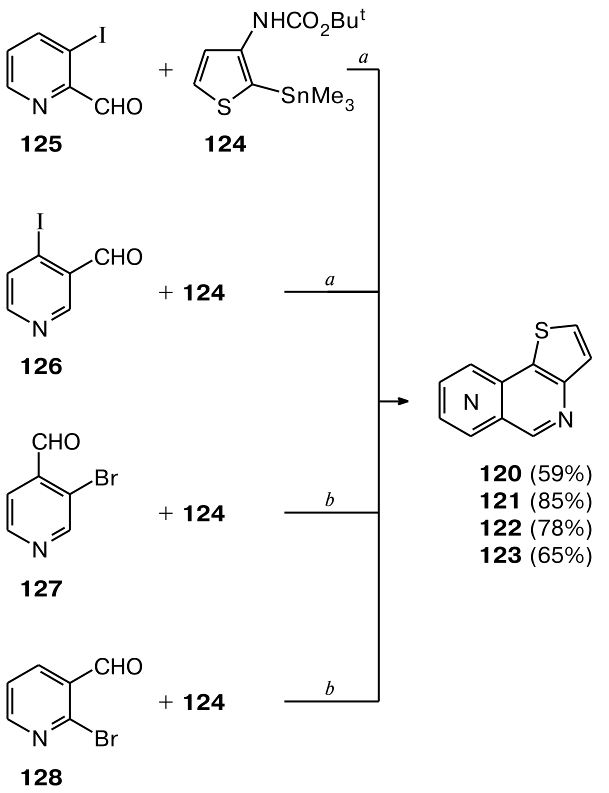
Reagents and conditions: *a*) $PdCl_2$(dppb), CuO, N_2, DMF, 100 °C; *b*) $Pd(PPh_3)_4$, CuO, N_2, DMF, 100 °C, HCl, 3 h; ($PdCl_2$(dppb) is dichloro(diphenylphosphinebutane)palladium(II)).

The pyridine ring can also be constructed by the Gould—Jacobs reaction.[102,108] This way of formation of the thienopyridine system can be exemplified by intramolecular cyclization of enamino diester **129** giving rise to compound **130**, which possesses antihypertensive and antibacterial actions (Scheme 40).[108c]

The cyclocondensation reaction of substituted thiophene **131** giving rise to compound **132** in good yield (Scheme 41)[74c] is a good example of the use of the 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.

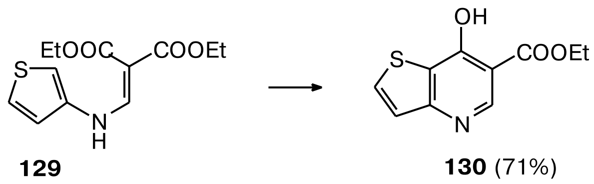
However, the synthesis of thieno[3,2-*b*]pyridines by cascade heterocyclization of simple and readily accessible reagents **60** and **133** holds more promise. In this process, the thiophene ring and then the pyridine ring are successively formed in the presence of a basic catalyst to give

Scheme 39



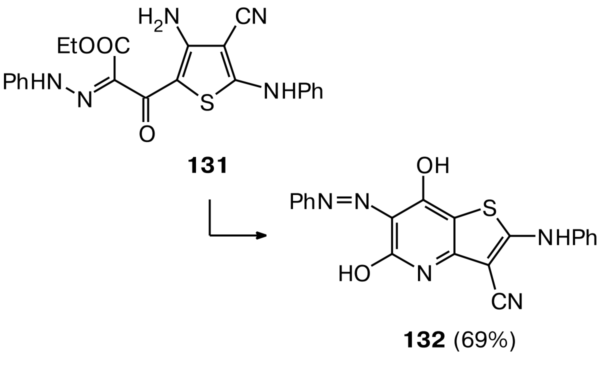
Reagents and conditions: *a*) $PdCl_2(dppb)$, N_2, DMF, 100 °C, 2 h; *b*) $PdCl_2(dppb)$, CuO, N_2, DMF, 100 °C, 2 h.

Scheme 40



Reagents and conditions: TsOH, Ac_2O, xylene, reflux, 26 h.

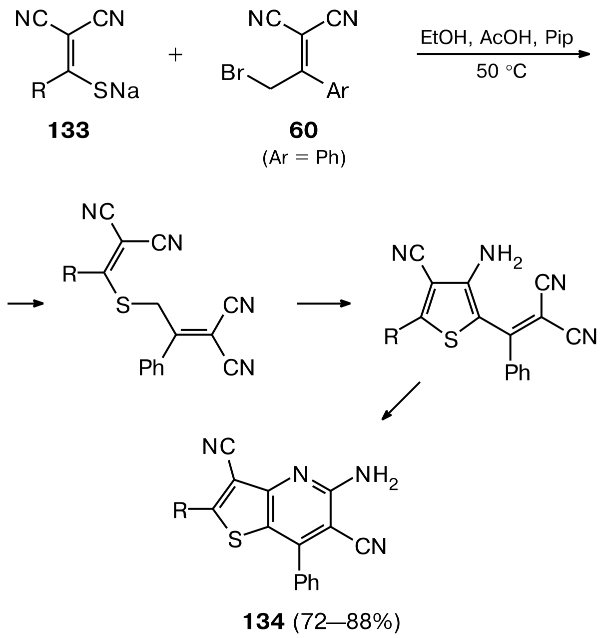
Scheme 41



Reagents and conditions: EtONa, EtOH, reflux, 8 h.

finally polyfunctionalized thieno[3,2-*b*]pyridine **134** (Scheme 42).[109]

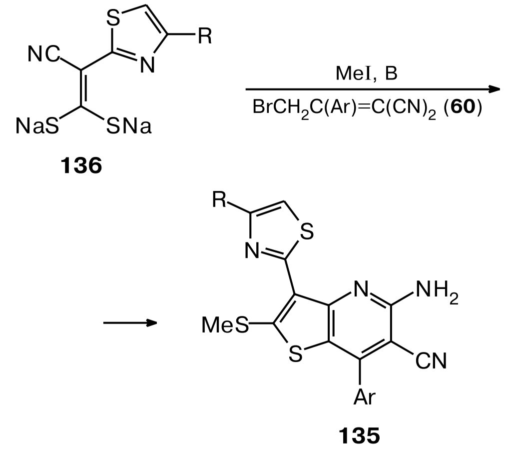
Scheme 42



R = NHPh, NHEt, $NHCH_2CH=CH_2$, SCH_3.

More recently, this approach was used in the synthesis of 3-(thiazol-2-yl)thieno[3,2-*b*]pyridines **135** from the corresponding ethyleneditiolates **136** (Scheme 43).[110]

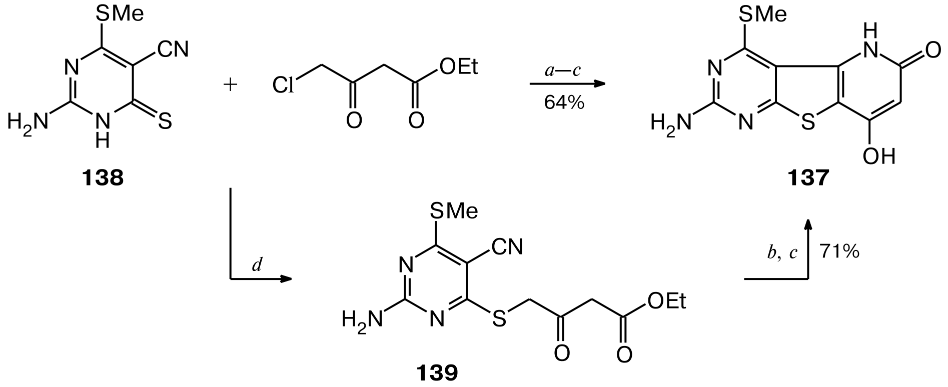
Scheme 43



Ar = $4\text{-}ClC_6H_4$; R = Ph, $4\text{-}ClC_6H_4$, $4\text{-}MeOC_6H_4$, $4\text{-}BrC_6H_4$;
B is a base.

This approach was also employed in the synthesis of pyrido[3´,2´:4.5]thieno[2,3-*d*]pyrimidine derivative **137**, which can be prepared according to the following two

Scheme 44



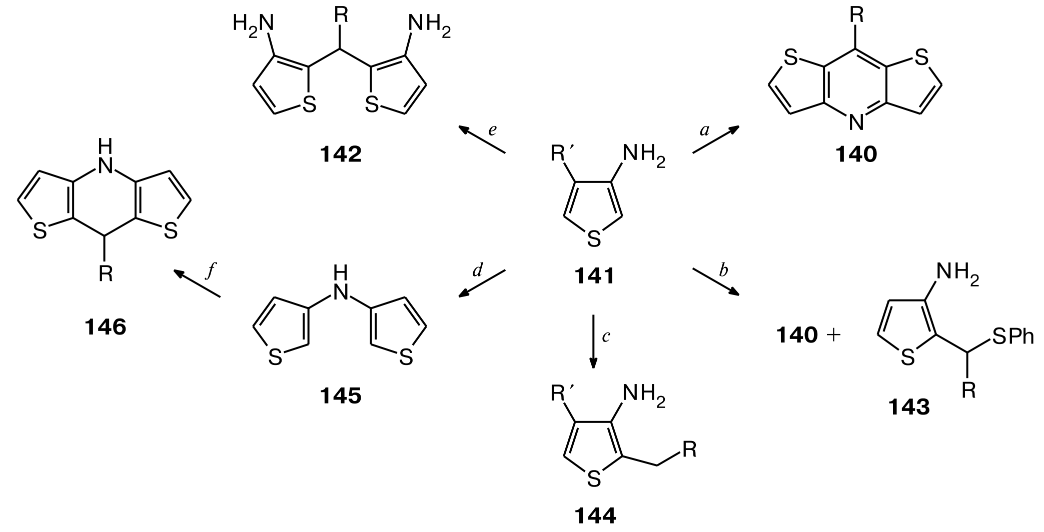
Reagents and conditions: *a*) KOH, EtOH, 20 °C; *b*) 2 equiv. of KOH, EtOH, reflux; *c*) HCl; *d*) KOH, DMF.

procedures: by the one-pot base-catalyzed reaction of pyrimidinethione **138** with ethyl 4-chloroacetoacetate or by cascade heterocyclization of pyrimidine **139** (Scheme 44).[56c]

Dithieno[3,2-*b*:2′,3′-*e*]pyridine derivatives **140** can be synthesized by the acid-catalyzed reaction of 3-aminothiophene or its 4-BocNH derivative **141** with aldehydes followed by transamination and dehydrogenation of bis(3-amino-2-thienyl)methane intermediates **142** (Scheme 45).[111] This reaction in the presence of PhSH was accompanied by the formation of thiophene **143**,[111d] whereas the reaction with selenophenol yielded only reductive alkylation products, *viz*., 2-alkyl-3-aminothiophenes **144** (see Scheme 45).[111a,111c,111d] It should be noted that bis(3-thienyl)amine (**145**) that formed by self-condensation of amine **141** can also be involved in condensation with aldehydes to give dihydrodithienopyridines **146**.[111b] In this case, the pyridine ring construction occurs *via* the pathway *L*.

The approach *L* assumes the formation of the C(4)—C(5) bond of the pyridine ring in the final step of cyclization. Thienopyridine **148a** was prepared from 3-(*N*-acetylamino)thiophene (**147**, R^1 = Ac) by the Vilsmeier—Haack reaction.[112] *N*-Acetylhomocysteine thiolactone **149** undergoes an analogous transformation, cyclocondensation being accompanied by formylation of the thiophene ring to give 5-chlorothieno[3,2-*b*]pyridine-3-carbaldehyde (**148b**) as the final product (Scheme 46).[113]

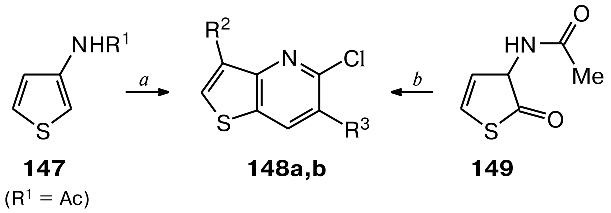
Scheme 45



R = H, Me, Et, Ar; R′ = H, BocNH.

Reagents, conditions, and yields: *a*) RCHO (0.5 equiv.), THF, 60—86%; *b*) RCHO (R = Me, Et), PhSH, TsOH, ~20 °C; *c*) RCHO (1 equiv.), PhSeH, CH_2Cl_2, H^+; *d*) AcOH, PhH, Δ; *e*) RCHO (0.5 equiv.), TsOH; *f*) RCHO, H^+, 0 °C.

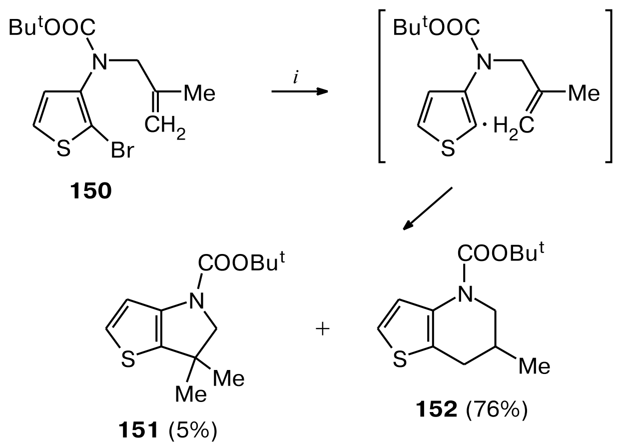
Scheme 46



Reagents, conditions, and yields: *a*) R^2 = H, R^3 = CN; $POCl_3$, DMF, reflux, 1.5 h; $NH_2OH \cdot HCl$; *b*) R^2 = CHO, R^3 = H; $POCl_3$, DMF, 90 °C, 60%.

Radical cyclocondensation of *tert*-butyl-*N*-(2-bromo-3-thienyl)-*N*-metallylcarbamate (**150**) affords a mixture of 5-*exo* (**151**) and 6-*endo* products (**152**), with the latter predominating (Scheme 47).[114]

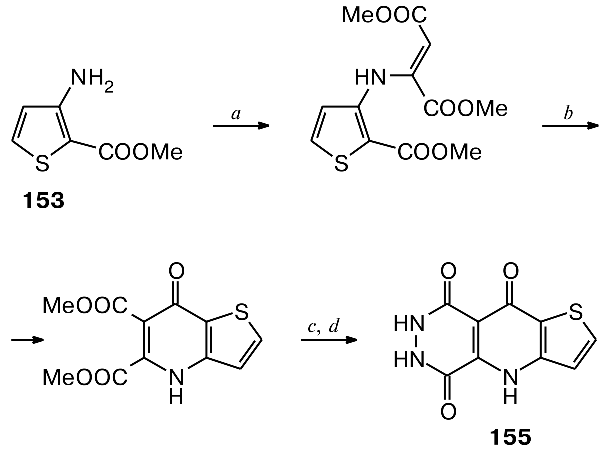
Scheme 47



Reagents and conditions: *i*) Bu_3SnH, AIBN, $PhCH_3$, reflux, 8 h.

The construction of the thieno[3,2-*b*]pyridine system *via* the 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 in reactions with 2C-components, which introduce two carbon atoms, *viz*., C(2) and C(3), into the pyridine ring. For example, the reaction of amino ester **153** with dimethyl acetylenedicarboxylate (**154**) involves intramolecular cyclocondensation followed by hydrazinolysis to give derivatives of the new heterocyclic system, *viz*., thieno[2´,3´:5,6]pyrido[2,3-*d*]pyridazine (**155**) (Scheme 48).[115]

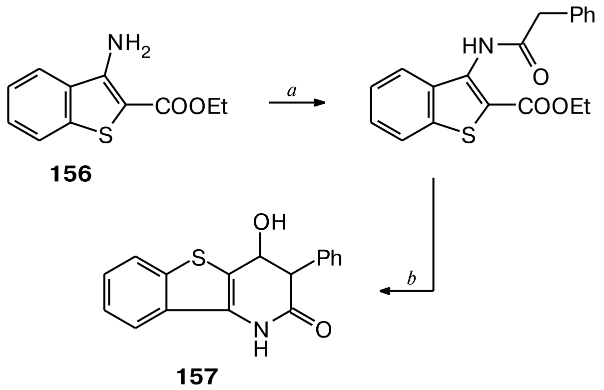
Scheme 48



Reagents, conditions, and yields: *a*) **154**, MeOH, reflux, 16 h, 62%; *b*) Bu^tOK, Bu^tOH, Δ, 45%; *c*) N_2H_4, MeOH, reflux, 72 h; *d*) 2 N HCl, Δ, 87%.

Phenylacetyl chloride can be used as the 2C-component in the *M*-type reactions. In these reactions, the N(1)—C(2) bond formation occurs due to acylation of 3-amino-2-ethoxycarbonylbenzothiophene (**156**); cyclization of the resulting amide in a basic medium affords the target benzothienopyridine **157** (Scheme 49).[116]

Scheme 49

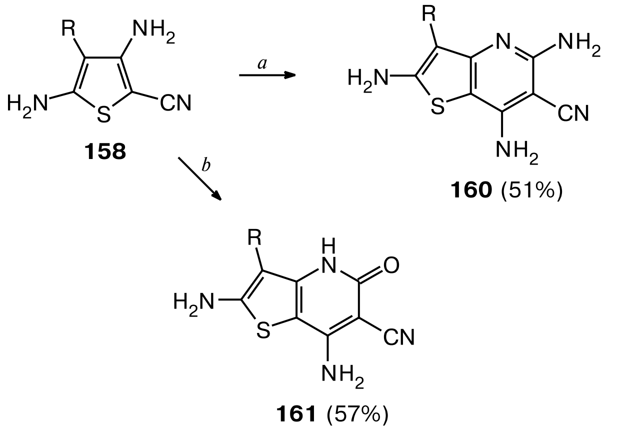


Reagents, conditions, and yields: *a*) $PhCH_2C(O)Cl$, Et_3N, THF, 0 °C → ~20 °C, 78.5%; *b*) $LiN(SiMe_3)_2$, THF, ~20 °C → reflux, 51%.

Thieno[3,2-*b*]pyridines **160** and **161** were synthesized starting from *o*-aminonitrile **158** and methylene-active compounds **159** (Scheme 50).[117]

The C(2)—C(3) bond formation provides the basis for the construction of the thieno[3,2-*b*]pyridine system according to the method *N*. Scarce examples of such transformations were, as a rule, based on nontrivial synthetic approaches. For example, it was found[118] that thienopyridazines **162** undergo unusual cyclization to give pyridothienopyridazines **163** under the conditions of the Vilsmeier—Haack reaction (Scheme 51).

Scheme 50



R is benzothiazol-2-yl.

Reagents and conditions: *a*) $NCCH_2CN$ (**159a**), AcOH, reflux, 4 h; *b*) $NCCH_2COOEt$ (**159b**), dioxane, Et_3N, reflux, 3 h.

An ingenious method for the construction of the pyridine ring based on the "*tert*-amino effect" was used[119] in the synthesis of a series of [3,2-*b*]-annelated thienoazines. Prolonged refluxing of diene aminodinitriles **164** in butanol affords thieno[3,2-*e*]indolizines and thieno[2,3-*c*]quinolizines of general formula **165** (Scheme 52).

In addition to the procedures for the pyridine ring closure based on the use of 3-aminothiophene derivatives, there are alternative methods for the construction of the thieno[3,2-*b*]pyridine system. One of approaches made successful use of cyclic β-keto sulfones, which proved to be convenient synthons for the modified Hantzsch synthesis of fused pyridines.[120] For example, the reactions of benzothiophene 1,1-dioxide **166** with enamines **167** or methylene-active compounds **168** in the presence of NH_4OAc produced fused dihydropyridines **169** (Scheme 53).[120c]

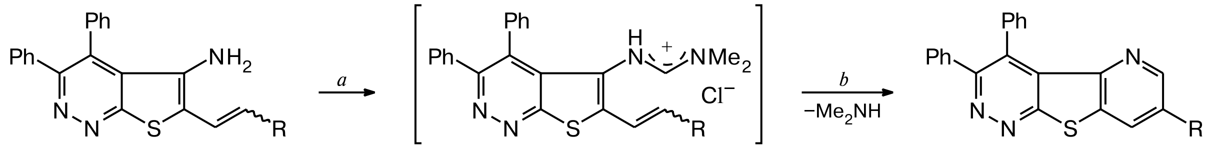
Three-component cyclocondensation of keto sulfone **170** (n = 1), enamino ester **167** (R = CO_2Me), and 2-nitrobenzaldehyde unexpectedly afforded hexahydrothieno[3,2-*b*]pyridine **171** (n = 1) instead of the 1,4-dihydropyridine derivative (Scheme 54). Heating of the latter led to its dehydration to form thienopyridine **172** (n = 1), which serves as a calcium channel blocker with a broad spectrum of biological activities.[120d]

The method based on the reaction of 3-bromo-2-cyanomethylpyridine (**173**, X = CN) or ester **173** (X = COOEt) with heterocumulenes, such as phenyl isothiocyanate or CS_2,[70] 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 **174** and **175** (Scheme 55). Low yields of the final products are attributed to low lability of the halogen atom at position 3 of the pyridine ring.

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 this aspect, 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 patended.[121] The use of nucleophilic substitution reactions[112,122] (see references cited in the studies[123]) and halogenation[122c] of these compounds was patended. Transformations giving rise to annelated products are of more interest. The reactions yielding polyfused thienopyridine-containing compounds were documented.[124] For example, tetra- and pentacyclic compounds **177** and **178** were synthesized with the use of different approaches starting from compound **176** (Scheme 56).

Bromination and nitration of some annelated thieno[3,2-*b*]pyridines were investigated. The reaction of thieno[3,2-*c*]isoquinoline *N*-oxide (**179**) with bromine yields 2,3-disubstituted product **180**, whereas treatment of **179** with HNO_3 affords 2-nitro derivative **181** (Scheme 57).[125]

Scheme 51

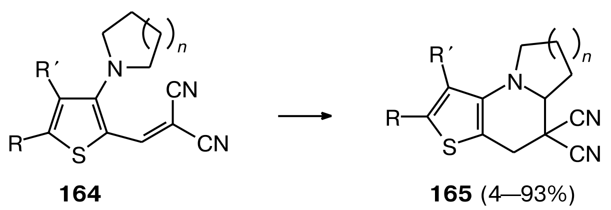


162 (R = COOEt, CN)

163a (R = COOEt, 45%)
163b (R = CN, 49%)

Reagents and conditions: *a*) 1) $POCl_3$, DMF, −10—0 °C, 1 h; 2) ~20 °C, 12 h; *b*) DMF, reflux, 24 h.

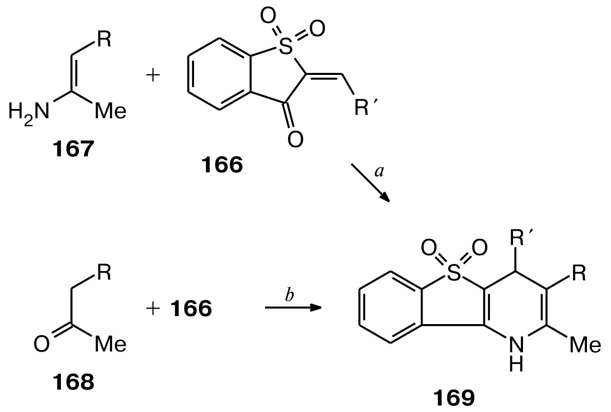
Scheme 52



R, R′ = H, Me, Ph, or R + R′ = C_4H_4; *n* = 1, 2.

Reagents and conditions: BuOH, N_2, reflux, 35—120 h.

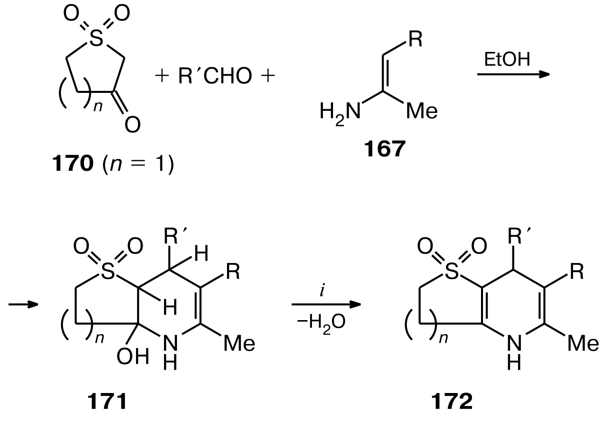
Scheme 53



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

Reagents and conditions: *a*) AcOH, reflux, 0.5 h; *b*) NH_4OAc, AcOH, reflux, 10 min.

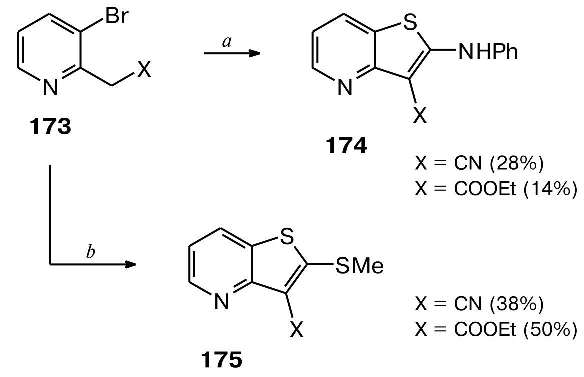
Scheme 54



R = COOMe, R′ = 2-$NO_2C_6H_4$; *n* = 1.

Reagents and conditions: *i*. $PhCH_3$, reflux, 24 h.

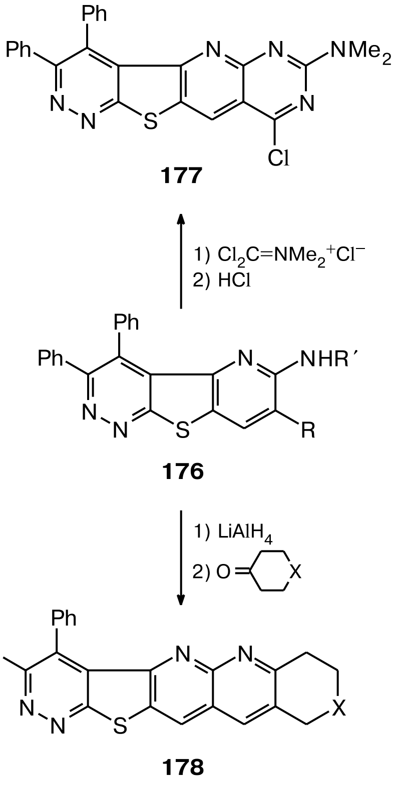
Scheme 55



X = CN, COOEt.

Reagents and conditions: *a*) 1) PhNCS, N_2, NaH, DMSO, 110 °C; 2) MeI; *b*) 1) CS_2, N_2, NaH, DMSO, 90 °C; 2) MeI.

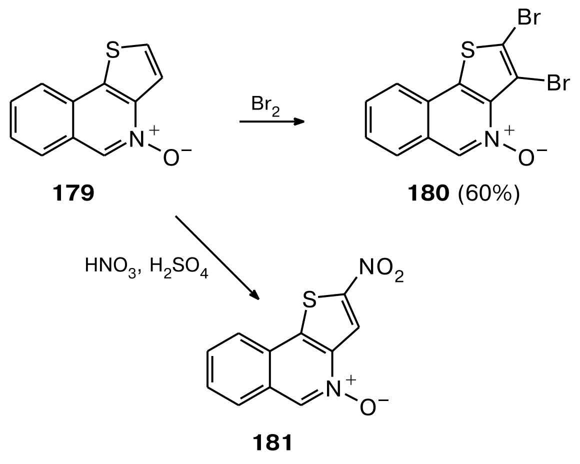
Scheme 56



R = CN; R′ = H; X = CH_2, NBz, O, S.

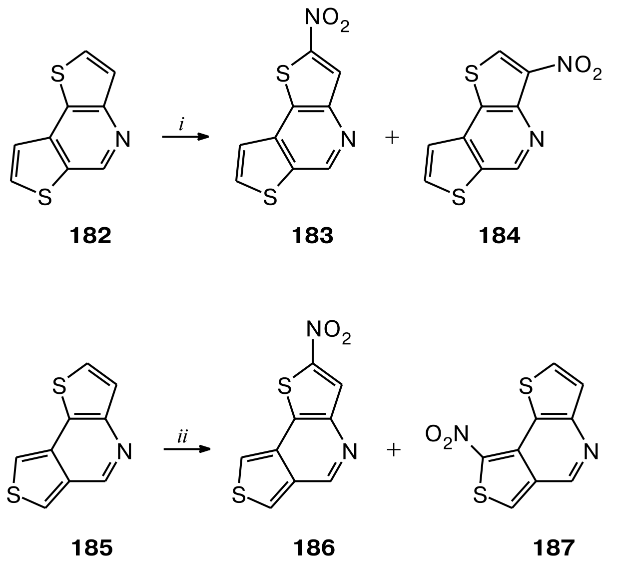
Nitration of dithieno[3,2-*b*:3′,2′-*d*]pyridine (**182**) occurs at both positions of the [3,2-*b*]-annelated thiophene ring to form a mixture of isomers **183** and **184** in a ratio of 40 : 60 (Scheme 58).[126] For dithieno[3,2-*b*:3′,4′-*d*]pyridine (**185**), the replacement occurs predominantly at the

Scheme 57



3,4-annelated ring. The 2-nitro- and 8-nitro isomers (**186** and **187**, respectively) were obtained in a ratio of 33 : 67.

Scheme 58



Reagents and conditions: *i*) TFA, HNO$_3$, (NH$_2$)$_2$C(O), 73 °C, 4 h; *ii*) TFA, HNO$_3$, (NH$_2$)$_2$C(O), 25 °C, 7 h.

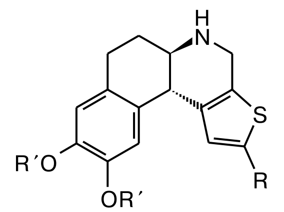
3. Thieno[2,3-*c*]pyridines

More than two hundred of studies devoted to the synthesis and transformations of thieno[2,3-*c*]pyridines have been published during the period under consideration. In several reviews,[3,12–14,19,42,43] great attention was given to the chemistry of this class of compounds. Evidently, this interest is equally associated with the prospects for their use as synthons in the synthesis of polycyclic structures and biological activities exhibited by many thieno[2,3-*c*]pyridine derivatives. The spectrum of practical applications of such compounds is wide. Thus, compounds possessing cardioprotective, antiproliferation, 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 erythropoeisis, 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 supressants.

Series of related polyfused [2,3-*c*]-annelated thienoazines exhibiting specific biological activities were documented. For example, tetracyclic compounds **188** belong to a new class of selective dopamine agonists.[127] Pyrimidine derivatives **189** having affinity for serotonin receptors were proposed for the treatment of central nervous system diseases.[128] A group of benzothienopyridine derivatives **190** and **191** exhibit psychotropic (anxiolytic) activity[129] and have strong ability to bind the 5-HT$_{1A}$ receptor.[130] Numerous studies (predominantly, patents) were devoted to the synthesis and transformations of pyridothienodiazepines **192** and, particularly, their triazolo[4,3-*a*]-fused derivatives **193**. These compounds are strong antagonists of platelet aggregation factor,[131] ligands of somatostatin receptors,[132] and benzodiazepine receptor antagonists[131j,133] and also possess antiallergic, antiischemic, antiasthmatic, and some other activities.[134] Earlier data on the biological activities of thieno[2,3-*c*]pyridines and related structures were summarized in the review.[14]

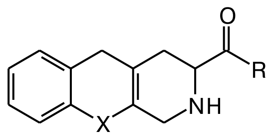
The majority of methods for the synthesis of thieno[2,3-*c*]pyridines and related fused structures can be tentatively divided into two groups based on the construction of the pyridine or thiophene ring, respectively.

Oxidative photochemical cyclization of *N*-aryl(hetaryl)-substituted 3-chlorothiophene-2-carboxamides **194** is one of the best studied approaches involving the pyridine ring construction. Although this method was known since the late 1970s[135] and was successfully used by other researchers,[136] Castle and coworkers have made the most prominent contribution to this field of chemistry of thienoazines. This research team succeeded in preparing new parent heterocyclic systems along with a large number of their derivatives[137] and performed experiments on the complete assignment of the signals in the ^{1}H and ^{13}C NMR spectra of some of these compounds.[138] Photo-

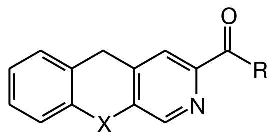


188

(R = H, Alk, Ph; R′ = H, Me, Ac)

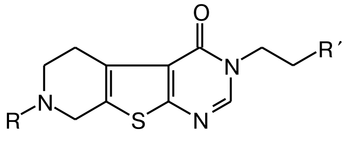


189



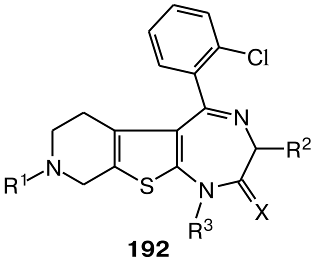
190

(X = S, SO, SO_2; R = NHR′, OAlk, $NHNH_2$)



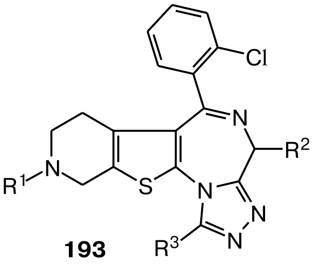
191

(R = H, Alk, Ac; R′ = Het)



192

(X = O, S; R^1 = H, C(X)NHR^4; R^2, R^3 = H, Alk)

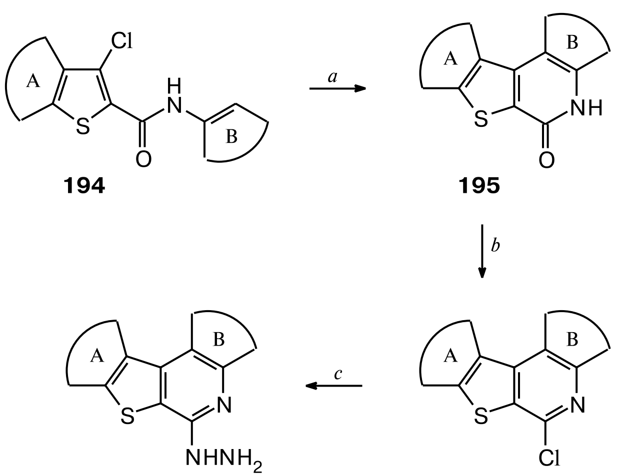


193

(R^1 = Alk; R^2, R^3 = H, Alk)

cyclization products of amides **194**, *viz.*, lactams **195**, were successively transformed into chlorides **196** and hydrazines **197** according to the most typical procedure (Scheme 59).

Scheme 59

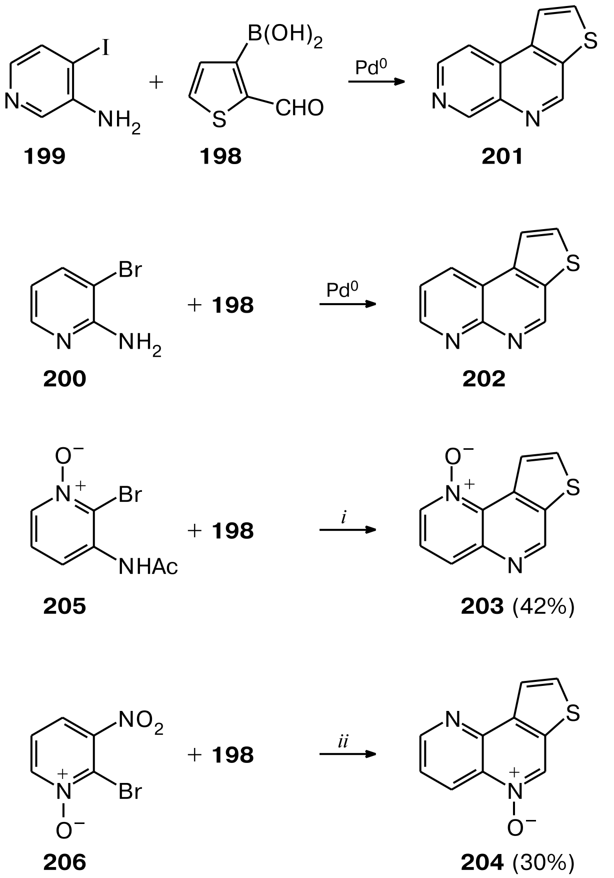


Reagents, conditions, and yields: *a*) *h*ν (UV), O_2, PhH or PhH—C_6H_{12}, or C_6H_{12}, Et_3N, 4—12 h, 22—92%; *b*) $POCl_3$, 100—120 °C, 4—24 h, 24—87%; *c*) N_2H_4, EtOH—PhH (1 : 1), reflux, 60—98%.

Fragments A and B represent annelated aromatic mono- or poly(hetero)cycles.

Isomeric thienonaphthyridines were synthesized using approaches based on the Suzuki reaction. For example, the reaction of 2-formyl-3-thiopheneboronic acid (**198**) with aminopyridines **199** and **200** produced thieno[2,3-*c*][1,7]naphthyridine (**201**) and thieno[2,3-*c*][1,8]naphthyridine (**202**), respectively (Scheme 60).[139] This method was also used to synthe-

Scheme 60

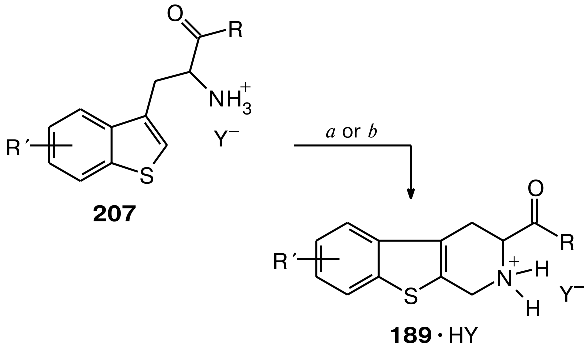


Reagents and conditions: *i*) $Pd(PPh_3)_4$, Na_2CO_3, $(MeOCH_2)_2$, reflux, 2 h; *ii*) 1) $Pd(PPh_3)_4$, Na_2CO_3; 2) $FeSO_4$, NH_4OH.

size[140] isomeric *N*-oxides **203** and **204** from pyridine *N*-oxides **205** and **206**, respectively.

Thieno[2,3-*c*]pyridine derivatives are often prepared according to methods based on the Pictet—Spengler reaction. For example, thiotryptophane esters and amides **207** undergo cyclocondensation under the action of formaldehyde to give biologically active benzothienopyridines **189** (as tosylates or hydrochlorides) (Scheme 61).[129b—h,130,141a,b]

Scheme 61



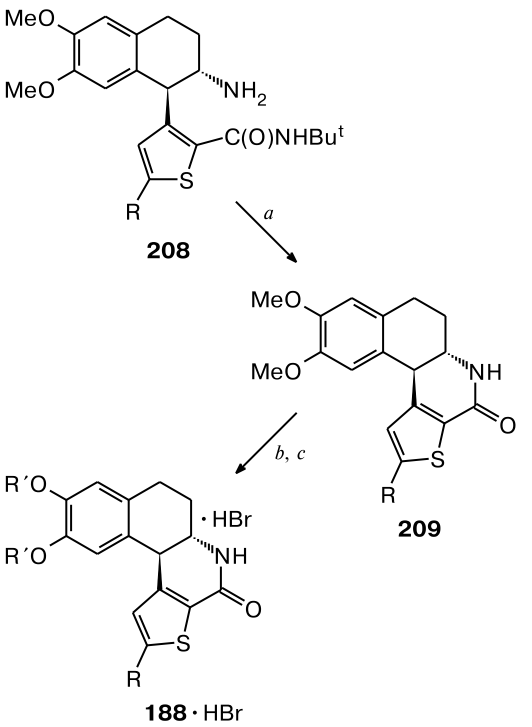
Y = Cl, TsO; R = OH, OMe, OEt, NHR^3.

Reagents, conditions, and yields: *a*) HCHO, EtOH—H_2O, reflux; *b*) 35% HCHO, HCl, MeOH—H_2O, 70—90 °C, 71—94%.

Multistep syntheses of dopamine agonists **188** were documented.[127] The pyridine ring can be constructed by either the Pictet—Spengler reaction[127e] or alternative methods. For example, intramolecular cyclization of compound **208** occurs in the presence of an acid catalyst to give lactams **209** in 60% yield; subsequent reduction and demethylation afford tetracyclic structure **188** (R = H, R´ = Bu^i) as hydrobromide.[127a] The strong medicine A-86929 was synthesized analogously (**188**, R = Pr, R´ = H) (Scheme 62).[127c]

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.[142]

Scheme 62

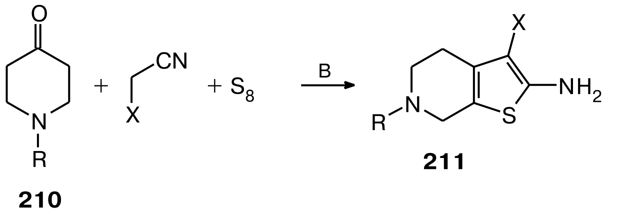


R = Pr; R´ = H; R = H; R´ = Bu^i.

Reagents, conditions, and yields: *a*) TsOH • H_2O, $PhCH_3$, reflux, 48 h, 60%; *b*) BH_3•THF, reflux, 14 h; *c*) BBr_3, CH_2Cl_2, −78 °C → Δ.

A smaller number of methods for the construction of thieno[2,3-*c*]pyridine systems is based on the formation of the thiophene fragment. Undoubtedly, the well-studied multicomponent Gewald reaction of *N*-substituted piperidin-4-ones **210** (X = NR), elemental sulfur, and methylene-active nitriles in the presence of secondary amines is the most popular of such methods. This approach was employed in more than 30 patents (see Refs 131b,e and 143). Data concerning this question are also available in the latest review[43] 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 °C) or, rarely, at 70—80 °C. The yields of the target tetrahydrothienopyridines **211** are, as a rule, 60—85% (Scheme 63). The products thus prepared serve as convenient precursors for the synthesis of various polyfused systems.

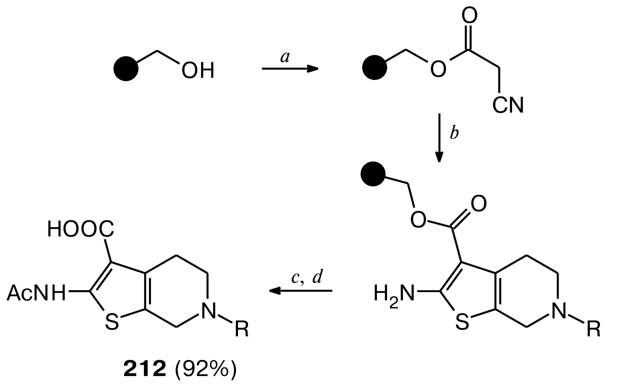
Scheme 63



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

The solid-state synthesis of thienopyridines by the Gewald reaction was documented. For example, compound **212** was prepared in 92% yield by cyanoacetylation of a polymer substrate and the reaction of the resulting ester on the polymer substrate with sulfur and piperidin-4-one **210** followed by acylation and elimination of the polymer matrix (Scheme 64).[144]

Scheme 64

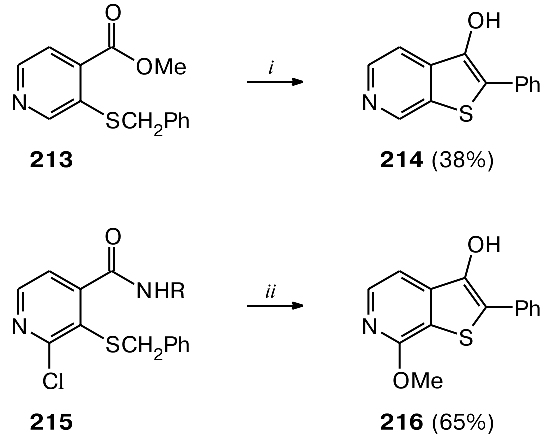


● — Argogel Wang Resin; R = $(CH_2)_5COOH$.

Reagents and conditions: *a*) $NCCH_2CO_2H$, $Pr^iN=C=NPr^i$, DMAP, CH_2Cl_2; *b*) **210** (X = NR), S_8, morpholine, EtOH, Δ; *c*) AcCl, CH_2Cl_2, $EtNPr^i_2$; *d*) TFA, H_2O, CH_2Cl_2.

Cyclocondensation of 3-(alkylthio)isonicotinic acid derivatives catalyzed by strong bases also provides a convenient method for the thiophene ring closure. For example, treatment of isonicotinate **213** with sodium hydride produced thienopyridine **214** (Scheme 65).[145] Cyclization of isonicotinamide **215** 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 (**216**).[146]

Scheme 65

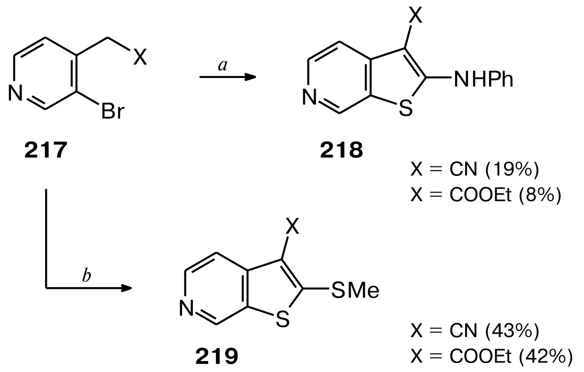


R = 4-MeOC₆H₄.

Reagents and conditions: *i*) NaH, DMF—THF, 60 °C, 3 h; *ii*) 5 equiv. of MeONa, DMF, 100 °C.

The above-described universal approach to the synthesis of various thienopyridines,[70] including [2,3-*c*]-annelated derivatives, deserves attention. The method is based on the reaction of halopyridines **217** with CS_2 or PhNCS (Scheme 66). Unfortunately, the yields of the target products **218** and **219** are low, evidently, due to low mobility of the bromine atom at position 3 of the pyridine ring.

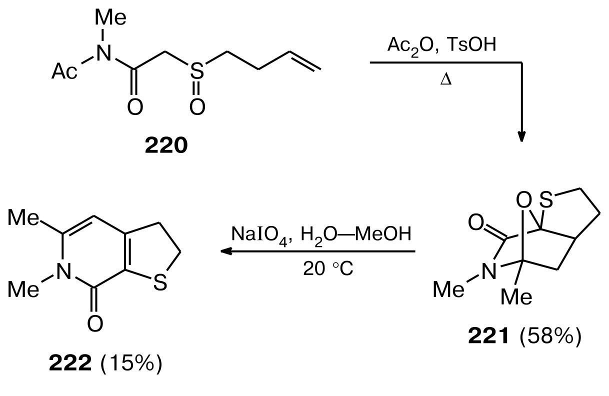
Scheme 66



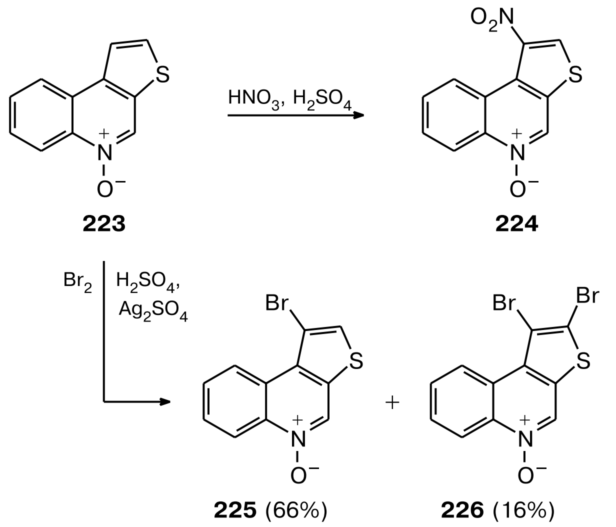
Reagents and conditions: *a*) 1) PhNCS, N_2, NaH, DMSO, 100 °C; 2) MeI, ~20 °C; *b*) 1) CS_2, N_2, NaH, DMSO, 90 °C; 2) MeI, ~20 °C.

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 **220** underwent the cascade transformation into compound **221**, which was oxidized to fused lactam **222** in low yield (Scheme 67).[147a] Data on the use of cascade transformations, including the Pummerer rearrangement—cycloaddition sequence, in the synthesis

Scheme 67



Scheme 68



of complex heterocyclic systems were summarized in the review.[147b]

In recent years, the reactivities of thieno[2,3-*c*]pyridine and its fused analogs have received considerable attention. It is of interest that nitration of thieno[2,3-*c*]quinoline 5-*N*-oxide (**223**) gives rise to 1-nitro derivative **224**,[125a] whereas bromination affords a mixture of bromide **225** and dibromide **226** (Scheme 68).[125b]

Annelation reactions, in which thieno[2,3-*c*]pyridines and, in particular, tetrahydrothienopyridines of general formula **227**, serve as building blocks, are of considerable interest. This choice is associated primarily with the ease of the preparation of these compounds by the Gewald reaction, as well as with the presence of two vicinal functional groups, which is favorable for the formation of additional cycles.

Besides, many annelation products of thienopyridines possess interesting biological activities. Numerous studies[131b—j,132a,133,134] were devoted to the synthesis of tetracyclic antagonists of platelet aggregation factor **193**. One of the most typical approaches is presented in Scheme 69.

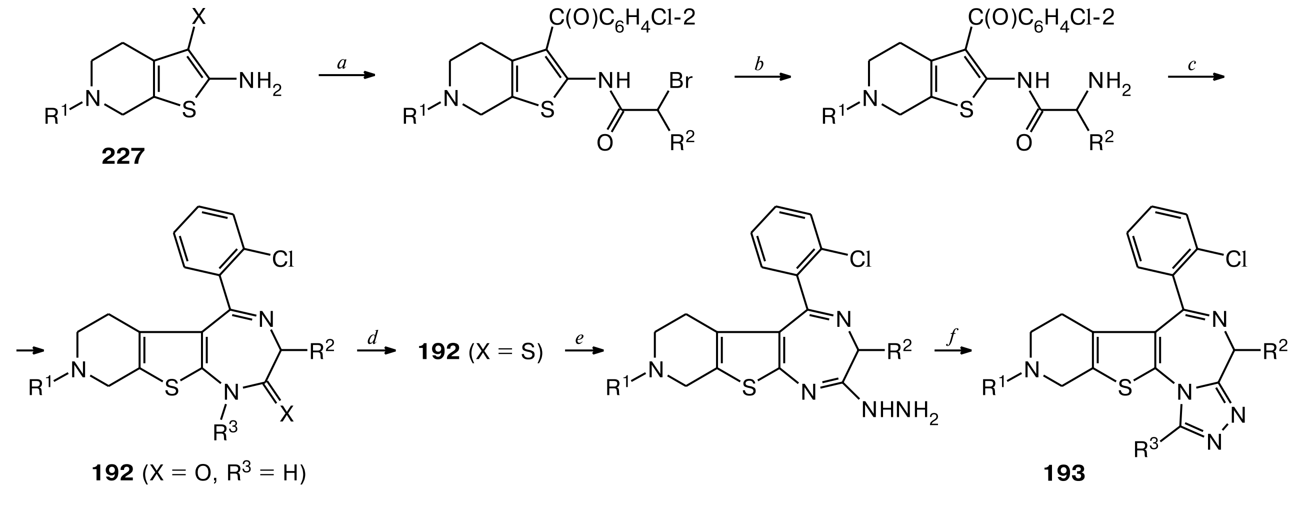
Hydrolysis of the ester group ($R^1 = CO_2Et$) in one of the steps of the synthesis affords finally compounds **192** and **193** (R^1 = H), which give a wide range of biologically active compounds upon treatment with various electrophilic reagents.[131,134] Interestingly, compounds **193** can be subjected to partial destruction in a strongly acidic medium to give a product of the diazepine ring opening in quantitative yield (Scheme 70).[148]

Ethyl *N*-[bis(methylthio)methylene]glycinate (**228**) and ethyl 2-*N*-(methylthiothiocarbonyl)glycinate (**229**) are convenient reagents for heteroannelation reactions. Heating of these compounds with thienopyridines **211** affords tri- and tetracyclic structures **230—233**.[149] Compounds **232** and **233** were also prepared by the independent synthesis starting from ethyl isothiocyanoacetate **234** (Scheme 71).[150a,b]

Annelation of thienopyridines **235** was studied. Treatment of these compounds with various electrophilic reagents gives rise to compounds **236—239** (Scheme 72).[151]

It should be noted that compound **237** cannot be prepared directly from thienopyridine **235** (R = H, X = CN). An attempt to perform this transformation by heating the

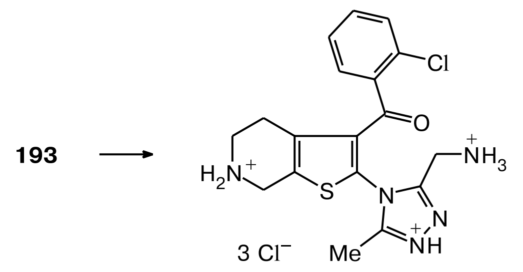
Scheme 69



$X = 2\text{-}ClC_6H_4C(O)$; R^1 = COOEt, Ac, *etc.*; R^2 = H, Me; R^3 = Alk.

Reagents and conditions: *a*) BrCH(R)C(O)Br, $HCCl_3$; *b*) NH_3; *c*) pyridine, N_2, reflux; *d*) Lawesson's reagent (LR) or P_2S_5; *e*) N_2H_4; *f*) $R^4C(OEt)_3$.

Scheme 70



193: R^1, R^2 = H, R^3 = Me.

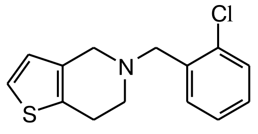
Reagents, conditions, and yield: HCl, H_2O, 20 °C, 16 h, 100%.

latter in formamide unexpectedly led to the formation of *ortho-peri*-fused thienopyridopyrimidine **240** (R´ = H) in 76% yield. Based on the results of investigation of the mechanism of this unusual cascade reaction, a general procedure was developed for the synthesis of such thienopyridopyrimidines from amides **241** (Scheme 73).[151b]

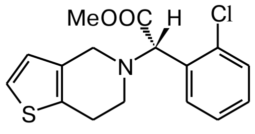
Selected properties of benzo[*b*]thieno[2,3-*c*]pyridines, which are associated predominantly with the transformations of the benzene ring, were documented.[152] Among the results of these investigations, interesting annelation reactions yielding tetranuclear fused heterocycles deserve notice.[152e] For example, dipyridobenzothiophenes **243—245** were prepared from amine **242** according to methods based on the pyridine ring construction in the Combes synthesis, the Gould—Jacobs reaction, and the Knorr synthesis, respectively (Scheme 74). Pyridothienoindole derivative **247** was synthesized in good yield from compound **246** in two steps.

4. Thieno[3,2-*c*]pyridines

Methods for the preparation of [3,2-*c*]-annelated thienopyridine derivatives and the properties of these compounds are well known and were described in the reviews.[3,14,19,35] The chemistry of this class of compounds has attracted interest because primarily of high biological activities of many thieno[3,2-*c*]pyridine derivatives. Let us mention the well-known drugs Ticlopidine **248** and Clopidogrel **249** possessing antithrombotic activity.

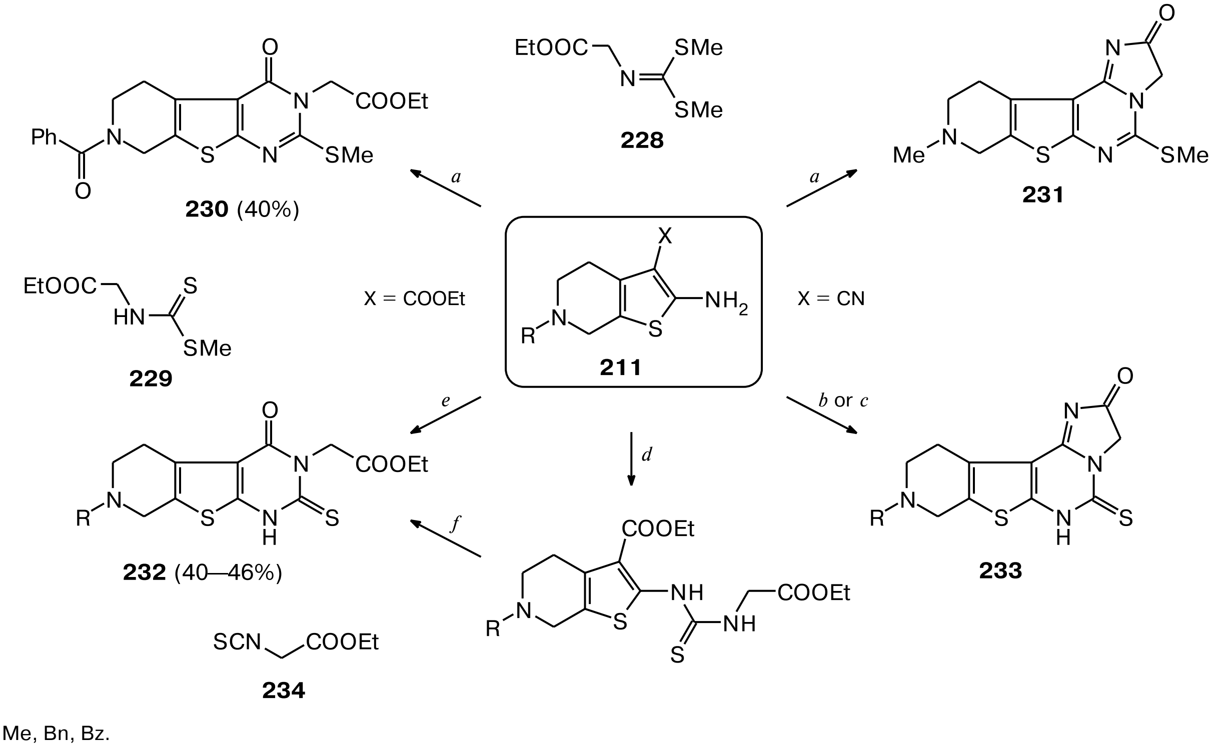


248



249

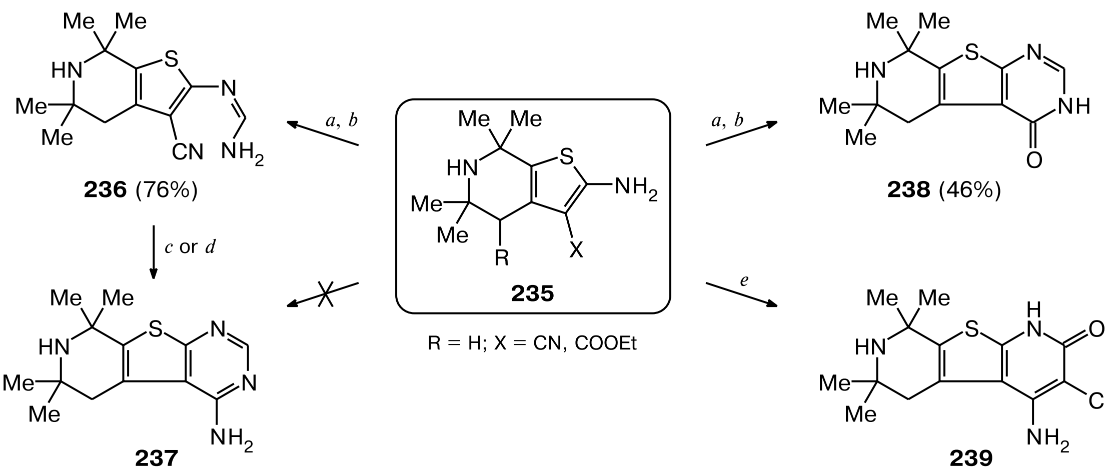
Scheme 71



R = Me, Bn, Bz.

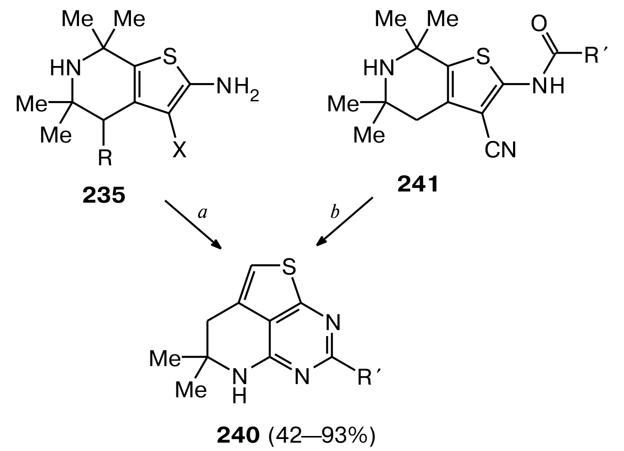
Reagents, conditions, and yields: *a*) **228**, AcOH, reflux, 2—5 h; *b*) **229**, DMF, reflux, 8—10 h, 36—44%; *c*) R = Me; **234**, 77%; *d*) **234**, pyridine, reflux; *e*) **229**, DMF, reflux, 8—10 h; *f*) EtONa.

Scheme 72



Reagents, conditions, and yields: *a*) HC(OEt)$_3$, reflux, 6—7 h; *b*) NH$_3$, ~20 °C; *c*) EtONa, EtOH, reflux, 4 h, 75%; *d*) HC(O)NH$_2$, Δ; *e*) XCH$_2$CN, EtONa, EtOH, reflux, 5 h, 54%.

Scheme 73

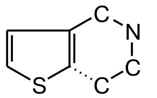


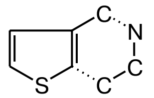
R = H; R′ = H, Me, Ph; X = CN; NMA is *N*-methylacetamide.

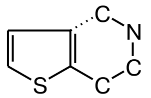
Reagents, conditions, and yields: *a*) HC(O)NH$_2$, 180 °C, 1 h, 76%; *b*) NH$_4$OAc, NMA, 140 or 185 °C, 1—4 h.

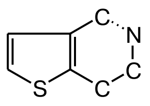
The antitumor activity of compound **248** and its salts was documented.[153] Methods for the synthesis of optically pure Clopidogrel **249**, its racemate, and the starting reagents were covered by patents.[154] The synthesis of ^{13}C-labelled Clopidogrel was described,[155] and its metabolic oxidation with hepatic cytochrome P450 monooxygenase was studied.[156] In addition to the above-mentioned compounds **248** and **249**, some thieno[3,2-*c*]pyridine derivatives serve as structurally different platelet aggregation inhibitors, possess antibacterial, antimicrobial, psychotropic, analgetic, antitumor, antiinflammatory, vasodilator, or hypotensive activities, and serve as 5-HT$_3$-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, serotonine 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 the review.[14]

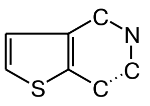
As in the case of the above-described isomeric structures, the thieno[3,2-*c*]pyridine system can be constructed by two radically different pathways, *viz.*, either by the pyridine ring construction starting from substituted thiophene or by annelation of the thiophene ring to the

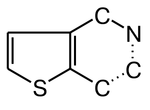

O

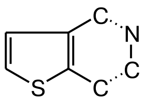

P


Q

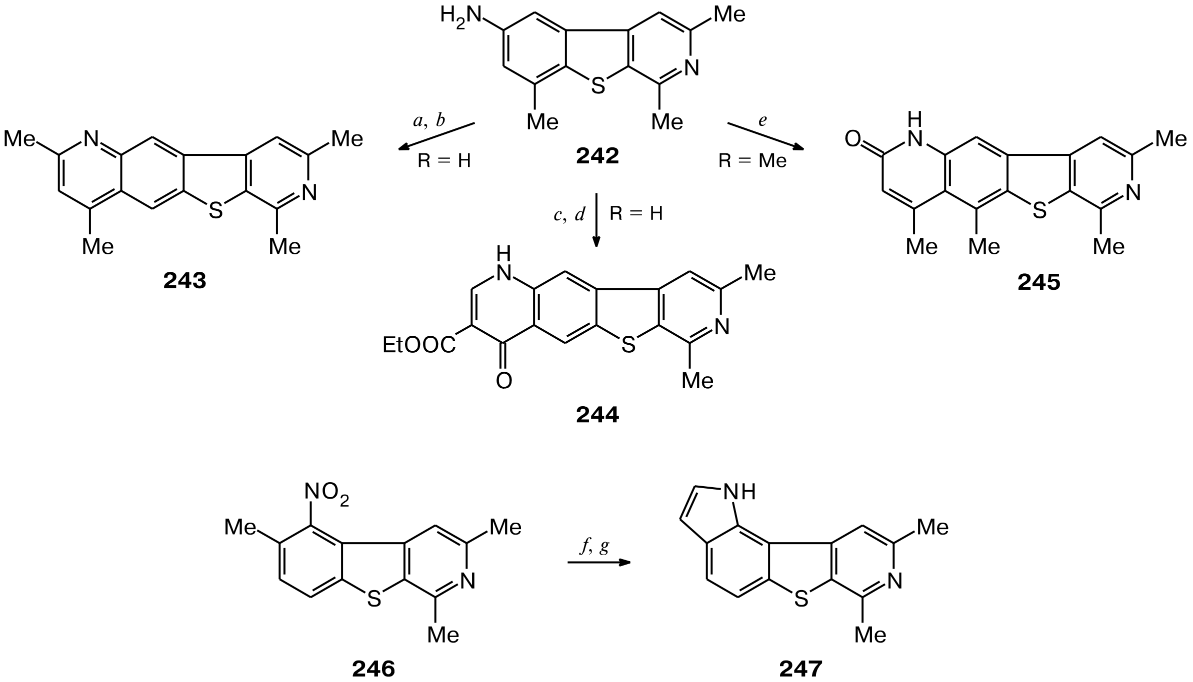

R


S


T


U

Scheme 74



Reagents, conditions, and yields: *a*) H_2CAc_2, reflux, 1.5 h; *b*) H_2SO_4, reflux, 0.5 h, 47%; *c*) (EtO)CH=C(COOMe)$_2$, toluene, reflux, 4 h; *d*) Ph_2O, Δ, 2 h, 27%; *e*) $AcCH_2COOEt$, H_2SO_4, reflux, 40%; *f*) $Me_2NCH(OMe)_2$, DMF, reflux, 5 h; *g*) H_2, Pd/C, MeOH, 68%.

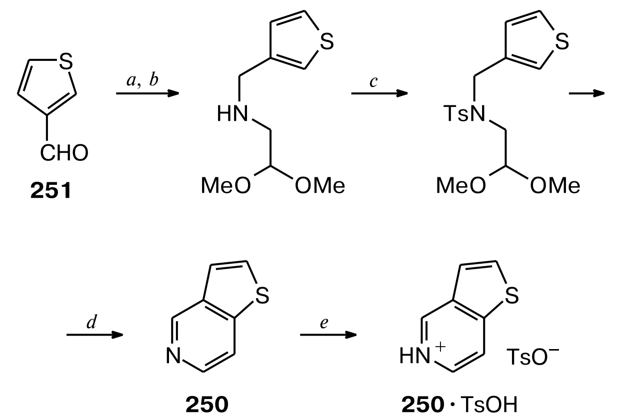
pyridine ring. The first method is more often used. For convenience, the types of the ring closure can be arbitrarily classified into the following main types, *O—Q*, and the modes *R—U* represented by a few examples

The 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 **250** in low yield (<10%), which was described for the first time in 1953,[157] provides an example of this approach. More recently, this procedure based on the Pomeranz—Fritsch reaction has been modified.[158a,b] The study[158b] demonstrated that thienopyridine **250** can be prepared in four steps from thiophene-3-carbaldehyde **251**; to facilitate the isolation and storage, the final product was transformed into the corresponding tosylate (Scheme 75).

Methods were developed for the preparation of thienoindolizines and thienoquinolizines from derivatives of proline and pipecolinic acid (Scheme 76).[159] Polyphosphoric acid (PPA) can be used as a cyclizing agent. The reaction can also be performed by the transformation of pipecolinic acids into acid chlorides followed by the intramolecular Friedel—Crafts reaction without isolation of the intermediate.

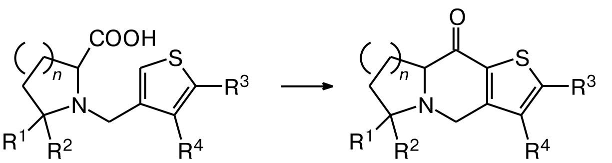
The pyridine ring construction according to the strategy *P* is based on the one-step formation of the C(4)—N(5) and C(7)—C(7a) bonds. For example, this approach provides the basis for the synthesis of the simplest isomeric dithienopyridines.[160a] The Stille cross-coupling reaction of 2-tributylstannyl-3-thiophenecarbaldehyde (**252**) with thienylcarbamates **113**, **253**, and **254** affords the target compounds **255—257**, respectively, in different yields (Scheme 77).

Scheme 75



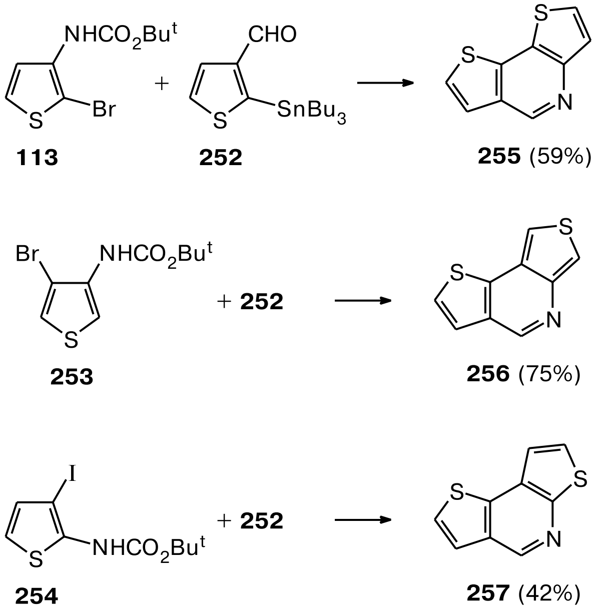
Reagents, conditions, and yields: *a*) $H_2NCH_2CH(OMe)_2$, ~20 °C, 16 h; *b*) H_2, 5% Pd/C, EtOH, 12 h, 95%; *c*) TsCl, Et_3N, EtOAc, ~20 °C, 12 h, 91%; *d*) HCl, dioxane, reflux, 16 h, 49%; *e*) TsOH · H_2O, Me_2CO, ~20 °C, 2 h, 85%.

Scheme 76



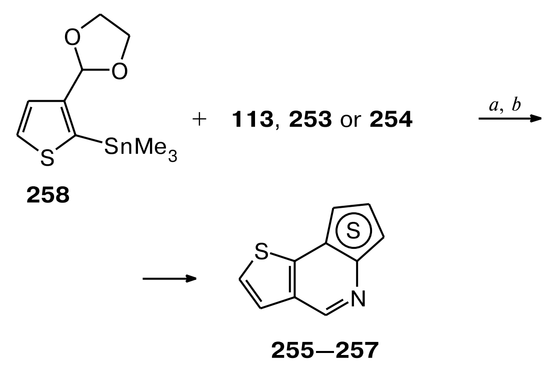
R^1, R^2 = H or R^1 + R^2 = O, S; R^3, R^4 = H or R^3 + R^4 = C_4H_4;
n = 1, 2.

Scheme 77



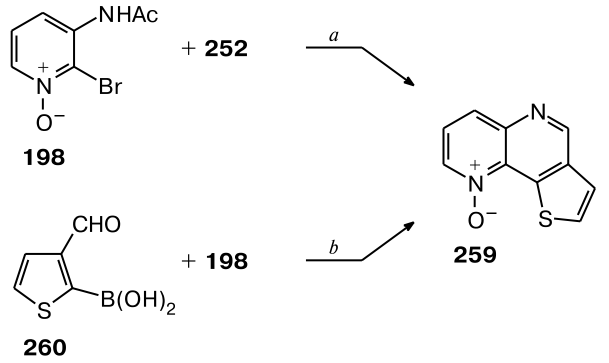
Reagents and conditions: $Pd(PPh)_3$, DMF, 100 °C, 24 h.

Scheme 78



Reagents, conditions, and yields: *a*) $Pd(PPh_3)_4$, DMF, 100—120 °C, 24 h; *b*) 2 *N* HCl, reflux, 1 h; **255** — 43%, **256** — 63%, **257** — 27%.

Scheme 79



Reagents, conditions, and yields: *a*) $Pd(PPh)_3$, CuO, DMF, 100 °C, 54%; *b*) $Pd(PPh_3)_4$, Na_2CO_3, $(MeOCH_2)_2$, reflux, 2 h, 20%.

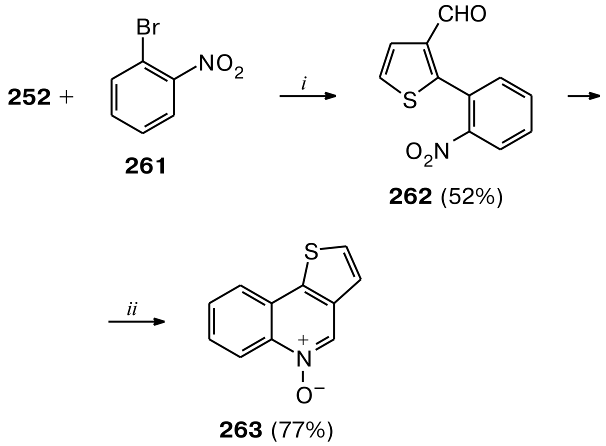
In an alternative procedure for the preparation of dithienopyridines **255—257**, acetal **258** is used instead of aldehyde **252**, and the reaction mixture is then treated with hydrochloric acid; however, this procedure affords the target products (Scheme 78) in lower yields (27—63%).[160b]

The tricyclic skeleton of thieno[3,2-*c*][1,5]naphthyridine 9-*N*-oxide (**259**) was constructed[140] in two ways: by condensation of aldehyde **252** with pyridine *N*-oxide **198** or (in lower yield) by the modified Suzuki reaction of the latter with 3-formylthiophene-2-boronic acid (**260**) (Scheme 79).

The one-pot Stille cross-coupling reaction of compound **252** produced all four isomeric thieno[3,2-*c*]naphthyridines.[139] 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 **252** reacts with arene **261** to give compound **262**; reduction of its nitro group is accompanied by cyclization to form thieno[3,2-*c*]isoquinoline *N*-oxide (**263**) (Scheme 80).[103]

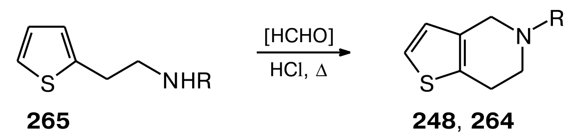
The method *Q* is based on the C(3a)—C(4) bond formation in the step of the direct pyridine ring closure and is most often used in the synthesis of the thieno[3,2-*c*]pyridine moiety. Of all the possible methods of this type, the Pictet—Spengler reaction has gained the most acceptance. This method provides a convenient and simple route to highly active drugs, including Ticlopidine **248** and Clopidogrel **249**. Ticlopidine or its precursor, *viz.*, 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine **264**, can be synthesized by treating 2-(2-thienyl)ethylamine derivative **265** (or its acid chloride) in the presence of acid (generally, HCl) at high temperature with a HCHO solution [161] or its synthetic equivalents, *viz.*, 1,3-dithiane, 1,3-dioxane,[153b,162] dimethoxymethane,[163] or 1,3-dioxolane,[153b,162,164a,b] which can also serve as the solvent (Scheme 81).

Scheme 80



i. Pd^0, DMF; *ii*. $FeSO_4$, 2 *N* HCl, aqueous NH_3.

Scheme 81



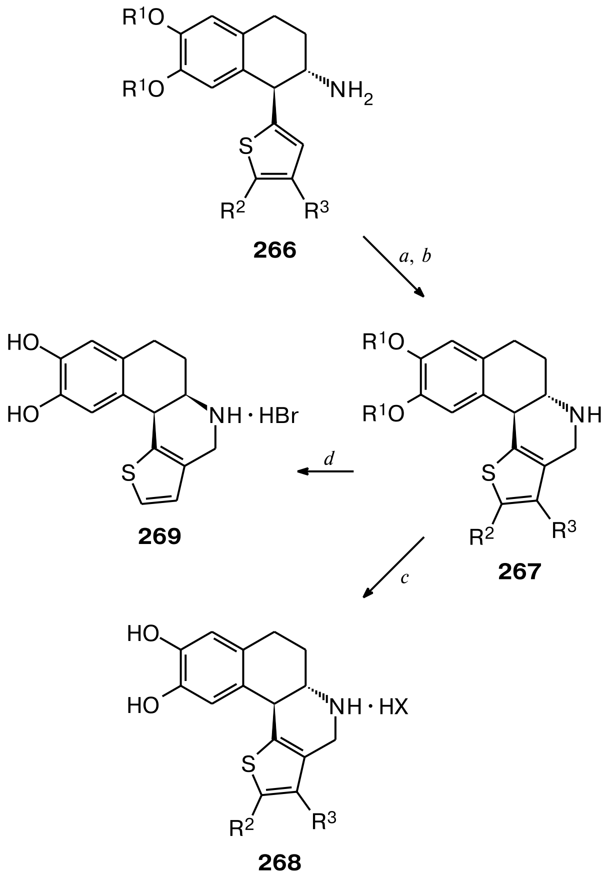
R = 2-$ClC_6H_4CH_2$ (**248**), H (**264**).

The approach *Q* was used to synthesize a series of selective dopamine agonists.[127a,g] The reaction of amines **266** with paraformaldehyde in an alkaline medium and then in an acidic medium produced benzothieno[3,2-*c*]quinolines **267**, which were transformed into the target products **268** (as the corresponding salts) by deprotection under the action of boron halides. Compounds **268** possess the above-mentioned activity. Interestingly, demethylation of compound **267** (R^1 = Me, R^2, R^3 = H) with HBr affords epimeric product **269** in quantitative yield (Scheme 82).

In one of the steps in the synthesis of thienopyridine inhibitors of metalloproteases possessing anticancer and antiinflammatory activities, the pyridine ring is constructed by treating β-(2-thienyl)-D-alanine (**270**) with formaline in an acidic medium.[165] In particular, this method was used to prepare 6-(*R*)-amino acid **271** in 91% yield (Scheme 83). *N*-Cbz-β-(2-Thienyl)-L-alanine amide **272** was transformed into 4,5,6,7-tetrahydrothienopyridine-(6*S*)-carboxamide under the action of dimethoxymethane in the presence of an acid.[166] Compound **273** serves as an intermediate in the synthesis of anti-AIDS drugs.

The method *R* involves the C(4)—N(5) bond formation in the cyclization step. This approach was used to synthesize compound **267** (R^2 = Bu^t, R^3 = H) starting from cyclic acetal **274** (Scheme 84).[127a]

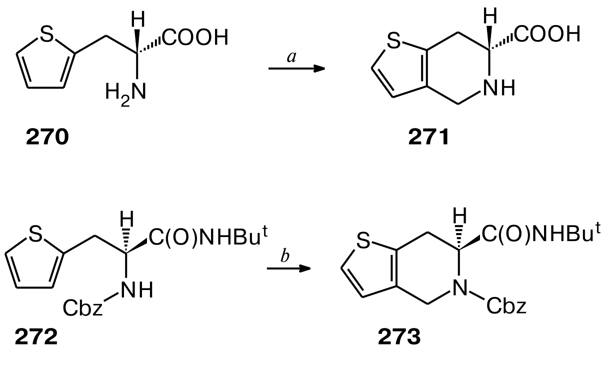
Scheme 82



R^1 = Me or $R^1 + R^1 = CH_2$; R^2 = H, Alk, Cl; R^3 = H, Pr.

Reagents, conditions, and yields: *a*) $(HCHO)_n$, K_2CO_3, MeOH, ~20 °C; *b*) TFA, CH_2Cl_2; *c*) BX_3 (X = Cl, Br), −78 °C → Δ; *d*) 48% HBr, AcOH, reflux, 2 h, 98%.

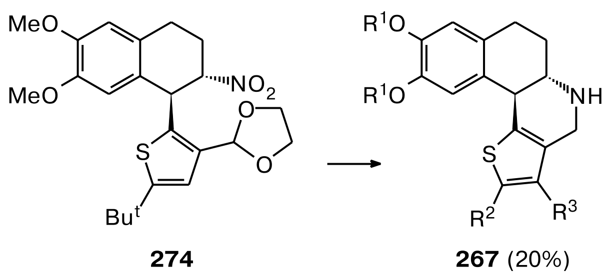
Scheme 83



Reagents, conditions, and yields: *a*) 37% HCHO, HCl—H_2O, 90 °C, 3 h, 91%; *b*) $(MeO)_2CH_2$, TFA, Cl_2CHCH_2Cl, reflux, 0.25 h, 69%.

An alternative approach[167] to the construction of the thieno[3,2-*c*]pyridine system is based on the C(6)—C(7)

Scheme 84

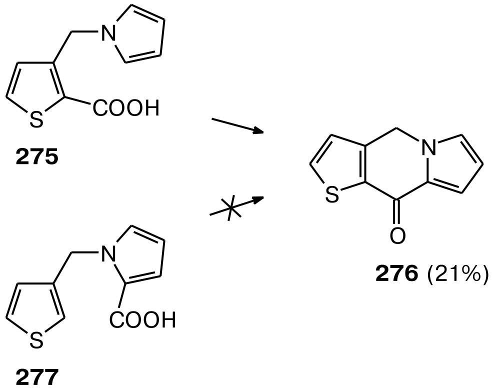


R^1 = Me; R^2 = Bu^t; R^3 = H.

Reagents and conditions: Zn, HCl, 60 °C, 0.25 h.

bond formation (approach *S*). For example, heating of carboxylic acid **275** in PPA resulted in its cyclization giving rise to 9-oxo-4*H*,9*H*-pyrrolo[1,2-*a*]thieno[2,3-*d*]pyridine (**276**) in low yield. An attempt to prepare this compound by an independent synthesis, *viz.*, by cyclization of isomeric acid **277** under analogous conditions, failed (Scheme 85).

Scheme 85

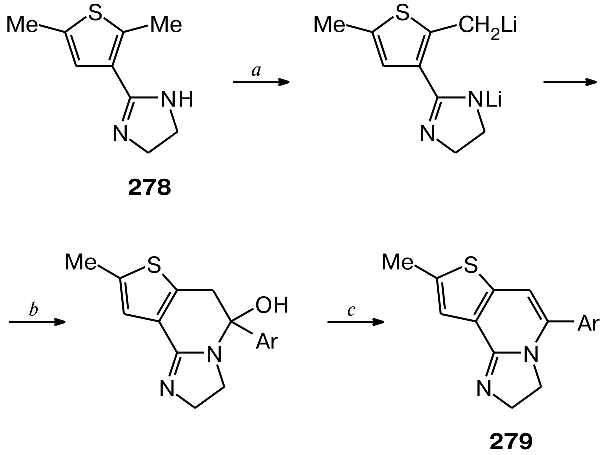


Reagents and conditions: PPA, 90 °C, 1 h.

The approach *T* (the one-step formation of the N(5)—C(6) and C(6)—C(7) bonds) was used only in the study,[168] where imidazothienopyridines **279** possessing antitumor activity were synthesized from 2-(3-thienyl)imidazoline derivatives **278** (Scheme 86).

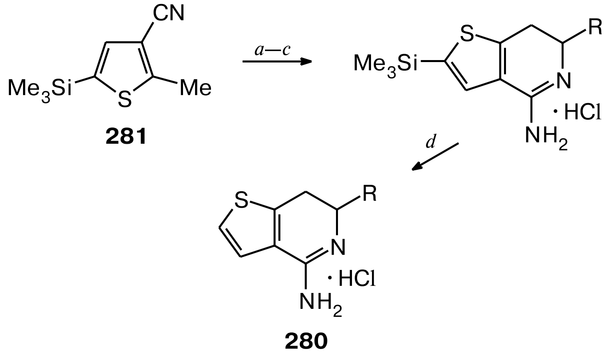
The method *U* (the pyridine ring construction through the N(5)—C(4) and C(6)—C(7) bond formation) can be exemplified by the scheme of the synthesis of 6,7-dihydrothieno[3,2-*c*]pyridines **280**. This method is based on the reaction of 2-methyl-5-trimethylsilylthiophene-3-carbonitirile (**281**) with aldimines generated *in situ* followed by desilylation of the intermediate (Scheme 87).[169]

Scheme 86



Reagents and conditions: *a*) BuLi, N_2, THF, –78 °C; *b*) $ArCO_2R$ (R = Me, Et), THF; *c*) $TsOH \cdot H_2O$, benzene, reflux.

Scheme 87



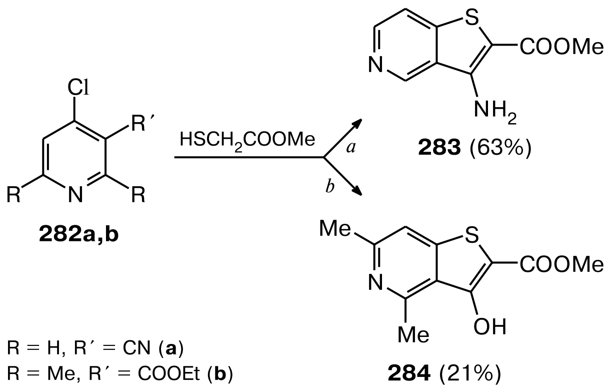
R = Ph, $Me_3SiC{\equiv}C$, *cyclo*-Pr.

Reagents and conditions: *a*) BuLi, Pr^i_2NH, DMPU, –78 °C; *b*) $LiN(SiMe_3)_2$, RCHO, $-78 \rightarrow 0$ °C; *c*) 6 *N* HCl; *d*) Bu_4NF, THF.

Methods based on the pyridine → 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 **282** with methyl thioglycolate produced compounds **283** and **284** in one step as a result of the replacement of the chlorine atom and Thorpe or Thorpe—Dieckmann cyclization (Scheme 88).[170]

The reaction of tetrachloropyridine **285** with sodium hydrosulfide giving rise only to 4-mercapto derivative **286** (Scheme 89), which was transformed[171] into compound **287** in 77% yield (with respect to mercaptopyridine **286**) by *S*-alkylation and Dieckmann cyclization, is another example of the application of this approach.

Scheme 88



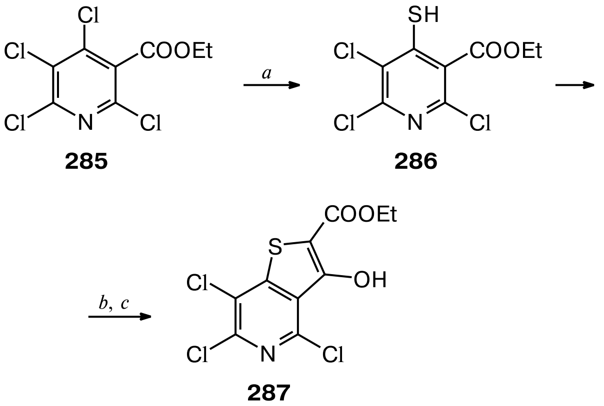
282a,b

283 (63%)

284 (21%)

Reagents and conditions: *a*) **282a**, MeONa, DMF, ~20 °C; *b*) **282b**, MeONa, DMF, Δ, 20 min.

Scheme 89



285

286

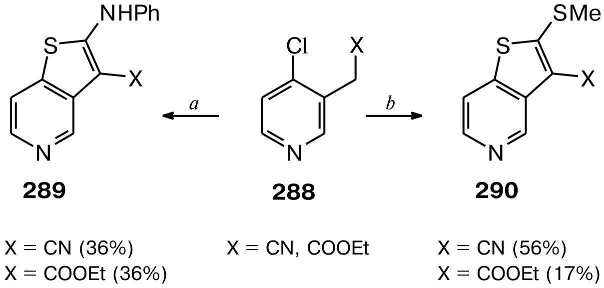
287

Reagents, conditions, and yields: *a*) NaSH, EtOH, ~20 °C, 0.5 h, 64%; *b*) $BrCH_2COOEt$, EtONa, EtOH, reflux, 3 h; *c*) NaH, THF, Δ, 5 min, 77%.

The thiophene ring can be constructed with the use of another sequence of reactions, where the nucleophilic displacement is the final step of cyclization.[70] The reaction of pyridines **288** with heterocumulenes in the presence of a strong base produces thieno[3,2-*c*]pyridines **289** and **290** (Scheme 90). This reaction proceeds through the intermediate formation of disodium salts of ketene *S*,*N*-acetal or ketene *S*,*S*-acetal derivatives, respectively.

Numerous syntheses covered by patents[153a,154a,b,172] were based on *N*-alkylation of tetrahydrothieno[3,2-*c*]pyridine **264** and related compounds (see Refs 173 and 174). Many biologically active compounds, including Ticlopidine **248**, were synthesized. A number of precursors of this drug were prepared by deamination of 3-aminothieno[3,2-*c*]pyridine derivatives.[173b,175] The synthesis of compound **291** from thienopyridine **292** (R = $2\text{-}ClC_6H_4CH_2$) (Scheme 91) provides an example.[173b]

Scheme 90



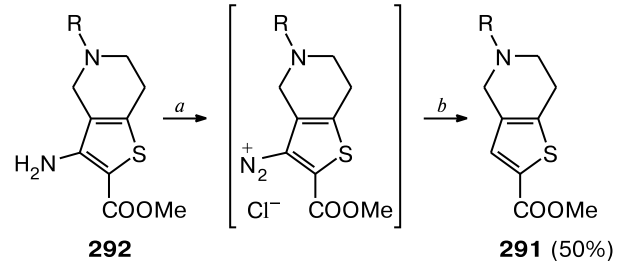
289

288

290

Reagents and conditions: *a*) 1) PhNCS, N_2, NaH, DMSO, 70—80 °C; 2) MeI, ~20 °C; *b*) 1) CS_2, N_2, NaH, DMSO, 90 °C; 2) MeI, ~20 °C.

Scheme 91



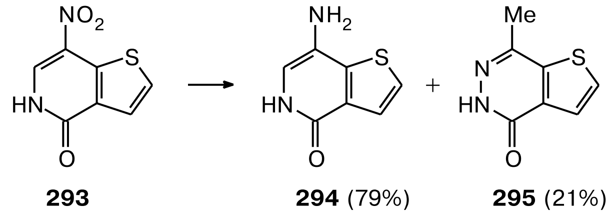
292

291 (50%)

Reagents and conditions: *a*) $NaNO_2$, H_2SO_4—H_2O, 0—5 °C, 0.5 h; *b*) polyphosphoric acid, ~20 °C, 1 h.

Of other transformations of thieno[3,2-*c*]pyridines, let us mention reduction of both functional groups and endocyclic multiple bonds,[174,176] which occur in a usual way. An attempt to reduce thienopyridone **293** with hydrazine hydrate led to the formation of thienopyridazine derivative **295** along with the expected product **294** (Scheme 92).[177]

Scheme 92



293

294 (79%)

295 (21%)

Reagents and conditions: $N_2H_4 \cdot H_2O$, 135—140 °C, 3 h.

Conclusions

The development of new chemo-, regio-, stereo-, and enantioselective procedures for the synthesis of poly-functional carbo- and heterocycles with practically useful properties is a fundamental problem of synthetic organic chemistry. The synthesis of derivatives of pyridine and its fused analogs is of special interest. These methods should not only be based on simple and industrially available substrates and reagents and characterized by low cost of the final products but also be ecologically safe. In this connection, one-pot syntheses have attracted great interest in recent years. These methods involve two groups of reactions: successive reactions, in the course of which another reagent, a substrate, or a catalyst is added or the reaction temperature is varied without isolation of intermediates, and the cascade reactions occurring under the same conditions without the addition of other reagents or catalysts, the transformations of the functional groups formed in previous steps being transformed in each subsequent step. Multicomponent cascade processes have attracted great interest, which was reflected in reviews (see for example, Ref. 178). These methods can serve as a basis for both the directed organic synthesis and combinatorial chemistry, which allows the simultaneous synthesis of thousands of samples for biological screening using automated high-technology procedures (see Ref. 179).

In our opinion, the one-pot multicomponent condensation occurring as cascade heterocyclization, will undoubtedly receive further development in this promising and rapidly evolving area of organic and bioorganic chemistry (which is evident from numerous investigations in the field of chemistry of thienopyridines considered in the present review). The design of new groups of biologically active compounds and a high pharmacological potential of thienopyridine derivatives 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.

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References

1. E. Lukevics, *Khim. Geterotsikl. Soedin.*, 1995, 723 [*Chem. Heterocycl. Compd.*, 1995 (Engl. Transl.)].
2. F. A. Selimov, U. M. Dzhemilev, and O. A. Ptashko, *Metallokompleksnyi kataliz v sinteze piridinovykh osnovanii* [*Metal-Complex Catalysis in Synthesis of Pyridine Bases*], Khimiya, Moscow, 2003 (in Russian).
3. J. M. Barker, *Adv. Heterocycl. Chem.*, 1977, **21**, 65.
4. V. P. Litvinov, L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and A. Senning, *Sulfur Rep.*, 1992, **13**, 1.
5. V. A. Artemov, V. L. Ivanov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 2000, 435 [*Chem. Heterocycl. Compd.*, 2000 (Engl. Transl.)].
6. Ya. Ozols, B. Vigante, and G. Duburs, *Khim. Geterotsikl. Soedin.*, 1994, 1603 [*Chem. Heterocycl. Compd.*, 1994 (Engl. Transl.)].
7. V. P. Litvinov, Ya. Yu. Yakunin, and V. D. Dyachenko, *Khim. Geterotsikl. Soedin.*, 2001, 41 [*Chem. Heterocycl. Compd.*, 2001 (Engl. Transl.)].
8. D. G. Kim and O. V. Pryakhina, *Khim. Geterotsikl. Soedin.*, 1996, 1026 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)].
9. B. C. Sekhar, S. R. Ramadas, and D. V. Ramana, *Heterocycles*, 2000, **53**, 941.
10. D. G. Kim and N. P. Brisyuk, *Khim. Geterotsikl. Soedin.*, 1991, 1155 [*Chem. Heterocycl. Compd.*, 1991 (Engl. Transl.)].
11. A. E. Sausin´sh and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 1992, 435 [*Chem. Heterocycl. Compd.*, 1992 (Engl. Transl.)].
12. M. A. Yurovskaya and O. D. Mit´kin, *Khim. Geterotsikl. Soedin.*, 1999, 437 [*Chem. Heterocycl. Compd.*, 1999 (Engl. Transl.)].
13. V. V. Dabaeva, A. S. Noravyan, B. D. Enokyan, and V. N. Madakyan, *Khim. Zh. Arm.* [*Arm. Chem. J.*], 1997, **50**, 83 (in Russian).
14. E. G. Paronikyan, A. S. Noravyan, and S. A. Vartanyan, *Khim.-farm. Zh.*, 1987, **21**, No. 5, 536 [*Pharm. Chem. J.*, 1987, **21**, No. 5 (Engl. Transl.)].
15. D. G. Kim and L. V. Gavrilova, *Khim. Geterotsikl. Soedin.*, 1997, 1603 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)].
16. V. P. Litvinov, S. G. Krivokolysko, and V. D. Dyachenko, *Khim. Geterotsikl. Soedin.*, 1999, 579 [*Chem. Heterocycl. Compd.*, 1999 (Engl. Transl.)].
17. V. P. Litvinov, *Usp. Khim.*, 1999, **68**, 817 [*Russ. Chem. Rev.*, 1999, **68** (Engl. Transl.)].
18. V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 2123 [*Russ. Chem. Bull.*, 1998, **47**, 2053 (Engl. Transl.)].
19. V. P. Litvinov, S. V. Roman, and V. D. Dyachenko, *Usp. Khim.*, 2000, **69**, 218 [*Russ. Chem. Rev.*, 2000, **69** (Engl. Transl.)].
20. V. P. Litvinov, S. V. Roman, and V. D. Dyachenko, *Usp. Khim.*, 2001, **70**, 343 [*Russ. Chem. Rev.*, 2001, **70** (Engl. Transl.)].
21. V. P. Litvinov, *Usp. Khim.*, 1999, **68**, 45 [*Russ. Chem. Rev.*, 1999, **68** (Engl. Transl.)].
22. Yu. A. Sharanin, M. P. Goncharenko, and V. P. Litvinov, *Usp. Khim.*, 1998, **67**, 442 [*Russ. Chem. Rev.*, 1998, **67** (Engl. Transl.)].
23. L. A. Rodinovskaya, A. M. Shestopalov, Yu. A. Sharanin, and V. P. Litvinov, in *Enaminy v organicheskom sinteze*

[*Enamines in Organic Synthesis*], Izd-vo UrO AN SSSR, Sverdlovsk, 1989, p. 48 (in Russian).
24. I. P. Skrastin´sh and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 1992, 781 [*Chem. Heterocycl. Compd.*, 1992 (Engl. Transl.)].
25. V. P. Litviniov, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1993, **74**, 139.
26. J. Becher, *Dan. Kemi*, 1986, **67**, 215; *RZhKhim*, 1987, 5Zh241.
27. G. Timari, G. Hajos, Z. Riedl, M. Beres, T. Soos, A. Messmer, and S. Gronowitz, *Molecules* (online journal), Avail. http://www/mdpi.net/molecules, 1996, **1**, 236.
28. K. Undheim, *Heterocycles*, 1981, **15**, 1349.
29. S. Gronowitz and A.-B. Hörnfeldt, in *Progress in Heterocyclic Chemistry*, Vol. **3**, Eds H. Suschitzky and E. F. V. Scriven, Pergamon Press, Oxford, 1991, P. 21.
30. E. V. Babaev, *J. Heterocycl. Chem.*, 2000, **37**, 519.
31. Yu. I. Gevaza and V. I. Staninets, *Ukr. Khim. Zz.* [*Ukr. Chem. J.*], 2002, **68**, 67 (in Russian).
32. M. H. Osterhout, W. R. Nadler, and A. Padwa, *Synthesis*, 1994, 123.
33. Y. Tominaga, *J. Heterocycl. Chem.*, 1989, **26**, 1167.
34. F. F. Abdel-Latif and R. Shaker, *Topics in Heterocyclic Systems — Synthesis, Reactions and Properties*, 1996, **1**, 87.
35. L. H. Klemm, *Trends Heterocycl. Chem.*, 1997, **5**, 37; *Chem. Abstr.*, 1999, **130**, 66406.
36. I. Hermecz, *Adv. Heterocycl. Chem.*, 1998, **72**, 225.
37. I. Hermecz, *Adv. Heterocycl. Chem.*, 1998, **69**, 89.
38. H. Maruoka, *Fukuoka Daigaku Yakugaku Kiyo*, 1998, **22**, 1; *Chem. Abstr.*, 1998, **128**, 192497.
39. V. P. Litvinov, V. K. Promonenkov, Yu. A. Sharanin, and A. M. Shestopalov, in *Itogi nauki i tekhniki. Ser. Org. khimii* [*Advances in Science and Technology. Ser. Organic Chemistry*], VINITI, Moscow, 1989, **17**, 72 (in Russian).
40. Yu. A. Sharanin and V. K. Promonenkov, in *Itogi nauki i tekhniki. Ser. Org. khimii* [*Advances in Science and Technology. Ser. Organic Chemistry*], VINITI, Moscow, 1989, **17**, 158 (in Russian).
41. G. V. Klokol, V. K. Promonenkov, Yu. A. Sharanin, and V. P. Litvinov, in *Itogi nauki i tekhniki. Ser. Org. khimii* [*Advances in Science and Technology. Ser. Organic Chemistry*], VINITI, Moscow, 1989, **17**, 296 (in Russian).
42. Yu. A. Sharanin, V. K. Promonenkov, and V. P. Litvinov, in *Itogi nauki i tekhniki. Ser. Org. khimii* [*Advances in Science and Technology. Ser. Organic Chemistry*], VINITI, Moscow, 1991, **20**, P. 1, 2 (in Russian).
43. R. W. Sabnis, D. W. Rangnekar, and N. D. Sonawane, *J. Heterocycl. Chem.*, 1999, **36**, 333.
44. E. A. Kaigorodova, V. K. Vasilin, and G. D. Krapivin, *Aminotieno[2,3-b]piridiny v sinteze kondensirovannykh geterotsiklov* [*Aminothieno[2,3-b]pyridines in Synthesis of Fused Heterocycles*], Krasnodar, 2001; Deposited in VINITI, No. 1901-V2001; *RZhKhim*, 02.04-19Zh213 DEP (in Russian).
45. F. S. Babichev, Yu. A. Sharanin, V. P. Litvinov, V. K. Promonenkov, and Yu. M. Volovenko, *Vnutrimolekulyarnoe vzaimodeistvie nitril´noi i CH-, OH- i S—H-grupp* [*Intramolecular Interactions of the Nitrile Group with the CH, OH, and SH Groups*], Naukova Dumka, Kiev, 1985, 200 pp. (in Russian).
46. F. S. Babichev, Yu. A. Sharanin, V. K. Promonenkov, V. P. Litvinov, and Yu. M. Volovenko, *Vnutrimolekulyarnoe vzaimodeistvie nitril´noi i aminogrupp* [*Intramolecular Interactions of the Nitrile and Amino Groups*], Naukova dumka, Kiev, 1987 (in Russian).
47. (a) L. A. Rodinovskaya, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1985 (in Russian); (b) E. E. Apenova, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1986 (in Russian); (c) G. V. Klokol, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1988 (in Russian); (d) V. N. Nesterov, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1988 (in Russian); (e) V. D. Dyachenko, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1990 (in Russian); (f) O. P. Bogomolova, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1992 (in Russian); (g) V. A. Artemov, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1995 (in Russian); (h) V. L. Ivanov, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1997 (in Russian); (i) S. G. Krivokolysko, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1997; (j) N. G. Frolova, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1997 (in Russian); (k) M. Yu. Yakovlev, Ph. D. (Chem.) Thesis, Center for Drug Chemistry—All-Russian Chemical-Pharmaceutical Research Institute, Moscow, 2000 (in Russian); (l) Ya. Yu. Yakunin, Ph. D. (Chem.) Thesis, Kharkov National University, Kharkov, 2001 (in Russian).
48. (a) Yu. A. Sharanin, Dr. Sc. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1988 (in Russian); (b) A. M. Shestopalov, Dr. Sc. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1991 (in Russian); (c) L. A. Rodinovskaya, Dr. Sc. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1994 (in Russian); (d) V. D. Dyachenko, Dr. Sc. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, 1998 (in Russian); (e) S. G. Krivokolysko, Dr. Sc. (Chem.) Thesis, Moscow State University, Moscow, 2001 (in Russian).
49. (a) W. Steinkopf and G. Lutzkendorf, *Chem. Ztg.*, 1913, **36**, 379; (b) W. Steinkopf and G. Lutzkendorf, *Liebigs Ann. Chem.*, 1914, **403**, 45.
50. D. W. Rangnekar and P. Y. Kamat, *Indian J. Fibre and Text. Res.*, 1992, **17**, 95; *RZhKhim*, 1993, 11Zh285.
51. (a) F. A. Attaby, L. I. Ibrahim, S. M. Eldin, and A. K. K. El-Louh, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1992, **73**, 127; (b) M. H. Elnagdi and A. W. W. Erian, *Arch. Pharm.*, 1991, **324**, 853; *Chem. Abstr.*, 1992, **116**, 41330.
52. A. I. Ozols, Yu. E. Pelcher, Z. A. Kalme, Yu. Yu. Popelis, I. V. Turovskis, and G. Ya. Duburs, *Khim. Geterotsikl. Soedin.*, 1996, 59 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)].

53. (a) V. V. Dotsenko, S. G. Krivokolysko, A. N. Chernega, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1432 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**,]; (b) S. Al-Mousaw, M. M. Abdelhalik, E. John, and M. H. Elnagdi, *J. Heterocycl. Chem.*, 2003, **40**, 689.
54. A. F. Abdel-Rahman, E. A. Bakhite, M. I. Abdel-Moneam, and T. A. Mohamed, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1992, **73**, 219; *Chem. Abstr.*, 1993, **119**, 28109.
55. Y. M. Elkholy, *Khim. Geterotsikl. Soedin.*, 2002, 1525 [*Chem. Heterocycl. Compd.*, 2002 (Engl. Transl.)].
56. (a) V. P. Kislyi, V. N. Nesterov, and V. V. Semenov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 1150 [*Russ. Chem. Bull.*, 1999, **48**, 1139 (Engl. Transl.)]; (b) L. A. Rodinovskaya and A. M. Shestopalov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 347 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 348]; (c) L. A. Rodinovskaya, A. M. Shestopalov, and A. V. Gromova, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 2069 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 2185]; (d) S. A. S. Ghozlan, *Sulfur Lett.*, 1991, **13**, 27; *RZhKhim*, 1992, 17Zh250.
57. Pat. Germany 19601264; *Chem. Abstr.*, 1997, **127**, 149139.
58. A. H. H. Elghandour, M. K. A. Ibrahim, F. M. M. Ali, and S. M. M. Elshikh, *Indian J. Chem.*, 1997, **36B**, 79.
59. (a) A. M. El-Sayed, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2000, **163**, 29; *RZhKhim*, 01.10-19Zh.290; (b) S. A. Shiba, M. M. Mohamed, M. A. Hassan, and A. M. El-Sayed, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2000, **158**, 91; *RZhKhim*, 01.03-19Zh.189P.
60. (a) V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1852 [*Russ. Chem. Bull.*, 1997, **46**, 1758 (Engl. Transl.)]; (b) V. N. Nesterov, S. G. Krivokolysko, V. D. Dyachenko, V. V. Dotsenko, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1029 [*Russ. Chem. Bull.*, 1997, **46**, 990 (Engl. Transl.)]; (c) S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1998, 1381 [*Chem. Heterocycl. Compd.*, 1998 (Engl. Transl.)]; (d) S. G. Krivokolysko, V. D. Dyachenko, V. N. Nesterov, Yu. A. Sharanin, and Yu. T. Struchkov, *Zh. Org. Khim.*, 1999, **35**, 966 [*Russ. J. Org. Chem.*, 1999, **35** (Engl. Transl.)]; (e) V. V. Dotsenko, S. G. Krivokolysko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 2003, 117 [*Chem. Heterocycl. Compd.*, 2003 (Engl. Transl.)].
61. (a) F. A. Attaby, S. M. Eldin, W. M. Bassyouni, and M. A. A. Elneairy, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1996, **119**, 1; *Chem. Abstr.*, 1997, **127**, 234265; (b) F. A. Attaby, S. M. Eldin, W. M. Basouni, and M. A. A. Elneairy, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1996, **108**, 31; *RZhKhim*, 1997, 7Zh185.
62. (a) V. A. Artemov, V. L. Ivanov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1996, 553 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)]; (b) S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Zh. Org. Khim.*, 1997, **33**, 1088 [*Russ. J. Org. Chem.*, 1997, **33** (Engl. Transl.)]; (c) V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1997, 666 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)]; (d) A. Krauze and G. Duburs, *Khim. Geterotsikl. Soedin.*, 2000, 794 [*Chem. Heterocycl. Compd.*, 2000 (Engl. Transl.)]; (e) A. A. Krauze, V. N. Garalene, and G. Ya. Dubur, *Khim.-farm. Zh.*, 1992, **26**, No. 5, 40 [*Pharm. Chem. J.*, 1992, No. 5 (Engl. Transl.)]; (f) V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Zh. Org. Khim.*, 1998, **34**, 750 [*Russ. J. Org. Chem.*, 1998, **34** (Engl. Transl.)].
63. (a) S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1997, 672 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)]; (b) S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 2000, 345 [*Chem. Heterocycl. Compd.*, 2000 (Engl. Transl.)]; (c) V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Zh. Org. Khim.*, 1998, **34**, 927 [*Russ. J. Org. Chem.*, 1998, **34** (Engl. Transl.)]; (d) V. D. Dyachenko, S. G. Krivokolysko, Yu. A. Sharanin, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1997, 909 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)]; (e) V. D. Dyachenko, S. G. Krivokolysko, V. N. Nesterov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1996, 1243 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)]; (f) M. A. A. Elneairy, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1999, **148**, 189.
64. (a) A. M. Shestopalov, V. Yu. Mortikov, Yu. A. Sharanin, A. V. Turov, and V. P. Litvinov, *Zh. Org. Khim.*, 1989, **25**, 1980 [*Russ. J. Org. Chem.*, 1989, **25** (Engl. Transl.)]; (b) V. A. Artemov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1994, 122 [*Chem. Heterocycl. Compd.*, 1994 (Engl. Transl.)].
65. A. Z. A. E. B. Hassanein, *Synth. Commun.*, 2000, **30**, 3883.
66. A. A. Geies and A. M. Kamal El-Dean, *Bull. Pol. Acad. Sci., Chem.*, 1997, **45**, 381; *Chem. Abstr.*, 1998, **128**, 244011.
67. A. A. Krauze, E. E. Liepin´sh, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 1990, 115 [*Chem. Heterocycl. Compd.*, 1990 (Engl. Transl.)].
68. (a) D. W. Rangnekar and P. Y. Kamat, *Indian J. Fibre and Text. Res.*, 1991, **16**, 223; *RZhKhim*, 1992, 7Zh262; (b) D. W. Rangnekar and P. Y. Kamat, *Indian J. Fibre and Text. Res.*, 1992, **17**, 98; *RZhKhim*, 1993, 13Zh235; (c) R. A. Mekheimer, E. K. Ahmed, H. A. El-Fahham, and L. H. Kamel, *Synthesis*, 2001, 97; (d) R. A. Mekheimer, E. K. Ahmed, H. A. El-Fahham, and L. H. Kamel, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2001, **175**, 49; (e) C. Peinador, M. Carmen Veiga, J. Vilar, and J. M. Quintela, *Heterocycles*, 1994, **38**, 1299; (f) C. G. Dave, P. R. Shah, and A. B. Shah, *Indian J. Chem.*, 1992, **31B**, 492; (g) M. Aadil and G. Kirsch, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1993, **82**, 91; (h) J. Woller, K. Spindler, G. Sardonick, and G. Kempter, *Pharmazie*, 1996, **51**, 937; (i) M. Yu. Yakovlev, A. V. Kadushkin, and V. G. Granik, *Khim.-farm. Zh.*, 1996, **30**, No. 2, 36 [*Pharm. Chem. J.*, 1996, No. 2 (Engl. Transl.)]; (j) M. Yu. Yakovlev, A. V. Kadushkin, and V. G. Granik, *Khim.-farm. Zh.*, 1997, **31**, No. 7, 18 [*Pharm. Chem. J.*, 1997, No. 7 (Engl. Transl.)]; (k) M. Yu. Yakovlev, O. B. Romanova, S. I. Grizik, A. V. Kadushkin, and V. G. Granik, *Khim.-farm. Zh.*, 1997, **31**, No. 11, 44 [*Pharm. Chem. J.*, 1997, No. 11 (Engl. Transl.)]; (l) M. Y. Yakovlev, A. V. Kadushkin, N. P. Solov´eva, and V. G. Granik, *Heterocycl. Commun.*, 1998, **4**, 245; (m) M. Yu. Yakovlev, A. V. Kadushkin, N. P. Solov´eva, O. S. Anisimova, and V. G. Granik, *Tetrahedron*, 1998, **54**, 5775.
69. V. D. Dyachenko and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1997, 1384 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)].

70. (a) D. H. Bremner, A. D. Dunn, and K. A. Wilson, *Synthesis*, 1992, 528; (b) D. H. Bremner, A. D. Dunn, K. A. Wilson, K. R. Sturrock, and G. Wishart, *Synthesis*, 1997, 949; (c) D. H. Bremner, A. D. Dunn, K. A. Wilson, K. R. Sturrock, and G. Wishart, *Synthesis*, 1998, 1095.
71. D. M. Volochnyuk, A. O. Pushechnikov, D. G. Krotko, D. A. Sibgatulin, S. A. Kovalyova, and A. A. Tolmachev, *Synthesis*, 2003, 1531.
72. B. Fevrier, G. Dupas, J. Bourguignon, and G. Queguiner, *J. Heterocycl. Chem.*, 1993, **30**, 1085.
73. (a) Pat. USA 6437132; *RZhKhim*, 2003, 6O92P; (b) WO 9909033 PCT; *Chem. Abstr.*, 1999, **130**, 196644.
74. (a) R. M. Mohareb, *Gazz. Chim. Ital.*, 1992, **122**, 147; (b) R. M. Mohareb, *Monatsh. Chem.*, 1992, **123**, 341; (c) R. M. Mohareb, S. I. Aziz, and I. El-Saka, *Sulfur Lett.*, 1991, **13**, 229; (d) F. M. A. El-Taweel, A. A. Elagamey, A. A. El-Kenawy, and M. A. Waly, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2001, **176**, 215.
75. S. Deprets and G. Kirsch, *Eur. J. Org. Chem.*, 2000, 1353.
76. (a) M. M. El-Abadelah, S. S. Sabri, and H. A. Al-Ashgar, *Heterocycles*, 1997, **45**, 255; (b) M. M. El-Abadelah, M. Z. Nazer, S. F. Okasha, M. Calas, J. Bompart, and P. Mion, *Eur. J. Med. Chem.*, 1998, **33**, 33; (c) M. M. El-Abadelah, S. S. Sabri, H. A. Al-Ashgar, P. Mion, J. Bompart, and M. Calas, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1998, **134—135**, 21.
77. RF Patent 1417446; *RZhKhim*, 1996, 8O80P.
78. L. H. Klemm, T. J. R. Weakley, Myungok Yoon, and R. S. Clegg, *J. Heterocycl. Chem.*, 2000, **37**, 763.
79. V. L. Ivanov, V. A. Artemov, L. A. Rodinovskaya, A. M. Shestopalov, V. N. Nesterov, Yu. T. Struchkov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1996, 115 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)].
80. V. A. Artyomov, V. L. Ivanov, A. M. Shestopalov, and V. P. Litvinov, *Tetrahedron*, 1997, **53**, 13351.
81. (a) S. I. Moryashova, L. K. Salamandra, A. E. Fedorov, L. A. Rodinovskaya, A. M. Shestopalov, and V. V. Semenov, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 365 [*Russ. Chem. Bull.*, 1998, **47**, 357 (Engl. Transl.)]; (b) A. M. Shestopalov, K. G. Nikishin, A. V. Gromova, and L. A. Rodinovskaya, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 2087 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 1977]; (c) K. S. Chunikhin, L. A. Rodinovskaya, and A. M. Shestopalov, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 428 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 447]
82. V. L. Ivanov, V. A. Artemov, A. M. Shestopalov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1998, 263 [*Chem. Heterocycl. Compd.*, 1998 (Engl. Transl.)].
83. (a) V. V. Dotsenko, S. G. Krivokolysko, V. P. Litvinov, and A. N. Chernega, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 339 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 362]; (b) V. V. Dotsenko, S. G. Krivokolysko, A. N. Chernega, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 918 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 969]; (c) V. V. Dotsenko, S. G. Krivokolysko, and V. P. Litvinov, *Mendeleev Commun.*, 2003, 267.
84. (a) V. V. Dotsenko, S. G. Krivokolysko, and V. P. Litvinov, *Intern. Conf. "Chemistry of Nitrogen Containing Heterocycles" (CNCH-2003), Abstr.*, Kharkov, 2003, P. 48; (b) V. V. Dotsenko, S. G. Krivokolysko, and V. P. Litvinov, *Mendeleev Commun.*, 2004, 30.
85. A. V. Kadushkin, N. P. Solov´eva, and V. G. Granik, *Khim.-farm. Zh.*, 1993, **27**, No. 3, 40 [*Pharm. Chem. J.*, 1993, No. 3 (Engl. Transl.)].
86. (a) V. A. Artyomov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov, *Tetrahedron*, 1996, **52**, 1011; (b) V. A. Artyomov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov, *Mendeleev Commun.*, 1993, 149.
87. V. A. Artemov, A. M. Shestopalov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1995, 250 [*Chem. Heterocycl. Compd.*, 1995 (Engl. Transl.)].
88. V. L. Ivanov, V. A. Artemov, A. M. Shestopalov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1997, 837 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)].
89. (a) V. V. Dabaeva, A. S. Noravyan, V. N. Madakyan, and B. D. Enokyan, *Khim. Geterotsikl. Soedin.*, 1997, 847 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)]; (b) H. Vieweg, S. Leistner, N. Boehm, J. Prantz, and G. Wagner, *Pharmazie*, 1993, **48**, 26; *Chem. Abstr.*, 1993, **119**, 49330.
90. G. Wagner and N. Boehm, *Pharmazie*, 1993, **48**, 95.
91. A. A. A. Atalla, E. A. Bakhite, and S. M. Radwan, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1995, **101**, 83.
92. (a) L. A. Rodinovskaya, E. V. Belukhina, A. M. Shestopalov, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 181 [*Russ. Chem. Bull.*, 1994, **43**, 177 (Engl. Transl.)]; (b) L. A. Rodinovskaya, E. V. Belukhina, A. M. Shestopalov, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 489 [*Russ. Chem. Bull.*, 1994, **43**, 449 (Engl. Transl.)].
93. A. E. Abdel-Rahman, I. M. A. Awad, and E. A. Bakhite, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1991, **60**, 189.
94. C. Peinador, V. Ojea, and J. M. Quintela, *J. Heterocycl. Chem.*, 1992, **29**, 1693.
95. (a) L. A. Rodinovskaya, A. M. Shestopalov, E. V. Belukhina, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1995, 851 [*Chem. Heterocycl. Compd.*, 1995 (Engl. Transl.)]; (b) A. E. Abdel-Rahman, E. A. Bakhite, O. S. Mohamed, and E. A. Thabet, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2000, **166**, 149.
96. C. Peinador, M. Carmen Veiga, V. Ojea, and J. M. Quintela, *Heterocycles*, 1995, **41**, 37.
97. (a) A. F. Abdel-Rahman, E. A. Bakhite, M. I. Abdel-Moneam, and T. A. Mohamed, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1992, **73**, 219; *Chem. Abstr.*, 1993, **119**, 28109; (b) M. A. A. Elneairy, S. M. Eldin, F. A. Attaby, and A. K. K. El-Louh, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2000, **167**, 289; (c) F. A. Abu-Shanab, Y. M. Elkholy, and M. H. Elnagdi, *Synth. Commun.*, 2002, **32**, 3493; (d) A. A. Geies, A. A. Abdel-Hafez, J. C. Lancelot, and H. S. El-Kashef, *Bull. Chem. Soc. Jpn*, 1993, **66**, 3716; (e) G. Wagner, H. Vieweg, and S. Leistner, *Pharmazie*, 1993, **48**, 514; *Chem. Abstr.*, 1994, **120**, 134330; (f) G. Wagner, S. Leistner, H. Vieweg, U. Krasselt, and J. Prantz, *Pharmazie*, 1993, **48**, 576; *Chem. Abstr.*, 1993, **119**, 271114.
98. RF Patent 1282510; *Byul. Izobr.* [*Invention Bulletin*], 1995, No. 26, 290 (in Russian); *Chem. Abstr.*, 1996, **125**, 86672.
99. (a) M. M. Ghorab, O. M. Nassar, and A. Y. Hassan, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1998, **134—135**, 57; (b) M. M. Ghorab, A. Y. Hassan, and O. M. Nassar, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1998, **134—135**, 447.

100. (a) A. A. A. Hafez, A. Kamal El-Dean, A. A. Hassan, H. S. El-Kashef, S. Rault, and M. Robba, *J. Heterocycl. Chem.*, 1996, **33**, 431; (b) V. V. Dabaeva, A. S. Noravyan, and B. D. Enokyan, *Khim. Geterotsikl. Soedin.*, 1995, 250 [*Chem. Heterocycl. Compd.*, 1995 (Engl. Transl.)]; (c) E. A. Bakhite, M. S. Abbady, and S. M. Radwan, *Collect. Czech. Chem. Commun.*, 1993, **58**, 1457; (d) G. Wagner, H. Vieweg, and S. Leistner, *Pharmazie*, 1993, **48**, 63; *Chem. Abstr.*, 1993, **119**, 28075; (e) H. Vieweg, U. Krasselt, N. Böhm, J. Prantz, and G. Wagner, *Pharmazie*, 1990, **45**, 731.
101. E. A. Bakhite, *Collect. Czech. Chem. Commun.*, 1992, **57**, 2359.
102. G. Malicorne, J. Bompart, L. Giral, and E. Despaux, *Eur. J. Med. Chem.*, 1991, **26**, 3; *Chem. Abstr.*, 1991, **115**, 49334.
103. S. Gronowitz and G. Timari, *J. Heterocycl. Chem.*, 1990, **27**, 1127.
104. P. Björk, A. B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, 1994, **31**, 1161.
105. (a) S. Gronowitz, in *IV Ibn Sina Intern. Symp. "Pure and Appl. Heterocycl. Chem.", Abstr.*, Cairo, 1992, P. 86; *RZhKhim*, 1993, 16Zh172; (b) S. Gronowitz, P. Björk, J. Malm, and A.-B. Hörnfeldt, *J. Organomet. Chem.*, 1993, **460**, 127; *Chem. Abstr.*, 1994, **120**, 164126.
106. P. Björk, T. Aakermann, A. B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, 1995, **32**, 751.
107. P. Björk, A.-B. Hörnfeldt, and S. Gronowitz, *Heterocycl. Commun.*, 1997, **3**, 183; *Chem. Abstr.*, 1997, **127**, 81373.
108. (a) K. Gorlitzer, C. Kramer, and C. Boyle, *Pharmazie*, 2000, **55**, 595; *Chem. Abstr.*, 2000, **133**, 309857; (b) D. H. Boschelli and Y. Fei, *J. Heterocycl. Chem.*, 2002, **39**, 783; (c) Pat. Jpn 10251264; *Chem. Abstr.*, 1998, **129**, 290126.
109. V. L. Ivanov, V. A. Artemov, A. M. Shestopalov, V. N. Nesterov, Yu. T. Struchkov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1996, 413 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)].
110. G. E. Khoroshilov and Y. V. Yarotcky, *Abstr. Intern. Conf. "Chemistry of Nitrogen Containing Heterocycles" (CNCH-2003),* Kharkov, 2003, P. 82.
111. (a) F. Outurquin and C. Paulmier, *Tetrahedron Lett.*, 1993, **34**, 5715; (b) F. Outurquin and C. Paulmier, *Tetrahedron Lett.*, 1993, **34**, 5719; (c) D. Brugier, F. Outurquin, and C. Paulmier, *Tetrahedron*, 1997, **53**, 10331; (d) M. Berkaoui, F. Outurquin, and C. Paulmier, *J. Heterocycl. Chem.*, 1996, **33**, 9.
112. Pat. USA 4593099; *RZhKhim*, 1987, 1O99P.
113. B. Balasundaram, M. Venugopal, and P. T. Perumal, *Tetrahedron Lett.*, 1993, **34**, 4249.
114. D. Brugier, F. Outurquin, and C. Paulmier, *J. Chem. Soc., Perkin Trans. 1*, 2001, 37.
115. (a) R. N. Castle and J. K. Luo, *Sci. Pharm.*, 1990, **58**, 203; *RZhKhim*, 1991, 3Zh291; (b) J. K. Luo and R. N. Castle, *J. Heterocycl. Chem.*, 1991, **28**, 205.
116. A. Genevois-Borella, M. Vuilhorgne, and S. Mignani, *Heterocycles*, 2002, **57**, 317.
117. S. M. Sherif, *Monatsh. Chem.*, 1996, **127**, 955.
118. R. Alvarez-Sarandes, C. Peinador, and J. M. Quintela, *Tetrahedron*, 2001, **57**, 5413.
119. W. Verboom, C. Verboom, I. M. Eissink, B. H. M. Lammerink, and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas*, 1990, **109**, 481.
120. (a) Pat. USA 6191140; *RZhKhim*, 2002 04.19O93P; (b) R. R. Dubure, B. A. Vigante, Ya. Ya. Ozols, G. Ya. Dubur, and G. I. Rozentale, *Khim. Geterotsikl. Soedin.*, 1986, 1563 [*Chem. Heterocycl. Compd.*, 1986 (Engl. Transl.)]; (c) J. H. Dodd, C. F. Schwender, and Y. Gray-Nunez, *J. Heterocycl. Chem.*, 1990, **27**, 1453; (d) L. D. Abramenko, S. G. Krivokolysko, and V. P. Litvinov, *Abstr. of Papers of the I All-Russian Conf. on Chemistry of Heterocycles Dedicated to the Memory of A. N. Kosta*, Suzdal´, 2000, p. 76 (in Russian).
121. (a) Pat. USA 5352685; *RZhKhim*, 1996, 5O41P; (b) Pat. FRG 4227747; *RZhKhim*, 1995, 12O297P; (c) Pat. USA 5219867; *RZhKhim*, 1994, 21O35P; (d) Eur. Pat. 505058; *Chem. Abstr.*, 1992, **117**, 251343; (e) Eur. Pat. 560348; *Chem. Abstr.*, 1994, **120**, 134449; (f) Eur. Pat. 1256581; *RZhKhim*, 2003, 08.19O86P.
122. (a) WO 9847903 PCT; *Chem. Abstr.*, 1998, **129**, 330658; (b) Pat. Jpn 0753557; *Chem. Abstr.*, 1995, **123**, 169614; (c) Pat. USA 6166203; *RZhKhim*, 2001, 24.19O117P.
123. (a) J. M. Barker, P. R. Huddleston, N. Chandwick, and G. J. Keenan, *J. Chem. Res. (S)*, 1980 (1)/*J. Chem. Res. (M)*, 113; *RZhKhim*, 1981, 9Zh197; (b) I. Antonini, D. Cola, P. Polucci, G. F. Palmieri, and S. Martelli, *Farmaco*, 1996, **51**, 41; *Chem. Abstr.*, 1996, **124**, 278185.
124. J. M. Quintela, M. C. Veiga, C. Peinador, and L. Gonzalez, *Heterocycles*, 1997, **45**, 1733.
125. (a) S. Gronowitz and G. Timari, *Chem. Scr.*, 1989, **29**, 305; (b) S. Gronowitz and G. Timari, *Chem. Scr.*, 1989, **29**, 309.
126. K. J. Szabo and S. Gronowitz, *J. Heterocycl. Chem.*, 1993, **30**, 561.
127. (a) M. R. Michaelides, Yufeng Hong, S. Di Domenico, Jr., E. K. Bayburt, K. A. Asin, D. R. Britton, Chun Wel Lin, and K. Shiosaki, *J. Med. Chem.*, 1997, **40**, 1585; (b) A. K. Gupta, S. R. Patel, and M. N. Desphande, *Synth. Commun.*, 1999, **29**, 1835; (c) M. R. Michaelides, Yufeng Hong, S. Di Domenico, Jr., K. A. Asin, D. R. Britton, Chun Wel Lin, M. Williams, and K. Shiosaki, *J. Med. Chem.*, 1995, **38**, 3445; (d) Gu Yu Gui, E. K. Bayburt, M. R. Michaelides, Chun Wel Lin, and K. Shiosaki, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1341; *Chem. Abstr.*, 1999, **131**, 102216; (e) Pat. USA 5659037; *Chem. Abstr.*, 1997, **127**, 248092; (f) WO 9422858 PCT; *Chem. Abstr.*, 1995, **123**, 143898; (g) Pat. USA 5597832; *RZhKhim*, 1998, 8O109P.
128. (a) Pat. Germany 19636769; *Chem. Abstr.*, 1998, **128**, 217381; (b) Pat. Germany 19900673; *RZhKhim*, 2001, 08.19O153P; (c) Pat. Germany 10031389; *RZhKhim*, 2002, 22.19O93P.
129. (a) WO 9413679 PCT; *Chem. Abstr.*, 1995, **123**, 340082; (b) WO 9321189 PCT; *Chem. Abstr.*, 1994, **121**, 9382; (c) Pat. USA 5621103; *RZhKhim*, 1998, 15O73P; (d) Pat. USA 5126448; *Chem. Abstr.*, 1992, **117**, 212482; (e) Pat. Jpn 04154785; *Chem. Abstr.*, 1992, **117**, 212480; (f) Pat. Jpn 05163278; *Chem. Abstr.*, 1994, **120**, 270355; (g) Pat. Jpn 04264087; *Chem. Abstr.*, 1993, **118**, 101976; (h) Pat. Jpn 07109281; *Chem. Abstr.*, 1995, **123**, 285988.
130. H. Kawakubo, S. Takagi, Y. Yamaura, S. Katoh, Y. Ishimoto, T. Nagatani, D. Mochizuki, T. Kamata, and Y. Sasaki, *J. Med. Chem.*, 1993, **36**, 3526.
131. (a) Eur. Pat. 624588; *Chem. Abstr.*, 1995, **122**, 81418; (b) S. Miyazawa, K. Okano, N. Shimomura, R. S. J. Clark, T. Kawahara, O. Asano, H. Yoshimura, M. Miyamoto,

Y. Sakuma, K. Muramoto, H. Obaishi, K. Harada, T. Kajima, K. Yamada, H. Tsunoda, S. Katayama, S. Abe, N. Asakawa, S. Souda, T. Horie, T. Sato, Y. Machida, K. Katayama, and I. Yamatsu, *Chem. Pharm. Bull.*, 1991, **39**, 3215; (c) S. Miyazawa, K. Okano, N. Shimomura, T. Kawahara, O. Asano, H. Yoshimura, T. Kawai, S. Souda, Y. Yoshida, T. Sato, Y. Machida, and I. Yamatsu, *Chem. Pharm. Bull.*, 1992, **40**, 521; (d) Pat. Finland 93120; *RZhKhim*, 1995, 22O65P; (e) S. Miyazawa, K. Okano, T. Kawahara, Y. Machida, and I. Yamatsu, *Chem. Pharm. Bull.*, 1992, **40**, 762; (f) Pat. Germany 4010315; *Chem. Abstr.*, 1991, **115**, 280072; (g) Pat. Germany 4015137; *Chem. Abstr.*, 1991, **114**, 122433; (h) Pat. Germany 4010316; *Chem. Abstr.*, 1991, **114**, 122431; (i) Pat. Germany 4010361; *Chem. Abstr.*, 1991, **114**, 122430; (j) Pat. France 2661911; *Chem. Abstr.*, 1992, **116**, 235664.

132. (a) Pat. France 2779652; *RZhKhim*, 2000, 22.19O86P; (b) Pat. France 2791980; *RZhKhim*, 2001, 08.19O154P; (c) WO 0061587 PCT; *Chem. Abstr.*, 2000, **133**, 309912.
133. Pat. France 2660311; *Chem. Abstr.*, 1992, **117**, 26595.
134. (a) Pat. USA 5482937; *RZhKhim*, 1997, 24O84P; (b) Pat. USA 5438045; *RZhKhim*, 1997, 8O68P; (c) Pat. USA 5409909; *RZhKhim*, 1997, 2O56P; (d) Pat. USA 5304553; *RZhKhim*, 1995, 18O91P; (e) Pat. USA 5221671; *RZhKhim*, 1995, 9O115P; (f) Pat. Switzerland 681010; *RZhKhim*, 1993, 18O56P; (g) Pat. Great Britain 2243829; *RZhKhim*, 1993, 2O102P; (h) Pat. Austria 394562B; *RZhKhim*, 1993, 2O104P; (i) Pat. Finland 95035; *RZhKhim*, 1996, 20O54P; (j) Pat. Norway 173140; *RZhKhim*, 1994, 11O44P; (k) Pat. Norway 173504; *RZhKhim*, 1995, 24O48P; (l) Pat. FRG 4015136; *RZhKhim*, 1993, 1O79P; (m) Pat. Great Britain 2229723; *RZhKhim*, 1991, 14O74P; (n) Pat. Great Britain 2242427; *Chem. Abstr.*, 1992, **116**, 41492; (o) Pat. Great Britain 2229724; *RZhKhim*, 1991, 14O75P; (p) WO 9858930 PCT; *Chem. Abstr.*, 1999, **130**, 66518; (q) Pat. USA 6433167; *RZhKhim*, 03.05-19O.147P; (r) Pat. USA 5468740; *RZhKhim*, 1997, 19O73P; (s) Pat. USA 5382579; *RZhKhim*, 1996, 16O80P.
135. S. Kano, T. Ozaki, and S. Hibino, *Heterocycles*, 1979, **12**, 489.
136. (a) J. Dogan, G. Karminski-Zamola, and D. W. Boykin, *Heterocycles*, 1995, **41**, 1659; (b) M. Malesevic, G. Karminski-Zamola, M. Bajic, and D. W. Boykin, *Heterocycles*, 1995, **41**, 2691; (c) J. Dogan, G. Karminski-Zamola, and D. W. Boykin, *Heterocycl. Commun.*, 1996, **2**, 213; *Chem. Abstr.*, 1996, **125**, 275695; (d) H. K. Gakhar, R. Kaur, and S. B. Gupta, *Monatsh. Chem.*, 1995, **126**, 1253.
137. (a) S. Pakray and R. N. Castle, *J. Heterocycl. Chem.*, 1987, **24**, 231; (b) S. L. Castle, J.-K. Luo, H. Kudo, and R. N. Castle, *J. Heterocycl. Chem.*, 1988, **25**, 1363; (c) J.-K. Luo and R. N. Castle, *J. Heterocycl. Chem.*, 1990, **27**, 1031; (d) J.-K. Luo, S. L. Castle, and R. N. Castle, *J. Heterocycl. Chem.*, 1990, **27**, 2047; (e) M. J. Musmar and R. N. Castle, *J. Heterocycl. Chem.*, 1991, **28**, 203; (f) J.-K. Luo, A. S. Zektzer, and R. N. Castle, *J. Heterocycl. Chem.*, 1991, **28**, 737; (g) J.-K. Luo and R. N. Castle, *J. Heterocycl. Chem.*, 1991, **28**, 1825; (h) R. N. Castle, S. Pakray, and G. E. Martin, *J. Heterocycl. Chem.*, 1991, **28**, 1997; (i) K. Sasaki and R. N. Castle, *J. Heterocycl. Chem.*, 1992, **29**, 963; (j) K. Sasaki and R. N. Castle, *J. Heterocycl. Chem.*, 1992, **29**, 1613; (k) Ch. Camoutsis and R. N. Castle, *J. Heterocycl. Chem.*, 1993, **30**, 153; (l) M. J. Musmar, A. S. Zektzer, R. N. Castle, and N. K. Dalley, *J. Heterocycl. Chem.*, 1993, **30**, 487; (m) J.-K. Luo, A. S. Zektzer, R. N. Castle, R. C. Crouch, J. P. Shockcor, and G. E. Martin, *J. Heterocycl. Chem.*, 1993, **30**, 453; (n) J.-K. Luo, S. L. Castle, and R. N. Castle, *J. Heterocycl. Chem.*, 1993, **30**, 653; (o) J.-K. Luo and R. N. Castle, *J. Heterocycl. Chem.*, 1993, **30**, 1167; (p) M. J. Musmar and R. N. Castle, *J. Heterocycl. Chem.*, 1994, **31**, 553; (q) J.-K. Luo, H. Kudo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1995, **32**, 317; (r) J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1995, **32**, 659; (s) K. Sasaki, O. Tokuda, T. Hirota, J.-K. Luo, and R. N. Castle, *J. Heterocycl. Chem.*, 1995, **32**, 1735; (t) J.-K. Luo, R. F. Federspiel, R. N. Castle, and L. W. Castle, *J. Heterocycl. Chem.*, 1996, **33**, 185; (u) A. P. Halverson, L. W. Castle, and R. N. Castle, *J. Heterocycl. Chem.*, 1996, **33**, 179; (v) A. P. Halverson and L. W. Castle, *J. Heterocycl. Chem.*, 1996, **33**, 727; (w) J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1996, **33**, 923; (x) J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1997, **34**, 1597; (y) K. Sasaki, O. Tokuda, T. Hirota, J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1997, **34**, 1829; (z) J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1998, **35**, 1441; J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 2000, **37**, 171; J.-K. Luo, M. P. Cabal, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 2000, **37**, 997; J.-K. Luo, M. P. Cabal, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 2001, **38**, 137.
138. (a) L. W. Castle, M. D. Johnston, Jr., Ch. L. Camoutsis, and R. N. Castle, *J. Heterocycl. Chem.*, 1992, **29**, 1869; (b) L. W. Castle, M. D. Johnston, Jr., Ch. L. Camoutsis, and R. N. Castle, *J. Heterocycl. Chem.*, 1992, **29**, 1805; (c) Ch. E. Hadden, G. E. Martin, J.-K. Luo, and R. N. Castle, *J. Heterocycl. Chem.*, 2000, **37**, 821.
139. J. Malm, B. Rehn, A.-B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, 1994, **31**, 11.
140. J. Malm, A.-B. Hörnfeldt, and S. Gronowitz, *Heterocycles*, 1993, **35**, 245.
141. (a) Pat. Jpn 63-96188; *RZhKhim*, 1989, 10O61P; (b) Pat. Jpn 1100172; *RZhKhim*, 1991, 13O69P.
142. (a) WO 9834112 PCT; *Chem. Abstr.*, 1998, **129**, 149262; (b) Pat. USA 5856107; *RZhKhim*, 1999, 16O377P.
143. (a) A. Baba, A. Mori, T. Yasuma, S. Unno, H. Makino, and T. Sohda, *Chem. Pharm. Bull.*, 1999, **47**, 993; (b) H. S. El-Kashef, A. A. Geies, A. M. Kamal El-Dean, and A. A. Abdel-Hafez, *J. Chem. Technol. Biotechnol.*, 1993, **57**, 15; *Chem. Abstr.*, 1994, **120**, 771913; (c) A. Z. M. Shaifullah Chowdhury and M. M. Matin, *Chittagong Univ. Stud., Part II*, 1997, **21**, 47; *Chem. Abstr.*, 1999, **130**, 237529; (d) F. Sauter, U. Jordis, J. Froehlich, K. Gewald, F. Grohmann, and E. K. Ahmed, *ACH — Models Chem.*, 1994, **131**, 489; *Chem. Abstr.*, 1995, **122**, 105800.
144. G. M. Castanedo and D. P. Sutherlin, *Tetrahedron Lett.*, 2001, **42**, 7181.
145. Pat. USA 4904672; *RZhKhim*, 1991, 5O52P.
146. S. W. Wright and R. L. Corbett, *Tetrahedron Lett.*, 1993, **34**, 2875.

147. (a) A. Padwa, T. M. Heidelbaugh, and J. T. Keuthe, *J. Org. Chem.*, 1999, **64**, 2038; (b) A. Padwa, D. E. Gunn, Jr., and M. H. Osterhout, *Synthesis*, 1997, 1353.
148. B. Legouin and J.-L. Burgot, *J. Heterocycl. Chem.*, 2000, **37**, 127.
149. (a) F. Sauter, J. Fröhlich, and A. Z. M. Shaifullah Chowdhury, *Sci. Pharm.*, 1996, **64**, 647; *RZhKhim*, 1997, 15Zh200; (b) F. Sauter, J. Fröhlich, K. Blasl, and K. Gewald, *Heterocycles*, 1995, **40**, 851; (c) A. Z. M. Shaifullah Chowdhury, Y. Shibata, M. Morita, K. Kaya, and T. Sano, *Heterocycles*, 2001, **55**, 1747.
150. (a) A. Z. M. Shaifullah Chowdhury and M. M. Matin, *Chittagong Univ. Stud., Part II*, 1997, **21**, 47; *Chem. Abstr.*, 1999, **130**, 237529; (b) F. Sauter, J. Fröhlich, A. Z. M. Shaifullah Chowdhury, and C. Hametner, *Acta Chim. Sloven.* [*Vestn. Sloven. Kem. Drus.*], 1996, **3**, 365; *RZhKhim*, 1998, 1Zh255.
151. (a) U. Sensfuss and W. D. Habicher, *Heteroatom Chem.*, 1998, **9**, 529; (b) U. Sensfuss and W. D. Habicher, *Heterocycles*, 2001, **55**, 171.
152. (a) S. V. Tolkunov, M. N. Kal´nitskii, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, 1993, 706 [*Chem. Heterocycl. Compd.*, 1993 (Engl. Transl.)]; (b) S. V. Tolkunov, M. N. Kal´nitskii, S. N. Lyashchuk, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, 1994, 701 [*Chem. Heterocycl. Compd.*, 1994 (Engl. Transl.)]; (c) S. V. Tolkunov, M. N. Kal´nitskii, A. I. Khizhan, S. Yu. Suikov, M. Yu. Zubritskii, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, 1995, 1124 [*Chem. Heterocycl. Compd.*, 1995 (Engl. Transl.)]; (d) S. V. Tolkunov, M. N. Kal´nitskii, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, 1997, 406 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)]; (e) S. V. Tolkunov, M. N. Kal´nitskii, S. N. Lyashchuk, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, 1997, 1199 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)].
153. (a) Pat. USA 4730049; *RZhKhim*, 1989, 1O76P; (b) Pat. USA 6043368; *RZhKhim*, 2001, 07.19O132P.
154. (a) Eur. Pat. 465358; *Chem. Abstr.*, 1992, **116**, 194139; (b) WO 9918110 PCT; *Chem. Abstr.*, 1999, **130**, 296510; (c) WO 9851682 PCT; *Chem. Abstr.*, 1999, **130**, 24964; (d) WO 9851681 PCT; *Chem. Abstr.*, 1999, **130**, 24963; (e) WO 0027840 PCT; *Chem. Abstr.*, 2000, **132**, 334447; (f) WO 9851689 PCT; *Chem. Abstr.*, 1999, **130**, 25057; (g) Eur. Pat. 466569; *Chem. Abstr.*, 1992, **117**, 90266.
155. A. Burgos, J. M. Herbert, I. Simpson, and J. Labell, *Compounds Radiopharm.*, 2000, **43**, 891; *RZhKhim*, 2001 01.19O92.
156. A. Badorc, M.-F. Bordes, D. Frehel, and J.-P. Maffrand, *15th Intern. Symp. Org. Chem. Sulfur (ISOCS 15), Abstr.*, Caen, 1992, P. 226; *RZhKhim*, 1993, 2O48.
157. W. Herz and L. Tsai, *J. Am. Chem. Soc.*, 1953, **75**, 5122.
158. (a) J. Maffrand and F. Eloy, *J. Heterocycl. Chem.*, 1976, **13**, 1347; (b) J. H. Wikel, M. L. Denney, and R. T. Vasileff, *J. Heterocycl. Chem.*, 1993, **30**, 289.
159. (a) S. Marchalin, F. Szemes, N. Bar, and B. Decroix, *Heterocycles*, 1999, **50**, 445; (b) A. Daich and B. Decroix, *J. Heterocycl. Chem.*, 1996, **33**, 873; (c) A. Mamouni, P. Netchitailo, A. Daich, and B. Decroix, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1996, **119**, 169; (d) S. Marchalin and B. Decroix, *J. Heterocycl. Chem.*, 1994, **31**, 495; (e) D. Lebosquain and B. Decroix, *Heterocycles*, 1993, **36**, 2303.
160. (a) S. Gronowitz, A.-B. Hörnfeldt, and Y. Yang, *Chem. Scr.*, 1988, **28**, 281; (b) Y. Yang, A.-B. Hörnfeldt, and S. Gronowitz, *Synthesis*, 1989, 130.
161. J. Cen, *Zhongguo Yiyao Gongye Zazhi*, 1997, **28**, 197; *Chem. Abstr.*, 1997, **127**, 331417.
162. Eur. Pat. 829482; *Chem. Abstr.*, 1998, **128**, 244045.
163. Eur. Pat. 497695; *Chem. Abstr.*, 1992, **117**, 191851.
164. (a) Pat. Jpn 426690; *RZhKhim*, 1995, 22O42P; (b) K. Sumita, M. Koumori, and S. Ohno, *Chem. Pharm. Bull.*, 1994, **42**, 1676.
165. (a) Eur. Pat. 803505; *Chem. Abstr.*, 1998, **128**, 13253; (b) WO 9906410 PCT; *Chem. Abstr.*, 1999, **130**, 182449.
166. Pat. USA 5480887; *Chem. Abstr.*, 1996, **124**, 289512.
167. B. Decroix and J. Morel, *J. Heterocycl. Chem.*, 1991, **28**, 81.
168. Pat. USA 5141932; *RZhKhim*, 1996, 3O53P.
169. WO 9738977 PCT; *Chem. Abstr.*, 1994, **127**, 3587943.
170. A. D. Dunn and R. Norrie, *J. Heterocycl. Chem.*, 1987, **24**, 85.
171. A. M. Sipyagin, *Khim. Geterotsikl. Soedin.*, 1996, 364 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)].
172. (a) Pat. Jpn 61-85391; *RZhKhim*, 1987, 9O162P; (b) Pat. Jpn 61-271291; *RZhKhim*, 1987, 20O110P; (c) Pat. USA 5068360; *RZhKhim*, 1993, 8O53P; (d) Pat. Jpn 06298766; *Chem. Abstr.*, 1995, **122**, 133162; (e) Pat. France 2664276; *RZhKhim*, 1993, 2O49P; (f) Pat. USA 5334596; *Chem. Abstr.*, 1994, **121**, 230759; (g) WO 9927929 PCT; *Chem. Abstr.*, 1999, **131**, 190113.
173. (a) Eur. Pat. 573955; *Chem. Abstr.*, 1994, **120**, 245062; (b) Eur. Pat. 573975; *Chem. Abstr.*, 1994, **120**, 217645.
174. M. Okhudo, A. Kuno, K. Katsuta, Y. Ueda, K. Shirakawa, H. Nakanishi, T. Kinoshita, and H. Takasugi, *Chem. Pharm. Bull.*, 1996, **44**, 778.
175. (a) Eur. Pat. 573954; *Chem. Abstr.*, 1994, **120**, 270357; (b) Pat. Jpn 06271582; *Chem. Abstr.*, 1995, **122**, 290840; (c) Pat. USA 5364941; *RZhKhim*, 1996, 9O36P; (d) Pat. Jpn 2000, 273097; *Chem. Abstr.*, 2000, **133**, 266832.
176. (a) S. Marchalin, F. Szemes, N. Bar, and B. Decroix, *Heterocycles*, 1999, **50**, 445; (b) D. Berkes, P. Netchitailo, J. Morel, and B. Decroix, *Synth. Commun.*, 1998, **28**, 949.
177. Yu. M. Yutilov, N. N. Smolyar, and S. V. Gres´ko, *Zh. Org. Khim.*, 1995, **31**, 304 [*Russ. J. Org. Chem.*, 1995, **31** (Engl. Transl.)].
178. (a) V. P. Litvinov, *Usp. Khim.*, 2003, **72**, 75 [*Russ. Chem. Rev.*, 2003, **72**, 69 (Engl. Transl.)]; (b) I. Ugi, A. Domling, and B. Werner, *J. Heterocycl. Chem.*, 2000, **37**, 647; (c) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; (d) L. F. Tietze, *J. Heterocycl. Chem.*, 1990, **27**, 47; (e) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115.
179. (a) *Multicomponent Reactions and Combinatorial Chemistry (German-Polish Workshop)*, Eds Z. Hippe and I. Ugi, Tzesow, 1997, University of Technology, Tzesow/Technical University, Munich, 1998; (b) L. A. Thompson and J. A. Ellman, *Chem. Rev.*, 1996, **96**, 555; (c) E. S. Osborne and A. D. Ellington, *Chem. Rev.*, 1997, **97**, 349 (see also other reviews in this volume).

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