Recent advances in the chemistry of thieno[2,3-*b*]pyridines
1. Methods of synthesis of thieno[2,3-*b*]pyridines*

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The recent data (2007—2018) on the synthesis of thieno[2,3-*b*]pyridines are summarized and systematized.

Keywords: thieno[2,3-*b*]pyridines, Thorpe—Ziegler reaction, Gewald´s 2-aminothiophenes, nicotinonitriles, cyanothioacetamide, Friedländer reaction, Gould—Jacobs reaction.

1. Introduction

The chemistry of thieno[2,3-*b*]pyridine derivatives has been developing rapidly since the first works appeared in the middle of the 20th century and has repeatedly become the subject of detailed consideration in monographs, reviews, and theses.[1—18] Interest in thienopyridines is mainly caused by the wide range of their practically important properties: biologically active compounds, dyes, agrochemicals, *etc*. have been found among this class of compounds. The last work, which summarized and systematized data on the chemistry of thieno[2,3-*b*]pyridines in general, was published in 2007.[8] Since then, significant progress has been made in this area of heterocyclic chemistry, which is reflected in a number of new publications concerning synthetic methods, modification, and especially biological activity of thieno[2,3-*b*]pyridine derivatives. In the Scopus database for the key term "thieno-[2,3-*b*]pyridine" in the title, abstract, and keywords for the period from 2007 to 2019 inclusive (as of 01.04.2019), more than 300 articles and about 1000 patents were found (Fig. 1). The tremendous interest in thieno[2,3-*b*]pyridines reflected in a large number of publications, prompted us to summarize and systematize the data on the chemistry of these compounds for the period from the publication of the last review to the beginning of 2019. The material of the present review is systematized according to the type of construction of thienopyridine systems. Due to the large amount of information, the review focuses on the most significant, in the authors´ opinion, works; patents and routine works containing no fundamentally new data have limited citation. The issues of functionalization of substituents, biological activity of thieno[2,3-*b*]pyridines, and construction of polycyclic assemblies with a condensed thienopyridine fragment will be considered in subsequent reviews.

2. Construction of thienopyridine system through the annulation of the thiophene ring

Among many options for synthesizing thieno[2,3-*b*]-pyridines through annulation, two approaches are the most popular (Scheme 1). The first (approach ***A***) is based on the *S*-alkylation of available[19—24] 3-cyanopyridine-2(1*H*)-thiones **1** or their tautomeric 2-mercapto forms with methylene active alkylating agents $HalCH_2EWG$ (EWG is an electron-withdrawing group) followed by the Thorpe—Ziegler cyclization of intermediates **2**. The cyclization products in this case are 3-aminothienopyridines **3** usually containing a strong EWG at position 2. Intermediate products **2** can be easily isolated in the individual forms, but the yields of thienopyridines **3**, as a rule, are slightly higher when the synthesis is carried out in a one-pot version without isolation of these nitriles.

Approach ***B*** (see Scheme 1) is based on the reaction of 2-chloronicotinonitriles **4** with various mercaptans

* Based on the materials of the V All-Russian Conference with International Participation on Organic Chemistry (September 10—14, 2018, Vladikavkaz, Russia).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 1829—1858, October, 2020.
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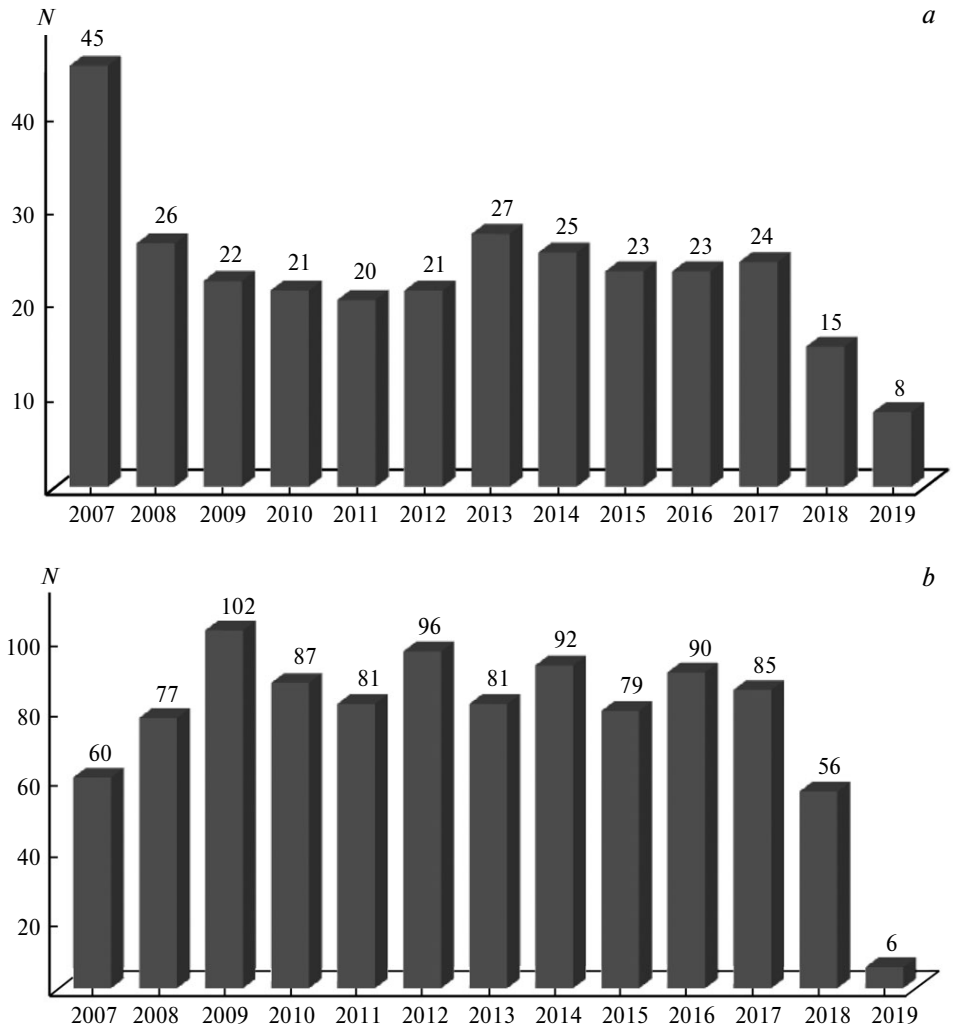


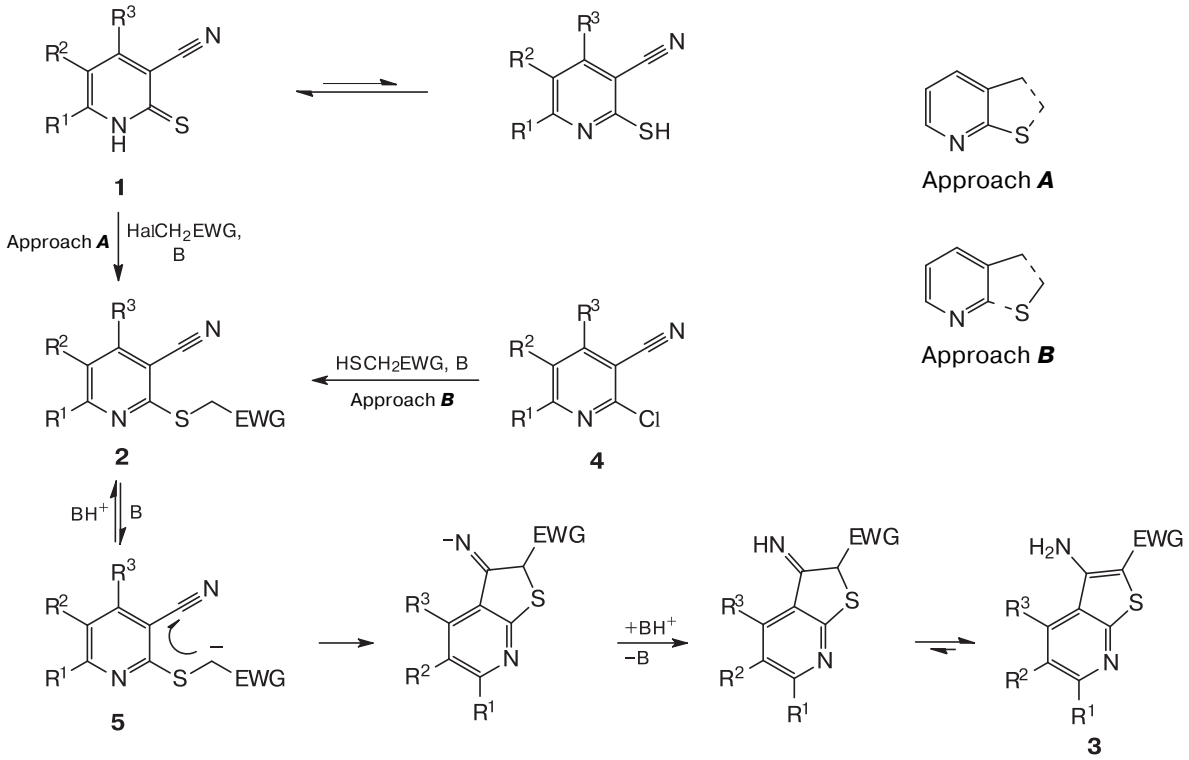
Fig. 1. Number (*N*) of papers (*a*) and patents (*b*) found in the Scopus database for the key term "thieno[2,3-*b*]pyridine" (for the period from 2007 to 01.04.2019).

bearing the α-positioned electron-withdrawing group, usually mercaptoacetic acid derivatives. This reaction also gives nicotinonitriles **2** as intermediate products, from which thienopyridines **3** are obtained as in approach ***A***. Thus, approaches ***A*** and ***B*** differ in the methods and order of the formation of the C—S—C thiophene bonds.

Let us consider first approach ***A*** in light of recent publications. As already noted, this approach suggests that a thienopyridine system can be constructed both in a one-pot version without isolation of compounds **2** and with their isolation. An important role is played by the basicity of the catalyst and the reaction temperature both of which can widely vary. Thus, the alkylation of thiones **1** with $EWGCH_2Hal$ can be carried out in the presence of K_2CO_3 in refluxing acetone,[25,26] in dioxane at 25 °C[27] or in DMF at 60 °C,[28] with catalysis with AcONa in refluxing ethanol[29,30] or at room temperature,[31,32] using the system AcONa/DMF.[33] Catalysis is also possible with Et_3N[34] or piperidine[35] in refluxing ethanol, with MeONa in MeOH[36—39] and with KOH in aqueous EtOH[40—43] at room temperature. The system NaOH/EtOH are also used at 10 °C,[44] as well as the system KOH/DMF/H_2O at room temperature.[45—53] It is often impossible to carry out the synthesis one-pot, since further cyclization of nicotinonitriles **2** requires more drastic conditions. In particular, stronger bases and a higher reaction temperature necessary for the generation of key cyclization intermediates, carbanions **5**. These conditions are met by cyclization in anhydrous ethanol in the presence of EtONa upon heating,[25,31,34—38,42,44,45] in DMF with CaO at 80 °C,[26] using the system K_2CO_3/Bu_4NBr/dioxane at 60—70 °C,[27] MeONa in MeOH at reflux,[28—30,32] KOH in refluxing EtOH,[33,39—41] in DMF with aqueous KOH,[43,46,48,50,52], and in the presence of piperidine in refluxing EtOH.[47]

A one-pot version of approach ***A*** (see Scheme 1) allows obtaining thienopyridines **3** directly from thiones **1** without isolation of nicotinonitrile **2**. This pathway supposes the treatment of thions **1** with alkylating agents and an

Scheme 1

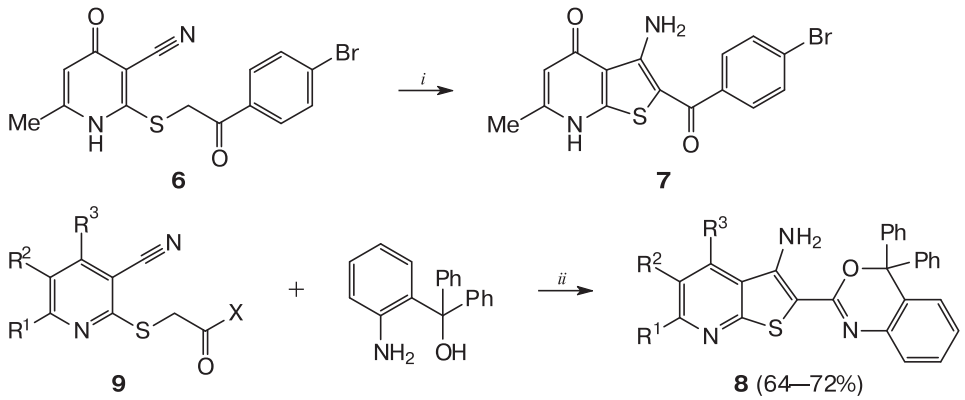


B is a base, EWG is an electron-withdrawing group.

excess of a base under more harsh conditions. In particular, a number of recently published works describe the synthesis of thienopyridines **3** on treatment with K_2CO_3 in refluxing ethanol,[31,54] in the presence of Bu_4NBr in dioxane at 60—70 °C,[27] in refluxing solutions of MeONa in MeOH,[29,30,32,38,39] EtONa in EtOH,[33—35,55—60] in a solution of KOH in EtOH[40,61] or MeOH,[62] on treatment with an excess of aqueous KOH in DMF,[46.48—51,53,63—72] and by mechanochemical treatment in the presence of K_2CO_3 in DMF.[71]

However, the catalyst-free Thorpe—Ziegler cyclization of compound **6** is also known[41] (Scheme 2), which gives thienopyridine **7** in a quantitative yield. It is obvious that the possibility of a catalyst-free reaction in this case is due to its drastic conditions and the presence of a strong methylene-activating aroyl substituent in the substrate.

Scheme 2



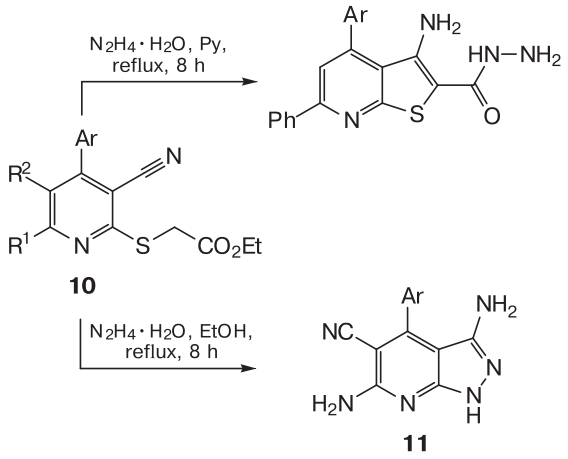
8, 9: X = OH, NH_2

Reagents and conditions: *i*. 210 °C, several seconds; *ii*. 1) 70% $HClO_4$, $MeNO_2$; 2) 10% aqueous NH_3.

A rare example of acid catalyzed synthesis of thienopyridines **8** from products of *S*-substitution is described in the work.[73] In this case, the formation of thienopyridines is explained by the specific nature of the reaction of nicotinonitriles **9** with an additional reagent, aminophenyl(diphenyl)carbinol. It was confirmed that the formation of the thienopyridine system in this reaction is preceded by the benzoxazine ring closure. In the presence of other cyclizing agents or in their absence, compounds **9** do not undergo Thorpe—Ziegler cyclization under acid catalysis conditions. Thus, this transformation is a particular case.

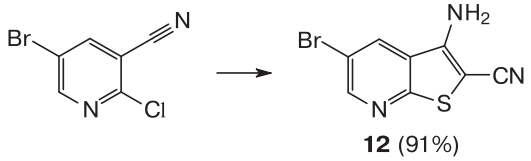
Spontaneous cyclization was observed[36] in the attempted hydrazinolysis of esters **10** in refluxing pyridine (Scheme 3). When ethanol is used instead of pyridine the reaction proceeded alternatively as the nucleophilic substitution of the sulfur-containing fragment with hydrazine to give pyrazolpyridine **11**.[36]

Scheme 3



Note that the starting thiones **1**, in turn, can also be generated *in situ* from 2-chloronicotinonitriles and 3-mercaptopropionitrile in a one-pot approach, as exemplified[74,75] by the synthesis of thieno[2,3-*b*]pyridine **12** (Scheme 4).

Scheme 4

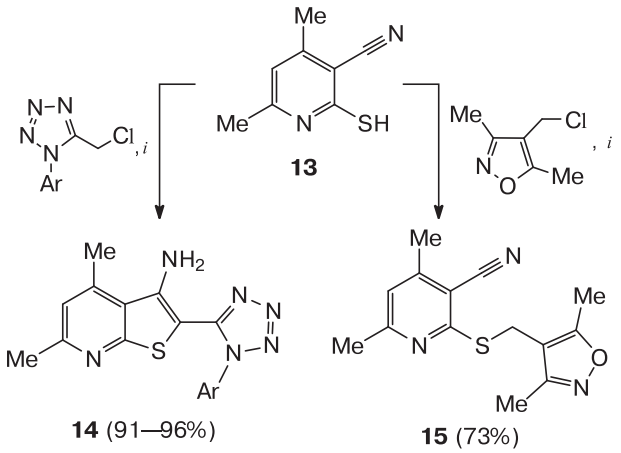


Reagents and conditions: 1) $HSCH_2CH_2CN$ (1.2 equiv.), KOH (3 equiv.), DMF, 0 °C, 1 h; 2) $BrCH_2CN$ (1.5 equiv.), DMF, 0 °C, ~20 °C, 2 h.

Probably the limiting stage of Thorpe—Ziegler cyclization is the formation of carbanionic intermediate **5**. The rate of this stage is determined by the degree of stabilization of **5**, which depends on the electron-withdrawing properties of the EWG (see Scheme 1). Judging by the empirical regularity observed,[4,5] the stabilizing effect of EWG decreases in the following order: NO_2 > ArC(O) > > CN > COOR > $C(O)NH_2$.

It is important that in recent years the reaction under consideration has been extended to the synthesis of bihetaryls based on thieno[2,3-*b*]pyridine. For this purpose, chloromethyl hetarenes were used as electrophilic alkylating agents in the first stage. Among them were 2-chloromethyl-4*H*-1,3-benzoxazine,[73] 3-chloromethylisoxazole,[61] 5-chloromethyl-1*H*-tetrazole,[76] 8-chloromethylxanthine,[77] and 6-chloromethyl-1-phenylpyrazolo[3,4-*d*]-pyrimidin-4(5*H*)-one[78] containing hetaryl groups with sufficient electron-withdrawing power to efficiently stabilize carbanions **5**. The reaction proceeds especially readily with 5-chloromethyltetrazole, which reacts with 2-mercaptonicotinonitriles **13** to give thienopyridines **14** in almost quantitative yields.[76] A similar reaction with 4-(chloromethyl)-3,5-dimethylisoxazole stops at the stage of *S*-alkyl derivative **15**, which does not cyclize even after prolonged treatment with MeONa (Scheme 5)[76] due to the impossibility of efficient stabilization of the anion and insufficient electron-withdrawing ability of the hetaryl group.

Scheme 5



Reagents and conditions: *i*. NaOH, MeOH, reflux, 2 h (for **14**) or 3 h (for **15**).

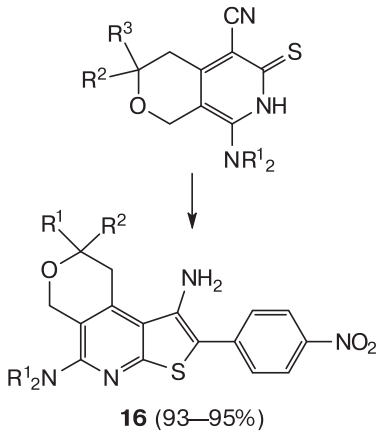
With the benzylic halides, Thorpe—Ziegler cyclization can be carried out only in the presence of sufficiently strong electron-withdrawing group in the benzene ring, such as 4-nitro-,[79] 2-CO_2Me,[80] 2-$CONH_2$,[81] and 2-C≡N.[82] The borderline case, obviously, is the presence of two chlorine atoms at different positions of benzene ring of benzylic halide.[79] In this case, cyclization can be carried out only in the presence of a five-fold excess of EtONa. In the

presence of one chlorine atom at *ortho* or *para* position, cyclization proceeds only in the first case.[79] At the same time, in the presence of the nitro group at *para* position of the benzene fragment, cyclization proceeds spontaneously to give compounds **16** (Scheme 6). The presence of suitable functional substituents at *ortho* position[80—82] promotes two cascade cyclizations to afford polycyclic products, pyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinolines **17**.[82] Hetarylmethylating reagents with a weak electron-withdrawing hetaryl fragment can be used quite efficiently for the synthesis of bihetaryls based on thieno[2,3-*b*]-pyridine if their hetaryl moiety has a suitable strong electron-withdrawing group. This is exemplified by the synthesis[83] of 5-(thieno[2,3-*b*]pyridin-2-yl)-2-thiophenecarboxylates **18** using 2-bromomethyl-5-carbmethoxythiophene (Scheme 7).

It was reported[84] that the direction of cyclization of compounds **20** containing an activated methine group instead of the methylene one proceeds either as expected to afford acids **21** (which can be easily decarboxylated, for example, to give 3-amino-2-phenylthienopyridine **22**), or leads to mesoionic compounds **19** (Scheme 8). Compound **22** was also obtained by the counter synthesis from 2-mercaptonicotinonitrile **13** and benzyl bromide in the presence of NaOH. However, because of the insufficient spectral evidence for the structure of compound **22** given in this work, as well as the general concept of the reduced reactivity of 2-(benzylthio)nicotinonitriles in Thorpe—Ziegler reaction, these results require further confirmation.

Contradictory results were obtained when studying the reaction of 3-(bromoacetyl)coumarin and its benzo analog with 3-cyanopyridine-2(1*H*)-thiones. Thus, according to the work[85] benzo[*f*]coumarin reacts with mercaptonicotinonitrile **13** in the usual way to give a compound with the structure of thienopyridine **23** (Scheme 9). At the same time, it was reported[35,58] that attempts to subject compound **24** to a similar cyclization were unsuccessful. In all the cases, the reaction gave only complex products mixtures, apparently due to the coumarin ring opening. The situation is further complicated by the fact that according to the work[86] in the reaction of 3-(bromoacetyl)coumarin with 3-cyanopyridine-2(1*H*)-thiones, thiazole cyclization can proceed alternatively to afford thiazolo[3,2-*a*]-pyridines of type **25**. Apparently, such competing processes can also hinder the formation of the thieno[2,3-*b*]pyridine system in other cases.

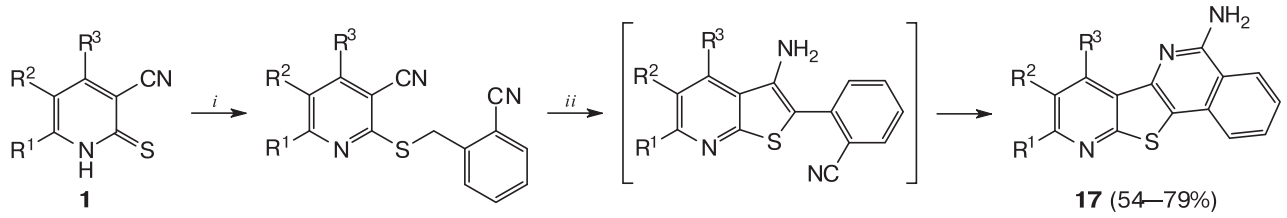
Scheme 6



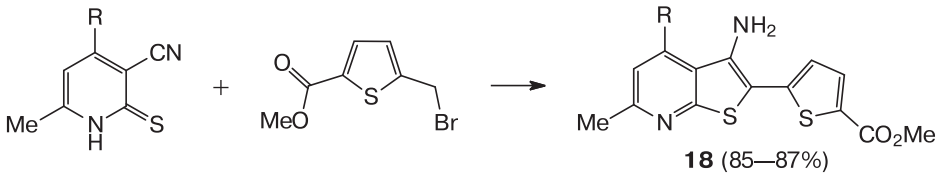
$R^1 + R^1 = (CH_2CH_2)_2O$, $R^2 = Pr^i$, $R^3 = H$
$R^1 + R^1 = (CH_2)_4$, $R^2 = R^3 = Me$

Reagents and conditions: 4-$O_2NC_6H_4CH_2Cl$, EtONa, EtOH, 60 °C, 3 h.

Scheme 7



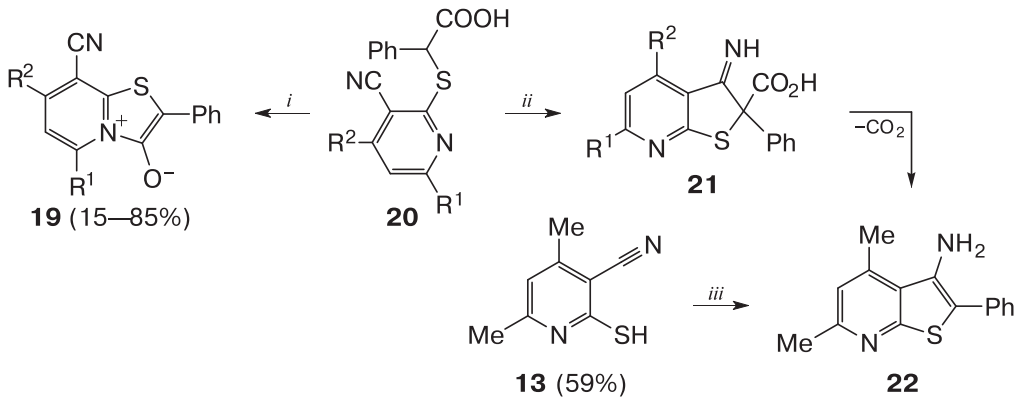
Reagents and conditions: *i*. 2-$NCC_6H_4CH_2Cl$, Et_3N, chloroform, reflux; *ii*. Bu^tOK, DMF, 55—60 °C, 40 min.



R = Me, CH_2OMe

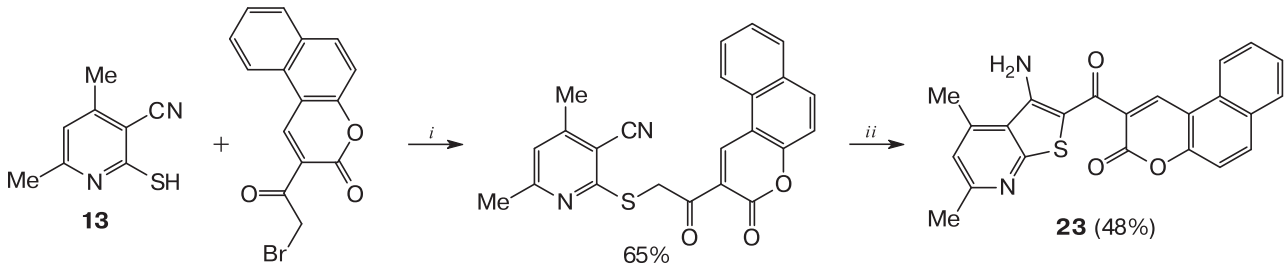
Reagents and conditions: KOH, DMF, 65—70 °C, reflux, 3 h.

Scheme 8

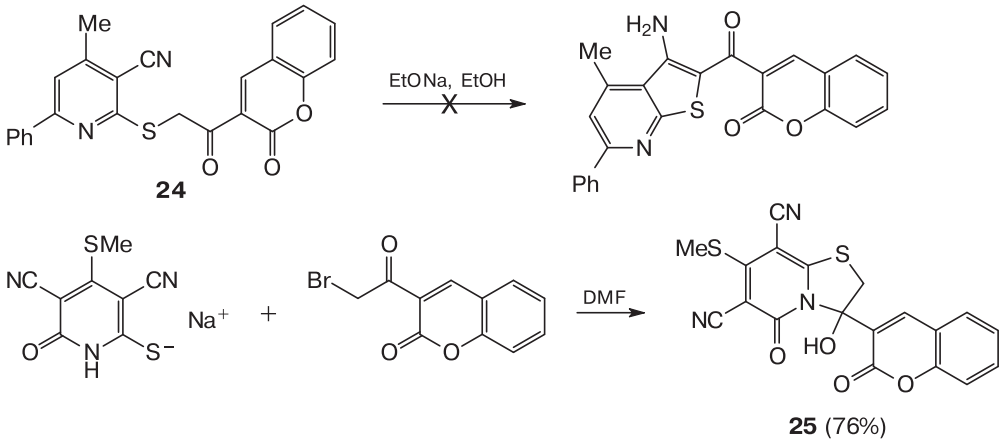


Reagents and conditions: *i*. Ac_2O, pyridine, 140 °C, 15 min; *ii*. Ac_2O, AcOH, 140 °C, 15 min; *iii*. $PhCH_2Br$, NaOH, DMF, 70 °C, 3 h.

Scheme 9



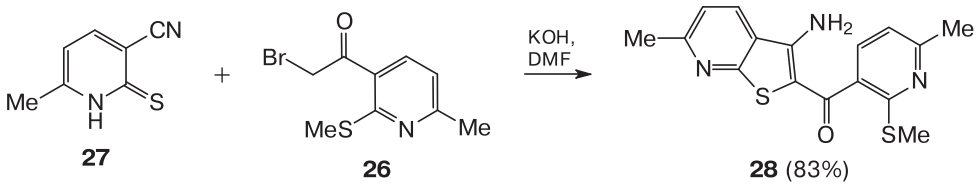
Reagents and conditions: *i*. AcONa, EtOH, reflux 3 h; *ii*. EtONa, EtOH, reflux 1 h.



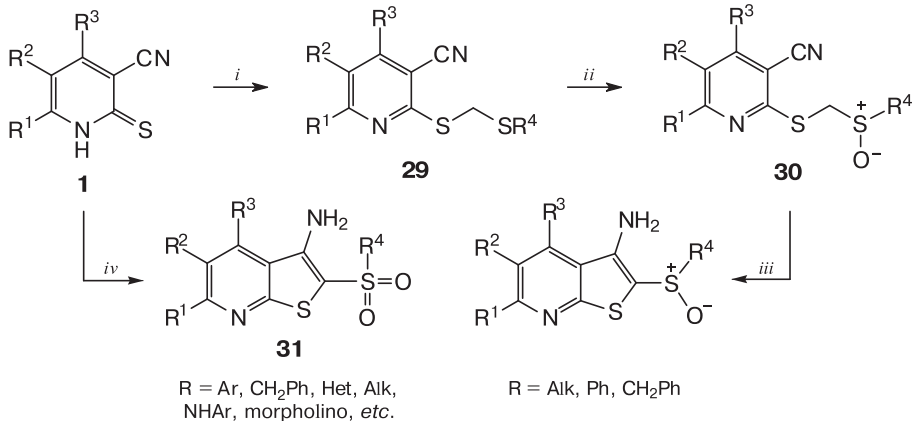
The reaction of bromoketone **26** with pyridine-2(1*H*)-thione **27**, despite the presence of a nucleofugic methylthio group, does not initiate[87] the cascade cyclization and is limited to only one cyclization into thienopyridine **28** (Scheme 10).

In recent years in the context of the discovered biological activity of some substituted thienopyridines,[88,89] considerable attention was paid to the synthesis of (3-aminothieno[2,3-*b*]pyridin-2-yl) sulfoxides, sulfones, and sulfonamides. Such compounds were prepared by two methods: by selective oxidation of dithiomethanes **29** followed by Thorpe—Ziegler cyclization of the resulting sulfoxides **30**[89,90] and by direct alkylation of 3-cyanopyridine-2(1*H*)-thiones with chloromethyl sulfones[89—91] and chloromethylsulfonamides[58,91] in the presence of an excess of base (Scheme 11). It was noted[91] that the yields of sulfones **31** strongly depend on the structure of substituent R^1, which determines the possibility of the side base-mediated Ramberg—Bäcklund reaction of the starting chloromethyl sulfone. The yields of sulfonamides (32—46%) are gener-

Scheme 10



Scheme 11



Reagents and conditions: *i*. $ClCH_2SR^4$, Et_3N, MeCN, reflux; *ii*. 30% H_2O_2, AcOH, chloroform, 30—35 °C; *iii*. KOH or Bu^tOK, MeOH, DMF; *iv*. $ClCH_2SO_2R^4$, Et_3N or AlkONa or K_2CO_3, DMF, 70—130 °C.

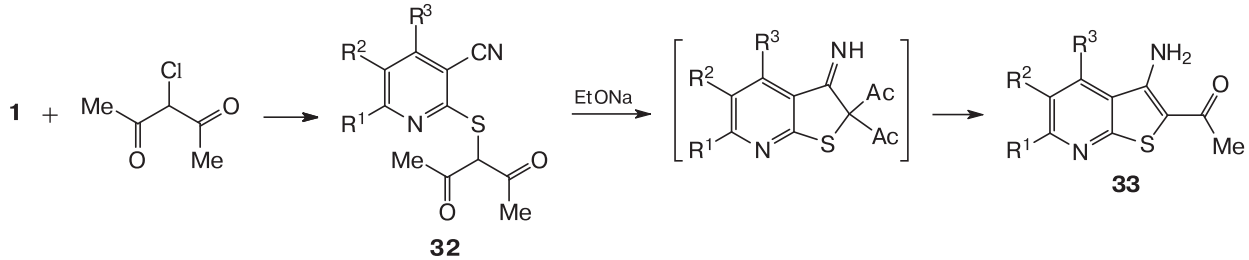
ally lower than those of sulfones (31—78%), which can be explained by the different electronic effects of methylene activating substituents.

It is known[5] that the reactions of 3-cyanopyridine-2(1*H*)-thiones **1** with 3-chloropentane-2,4-dione lead to compounds **32**. The latter treated with strong bases undergo cyclization and ketone cleavage to give 2-acetyl-3-aminothienopyridines **33**. Examples of the realization of such approach is shown in Scheme 12.[37,38,92—94] This approach is an alternative to the common synthesis of thienopyridines from thiones **1** and α-halo ketones and can be used when these halo ketones are scarcely available or, being strong lacrimators, are inconvenient to handle.

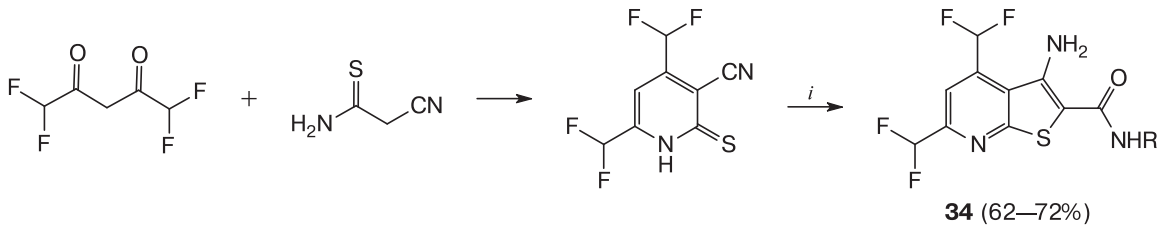
The Thorpe—Ziegler reaction is tolerant to a wide range of substituents and functional groups, including those traditionally considered as being unstable under alkaline hydrolysis conditions. The reason is the high rate of this reaction and the wide possibilities to vary reaction conditions, alkylating agents, and substituents at positions 4—6 of 2-thioxonicotinonitriles **1**. This makes the basis for the synthesis of combinatorial libraries of compounds, for example, fluorinated thienopyridines[95,96] and for functionally oriented molecular design. An example is the targeted synthesis of new fluorinated thienopyridines **34** as lipophilic representatives of this series of bicyclic systems[97,98] (Scheme 13).

An important development of the synthetic scheme under consideration is the possibility of its extension to 1,4-dihydro analogs of 3-cyanopyridine-2(1*H*)-thiones, *i.e.*, to 3-cyano-1,4-dihydropyridine-2-thiolates, as established in a number of publications. The latter, after alkylation at the sulfur atom, can also be subjected to

Scheme 12



Scheme 13



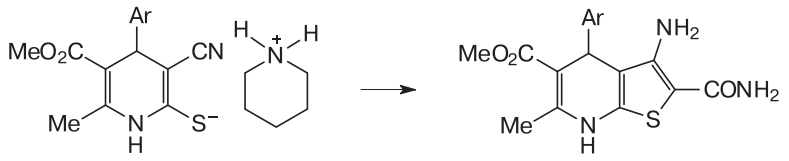
34 (62—72%)

Reagents and conditions: *i*. $ClCH_2C(O)NHR$, KOH, DMF.

Thorpe—Ziegler cyclization, as a rule, with the retention of a partially saturated pyridine system,[99—102] although spontaneous oxidation of the dihydropyridine system with atmospheric oxygen during the reaction are also known.[103] The resistance of the dihydropyridine fragment to oxidation, as shown earlier,[4,5,8,9] significantly depends on the nature of substituents at the pyridine ring (especially at position 4), as well as on the reaction conditions. This can be exemplified by transformations presented in Scheme 14. In some cases, instead of 3-cyano-1,4-dihydropyridine-2-thiolates their precursors can also be involved in the reaction, as was shown[104] for the transformation of Michael adduct **35** to thienoquinoline **36**.

In addition to 2-thioxo(mercapto)nicotinonitriles, other derivatives of nicotinic acid can be used to construct the thienopyridine system, in particular, 2-mercaptonicotinates.[91,105—107] In this case, the Dieckmann cyclization is used for the transformation of *S*-alkylation products into thienopyridines, which requires more drastic conditions than the Thorpe—Ziegler cyclization involving nicotinonitriles. The reaction products in this case are 3-hydroxythieno[2,3-*b*]pyridines and/or their prototropic 3-oxotautomeric forms. Thus, ester **37** reacts with chloromethyl sulfones to form tautomers **38** and **39** in the ratios from 90 : 10 to 40 : 60 (Scheme 15).[91] At the same time, mercaptonicotinates **40** gave rise only to 3-hydroxythienopyridines **41**,[107] while, on the contrary, compound **42** cyclized to the product assigned the structure of the corresponding 8-oxo derivative **43**[106] (Scheme 16). Thus, the relative thermodynamic stability of the ketone

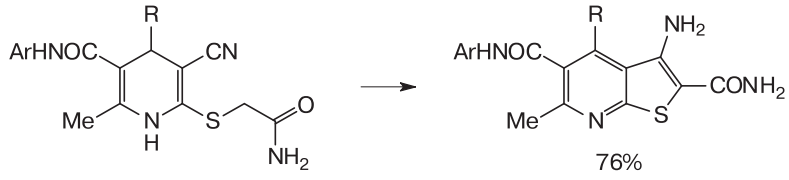
Scheme 14



(1)[100]

Ar = 3,4-$(OCH_2O)C_6H_3$

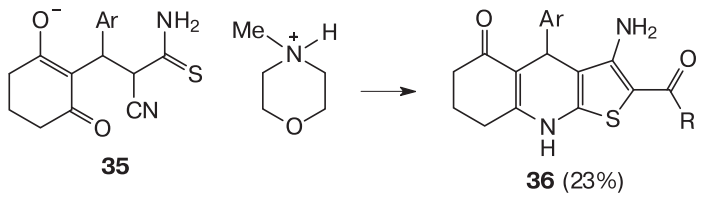
Reagents and conditions: 1) ICH_2CONH_2, EtOH; 2) 3 *M* NaOH, EtOH, H_2O.



(2)[103]

R = 5 methyl-2-thienyl, Ar = 2-$MeOC_6H_4$

Reagents and conditions: 10% KOH, DMF, ~20 °C.



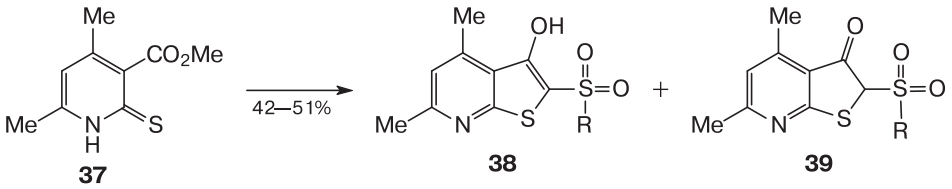
35 **36** (23%)

(3)[104]

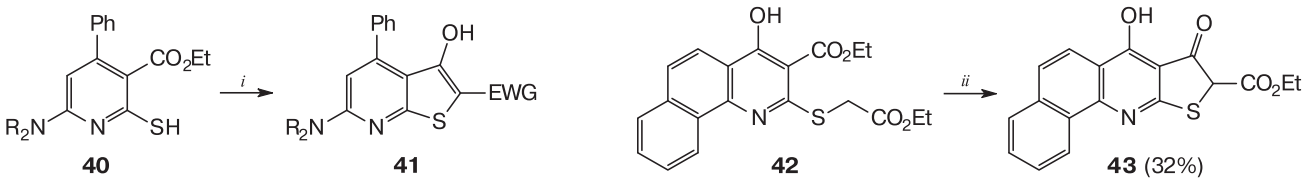
Ar = 4-MeC_6H_4, R = 4-ClC_6H_4

Reagents and conditions: $BrCH_2C(O)R$, EtOH, reflux, 10 h.

Scheme 15



Reagents and conditions: RSO_2CH_2Cl, K_2CO_3, DMF, 70—75 °C.

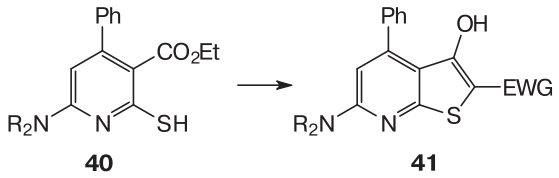


EWG = Bz, CONHR, CO_2Alk

Reagents and conditions: *i*. 1) $ClCH_2EWG$, EtOH, Na_2CO_3; 2) K_2CO_3, EtOH (anhydr.), reflux, 2 h; 3) HCl; *ii*. EtONa, EtOH, 4 h.

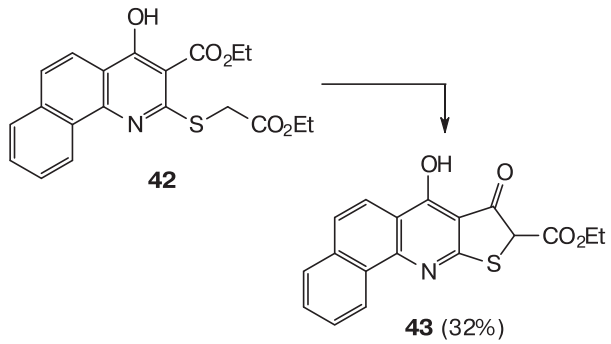
and the enol forms substantially depends on the electron-withdrawing properties of the group at position 2 of the thiophene ring.

Scheme 16



EWG = Bz, CONHR, CO_2Alk

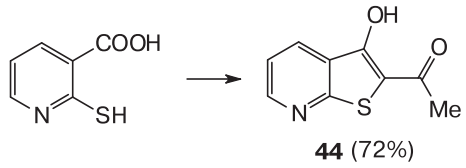
Reagents and conditions: 1) $ClCH_2EWG$, EtOH, Na_2CO_3; 2) K_2CO_3, EtOH (anhydr.), reflux, 2 h; 3) HCl.



Reagents and conditions: EtONa, EtOH, 4 h.

The condensation of iron(III) acetylacetonate with 2-mercaptonicotinic acid gave thienopyridine **44** Scheme 17.[108] It is assumed that this reaction follows a free radical mechanism and is promoted by trace amounts of peroxide present in the solvent.

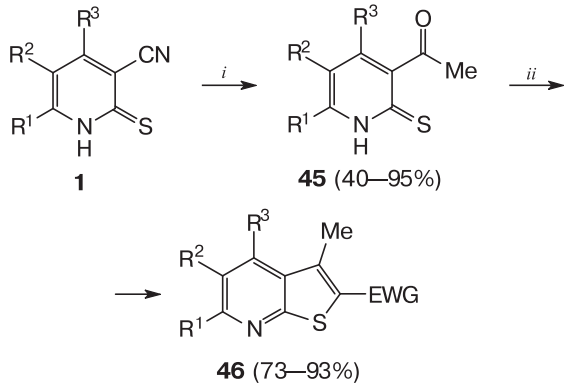
Scheme 17



Reagents and conditions: 1) $Fe(acac)_3$, $HOCH_2CH_2OH$, 120 °C; 2) H^+, ~20 °C.

3-Acetylpyridine-2(1*H*)-thiones **45** synthesized by the reaction of thiones **1** with methyllithium on treatment with chloroacetonitrile or 4-bromophenacyl bromide under mild conditions in the presence of an alkali excess gave 3-methylthienopyridines **46** (Scheme 18).[109]

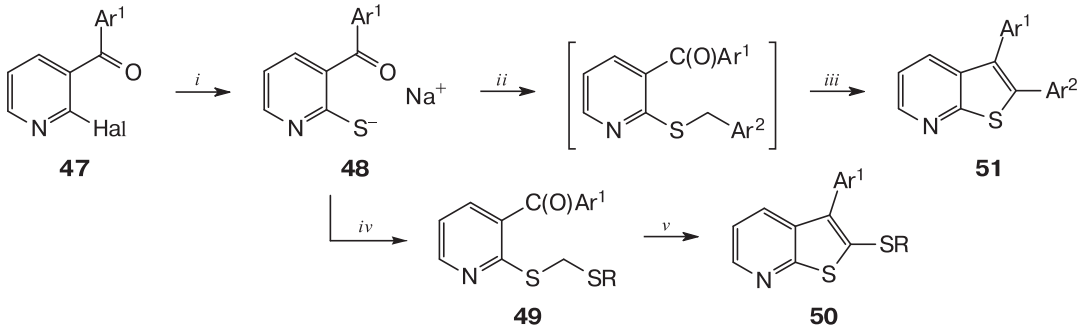
Scheme 18



R^1 = H; R^2, R^3 = Alk; EWG = CN, 4-$BrC_6H_4C(O)$

Reagents and conditions: *i*. 1) MeLi (3 equiv.), −3÷−5 °C, Et_2O, 2) H_2O, H^+; *ii*. $HalCH_2EWG$, KOH, EtOH, 45 °C.

Scheme 19



Hal = Cl, Br; Ar^2 = 4-$EWGC_6H_4$; R = Ph, Me, Bu^t

Reagents and conditions: *i*. $Na_2S \cdot 9H_2O$, DMF, 70 °C; *ii*. $BrCH_2Ar^2$, DMF; *iii*. NaH, DMF; *iv*. $ClCH_2SR$, ~20 °C; *v*. 1) LDA (3 equiv.), −78 °C, 2) H_3O^+, 3) $SOCl_2$, pyridine, THF, 0 °C.

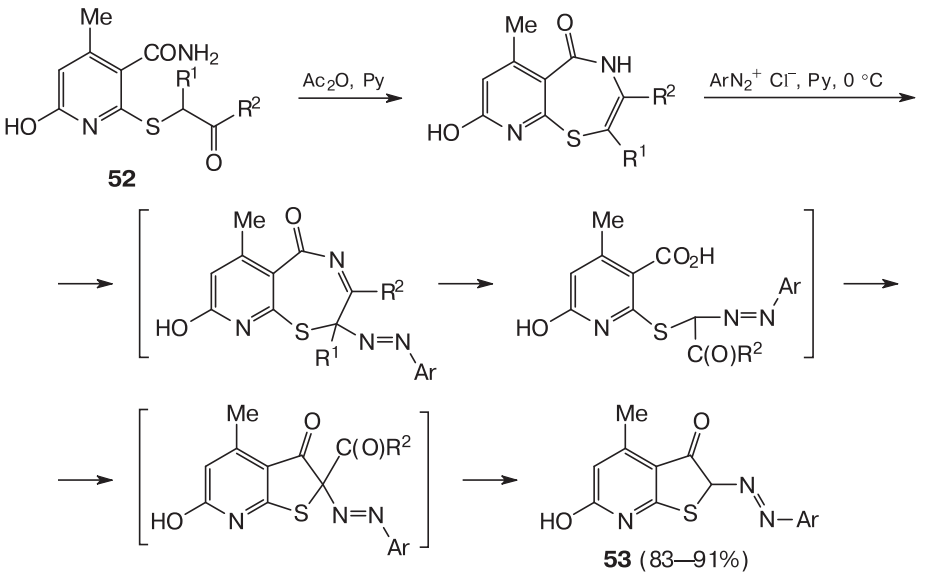
3-Aryl-substituted thienopyridines can be prepared by the approach described in the works.[110,111] The starting compounds are 2-halopyridines **47**, which are converted to thiolates **48** by treatment with Na_2S. The latter are *S*-alkylated with chloromethyl sulfides to dithioacetals **49**. Lithiation of compounds **49** with LDA is accompanied by intramolecular cyclization followed by dehydration to give 2-substituted 3-arylthienopyridines **50** in 47—54% yields (Scheme 19).[110] Thiolates **48** can also be alkylated with benzylic bromides and converted to 2,3-diarylthienopyridines **51** by treatment with NaH (46—79% yields).[111]

The work[112] proposed an unusual method for converting nicotinamides **52** into arylazo derivatives of thieno[2,3-*b*]-pyridine **53**. The reaction follows a rather complicated path *via* isolated 1,4-thiazepine intermediate, which is subjected to azo coupling. Further stages of the cascade transformations include the recyclization with a seven-membered ring contraction and Japp—Klingemann deacylation (Scheme 20).

2-Mercaptobenzo[*h*]quinoline-3-carbaldehyde (**54**) can also be used to construct a thiophene ring. It was shown[113] that it is readily *S*-alkylated with α-bromoketones in the presence of bases, giving *S*-acylmethyl derivative prone to intramolecular Knoevenagel condensation to give tetracyclic ketone **55** (Scheme 21). It was noted that KOH is a more preferable for this cyclization than K_2CO_3, since the reaction time with KOH is faster and the yields of the target thienoquinolines **55** are slightly higher (55—81% *versus* 54—78%).

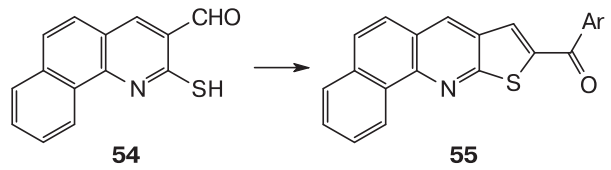
This synthesis of 3-unsubstituted thienoazines is actually very close to an alternative method for the preparation

Scheme 20



R^1 = H, Ac; R^2 = Me, Ph

Scheme 21

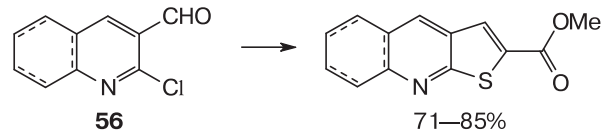


54 **55**

Reagents and conditions: $BrCH_2C(O)Ar$, KOH or K_2CO_3, EtOH.

of the related thieno[2,3-*b*]quinolines by reacting readily available[114–117] 2-chloroquinoline-3-carbaldehydes with thioglycolic acid esters. As examples of such reactions, let us mention the mild reaction of 2-chloropyridine(quinoline)-3-carbaldehyde **56** with methyl thioglycolate catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 22),[118] the reaction of pyridine **57** with mercaptoacetone[119] and benzyl mercaptan,[120] as well as the condensation involving thioglycolic acid to afford a mixture of quinoline **58**

Scheme 22



56 71—85%

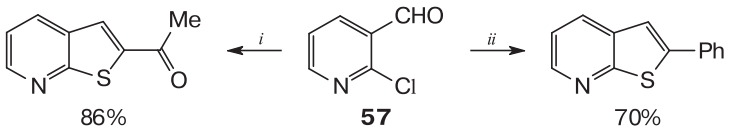
Reagents and conditions: $HSCH_2COOMe$, DBU, THF, ~20 °C.

and thienoquinoline **59**[121] (Scheme 23). The reaction of compounds **60** with ethyl thioglycolate proceeds similarly to give the thieno[2,3-*b*]pyridine system with the retention of the 1,4-dihydropyridine fragment (see Scheme 23).[122]

This approach to the thiophene ring construction is ideologically related to approach ***B*** (see Scheme 1), which suggests alternative to approach ***A*** strategy for the C—S—C fragment formation and is based on the reaction of 2-chloronicotinonitriles with thioglycolic acid derivatives. Examples when approach ***B*** is used are encountered in the literature less often than the syntheses based on strategy ***A***. This is obviously explained by the lower availability and variability of the starting reagents, as well as by the relative inconveniences of working with mercaptocarbonyl compounds due to their inherent unpleasant odor. The reaction of 2-chloronicotinonitriles with thioglycolates is usually carried out in the presence of K_2CO_3[123] or Na_2CO_3[124,125] in refluxing EtOH or in the presence of EtONa in DMF at 70 °C.[126] The following systems are also used: MeONa/MeOH and EtONa/EtOH,[127–129] as well as Bu^tOK in DMF at 0 °C.[130] There are examples of successful cyclization catalyzed by either Et_3N in refluxing EtOH[131] or Et_3N in DMSO at 130 °C under microwave irradiation.[132] Examples illustrating this strategy include the syntheses of thienopyridine **61**[131] and thienonaphthyridine **62**[129] (Scheme 24).

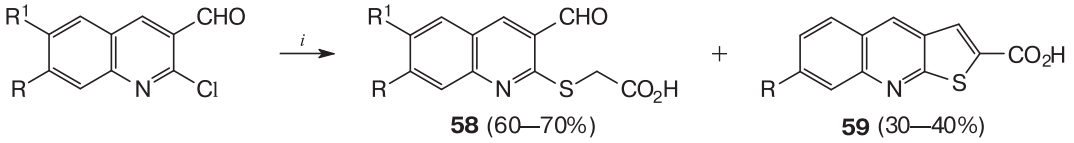
The nature of the base catalyzing the cyclization and the synthesis conditions have a decisive influence on the success of the reaction. Already in the first works describing the preparation of thienopyridines from 2-chloronic-

Scheme 23



86% **57** 70%

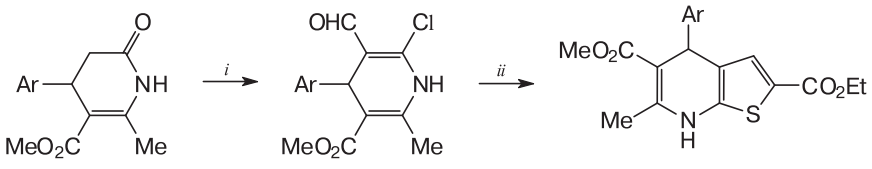
Reagents and conditions: *i*. $HSCH_2C(O)Me$, K_2CO_3, H_2O, 90 °C, 2 h; *ii*. $PhCH_2SH$, KOH, PEG-600, 100 °C, 2 h.



58 (60—70%) **59** (30—40%)

R = H, Me, Cl, F

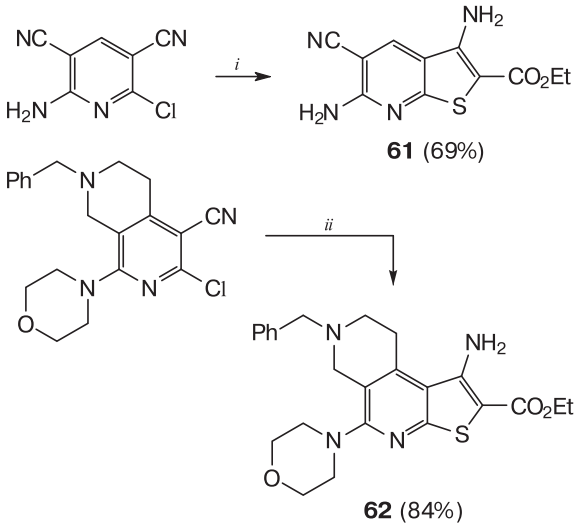
Reagents and conditions: *i*. $HSCH_2CO_2H$, NaOH, KI, EtOH, reflux.



60 (17—68%) 57—61%

Reagents and conditions: *i*. 1) $POCl_3$, DMF, 2) AcONa, H_2O; *ii*. $HSCH_2CO_2Et$, EtOH, EtONa, reflux, 3 h.

Scheme 24



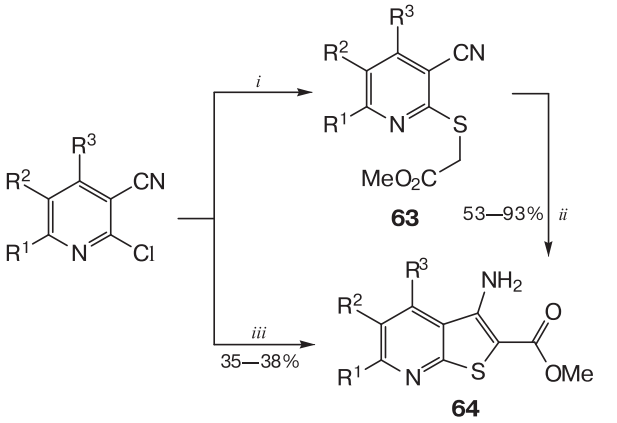
Reagents and conditions: *i*. $HSCH_2COOEt$, Et_3N, EtOH, reflux, 4 h; *ii*. $HSCH_2COOEt$, EtONa, EtOH, 5 h.

otinonitriles,[133,134] it was noted that the reaction proceeds smoothly with sodium ethylate, whereas with weaker bases such as Na_2CO_3 or Et_3N, the Thorpe—Ziegler cyclization either does not occur or gives complex mixtures of products with unsatisfactory yields of the targeted thienopyridines. At the same time, the disadvantages of using EtONa include the formation of 2-ethoxynicotinonitriles due to the side solvolysis reaction. There are indications[135] that under mild conditions the reaction of 2-chloronicotinonitriles with thioglycolates stops at the stage of the formation of nucleophilic substitution product **63** and further cyclization to thienopyridines **64** requires the use of stronger bases. A comparative analysis[135] of the efficiency of the above two-stage method for the synthesis of compounds **64** and a one-pot approach based on successive treatment of the starting 2-chloropyridine with Na_2S and $BrCH_2CO_2Et$ (Scheme 25) showed that in the latter case the product yields are noticeably lower.

The cyclocondensation of 2-chloronicotinonitriles with $HSCH_2CO_2Et$ in the presence of finely ground KOH under phase transfer catalysis conditions was studied.[136] It is interesting to note that when triethylbenzylammonium chloride (TEBA) was used, the reaction stopped at the stage of nicotinonitriles **65**, while cyclization products **66** were formed in the presence of 18-crown-6 (Scheme 26).

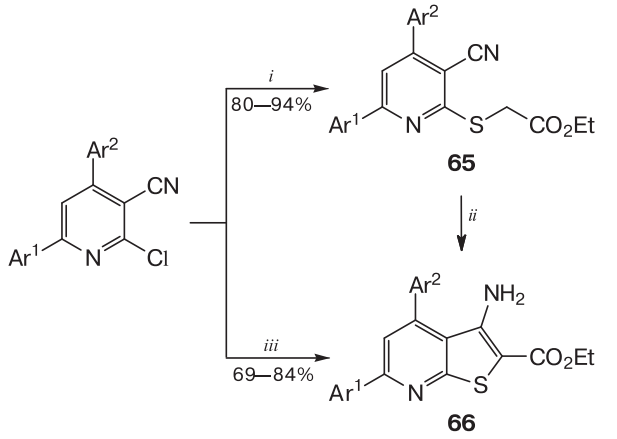
Mercaptoacetamides react with 2-chloronicotinonitriles similarly to thioglycolic acid esters (Scheme 27). The reaction proceeds in the presence of NaH in DMF,[137] K_2CO_3,[55,138] or Na_2CO_3[139] in refluxing EtOH and K_2CO_3 in DMSO at 80 °C.[140] As in the case of thioglycolates, only nucleophilic substitution products are formed under mild conditions, which was exemplified[141] by the synthe-

Scheme 25



Reagents and conditions: *i*. $HSCH_2Me$, DMF, K_2CO_3, ~20 °C, 1 h; *ii*. MeONa, MeOH, ~20 °C, 1 h; *iii*. 1) $Na_2S \cdot 9H_2O$, 2) $BrCH_2CO_2Me$, MeONa, MeOH, 50 °C, 3 h.

Scheme 26



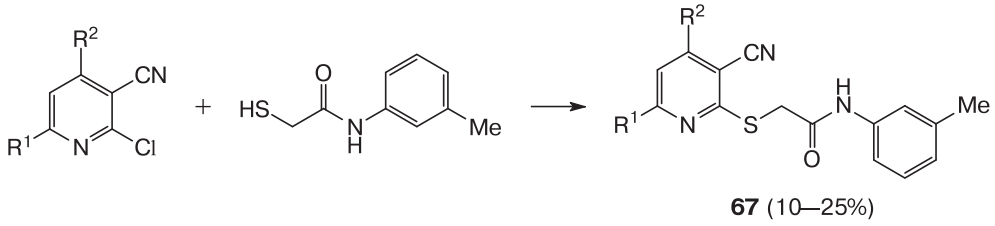
Reagents and conditions: *i*. TEBA, KOH, $HSCH_2CO_2Et$, toluene, 40—45 °C, 1—1.5 h; *ii*. 18-crown-6, KOH, $HSCH_2CO_2Et$, MeCN, 35—40 °C, 2.5—3 h; *iii*. 18-crown-6, KOH, $HSCH_2CO_2Et$, MeCN, 35—40 °C, 1.5—2 h.

sis of compounds **67**. Utilization of mercaptoacetamides in the synthesis of thienopyridines can be illustrated by preparation of compounds **68**[137] and hydrazones **69**[138].

Recently, a number of papers have been published describing fundamentally different approaches to the construction of a thienopyridine system, which do not use the Thorpe—Ziegler cyclization. Thus, the conversion of phosphonium ylides **70** derived from 2-(methylthio)nicotinic acid to 2-monosubstituted thienopyridines **71** under flash vacuum pyrolysis conditions was described[142] (Scheme 28).

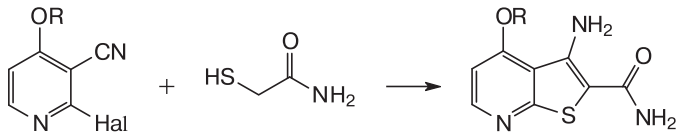
3-Arylthienopyridines **72** were obtained in good yields by an original method[143] based on the Wittig reaction of ketones **73** with phosphonium ylides and further treatment

Scheme 27



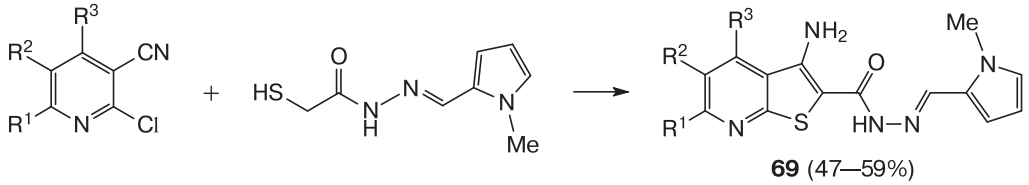
67 (10—25%)

Reagents and conditions: K_2CO_3, DMF or MeCN, ~20 °C, 1 h.



68 (40—60%)

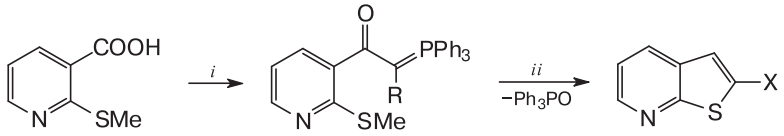
Reagents and conditions: $HSCH_2C(O)NH_2$, NaH, DMF, 60 °C.



69 (47—59%)

Reagents and conditions: K_2CO_3, EtOH, 80 °C, 16 h.

Scheme 28



70 (93—99%) **71a,b**

X = $CH{=}CH_2$ (**a**), Ph (**b**)

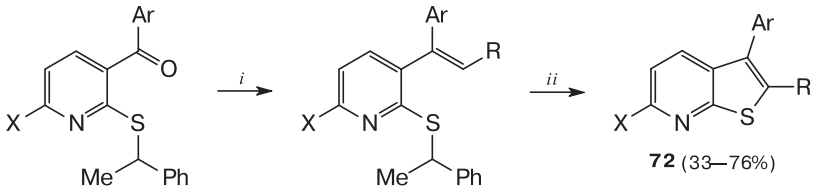
Reagents and conditions: *i*. 1) $SOCl_2$, 2) $Ph_3P{=}CHR$ (R = Et, Ph), THF; *ii*. flash vacuum pyrolysis, 850 °C.

of the resulting compounds **74** with iodine under mild conditions (Scheme 29). However, this reaction is not of general character. For example, it was not possible to introduce an alkyl substituent at position 3. It was also shown that the yields significantly decrease on going from R = H (67—76%) to R = Me (33—40%). An alternative approach[144] to 3-arylthienopyridines assumes Pummerer rearrangement involving sulfoxides **75** as a key step. It is noted that the yield of the target products and the reaction time critically depend on the structure of the aryl group: the yield is minimal (13%) at Ar = Ph, while the introduction of the donor substituents in the benzene ring helps to increase the yield and shorten the reaction time (see Scheme 29).

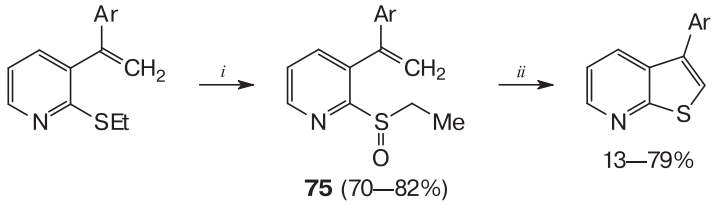
2-Arylthienopyridines can be obtained in high yields from 3-bromo-2-chloropyridine. The cross-coupling of the latter with terminal alkynes under Sonogashira conditions proceeds regioselectively at the position C(3) to give compounds **76**, the thiolysis of which with sodium sulfide leads to thienopyridines **77** (Scheme 30).[145] 3-Iodo-2-fluoropyridine can be used as a pyridine substrate under similar conditions giving 2-phenylthienopyridine in 61% yield.[146] The replacement of Na_2S with potassium ethylxanthate as a source of sulfur allowed one to increase the yields of the target compounds to almost quantitative.[147]

The reaction of propargyl alcohols **78** with potassium ethylxanthate in the presence of a copper-containing catalyst leads to ketones **79** in high yields (Scheme 31).[148]

Scheme 29

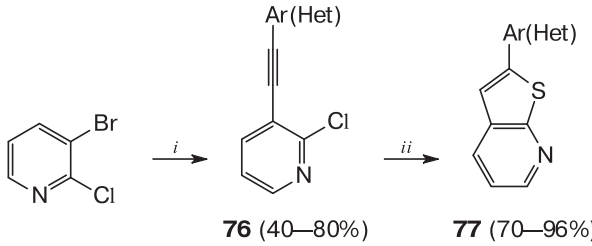


Reagents and conditions: *i*. $Ph_3P{=}CHR$, THF, 0 °C; *ii*. I_2, $NaHCO_3$, MeCN, heating.

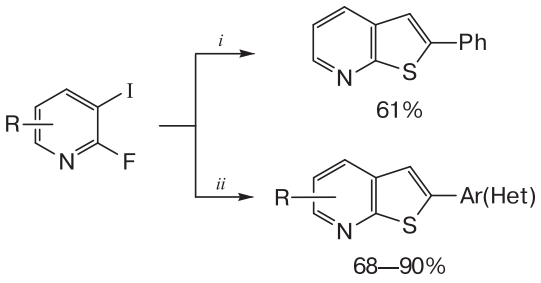


Reagents and conditions: *i*. $NaIO_4$, *ii*. Ac_2O, 100—110 °C.

Scheme 30



Reagents and conditions: *i*. HC≡CAr(Het), $PdCl_2(PPh_3)_2$ (3 mol.%), CuI (6 mol.%), Et_3N, 100 °C, 2 h; *ii*. Na_2S, 130 °C.

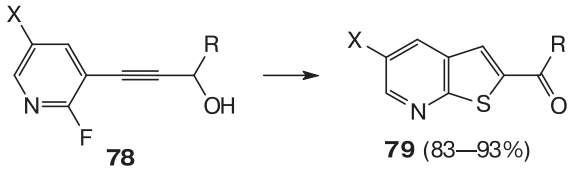


Reagents and conditions: *i*. HC≡CPh, 1) $PdCl_2(PPh_3)_2$ (5 mol.%), CuI (10 mol.%), Et_3N, ~20 °C.; 2) Na_2S, DMSO, 100 °C; *ii*. HC≡CAr(Het), 1) $PdCl_2(PPh_3)_2$ (5 mol.%), CuI (10 mol.%), Et_3N, DMSO; 2) $EtOCS_2K$, 35—90 °C.

As the authors of the work[148] noted, the mechanism of oxidation of the OH group to the oxo group under the synthesis conditions is unclear.

The Willgerodt—Kindler reaction of 3-acetyl-2-chloropyridine with primary amines and sulfur gives compounds **80**.[149] This reaction can be considered a convenient method for the synthesis of (2-R-amino)thienopyridines. The disadvantages of this method include the almost inevitable formation of nucleophilic substitution products **81** (Scheme 32).

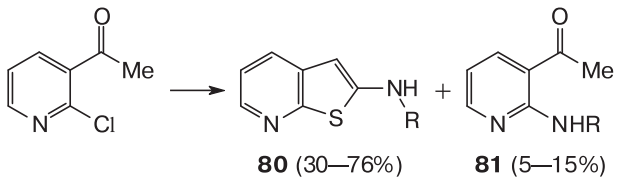
Scheme 31



X = H, Me; R = Alk, Ar

Reagents and conditions: $Cu(acac)_2$ (10 mol.%), EtOC(S)SK, DMSO, 100 °C.

Scheme 32

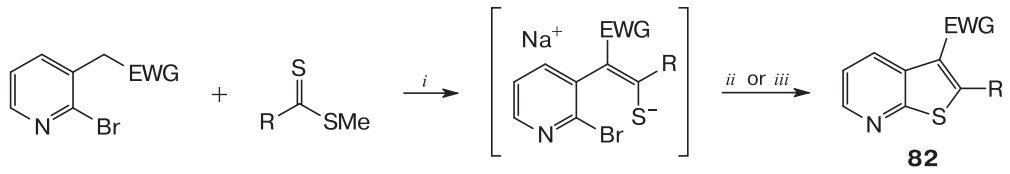


R = Alk, $PhCH_2$, *cyclo*-Alk

Reagents and conditions: RNH_2, S_8, AcONa, DMF, 90—120 °C, 20 min.

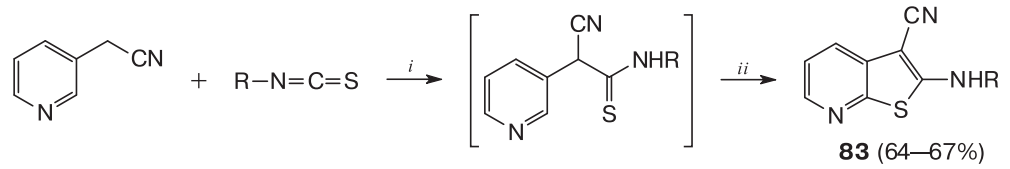
A number of recent publishions[150—152] describe the synthesis of functionally substituted thienopyridines **82** and **83** by the reaction of (pyridine-3-yl)acetonitriles and related methylene active compounds with dithiocarb-

Scheme 33



EWG = CN, C(O)Ar; R = Ar, Het, Alk

Reagents, conditions, and yields: *i*. NaH, DMF, 0 °C, 1 h; *ii*. $Pd(OAc)_2$, $Cu(OAc)_2$, Bu_4NBr, 90 °C, 4—6 h, 64—72%; *iii*. CuI, L-proline, 90 °C, 3—6 h, 68—90%.



Reagents and conditions: *i*. NaH, DMF; *ii*. $PdCl_2$, Bu_4NBr, CuI, 90 °C, 5—6 h.

oxylates or isothiocyanates followed by intramolecular arylthiolation in the presence of Pd or Cu catalysts (Scheme 33).

3. Construction of thienopyridine system through the formation of the pyridine ring

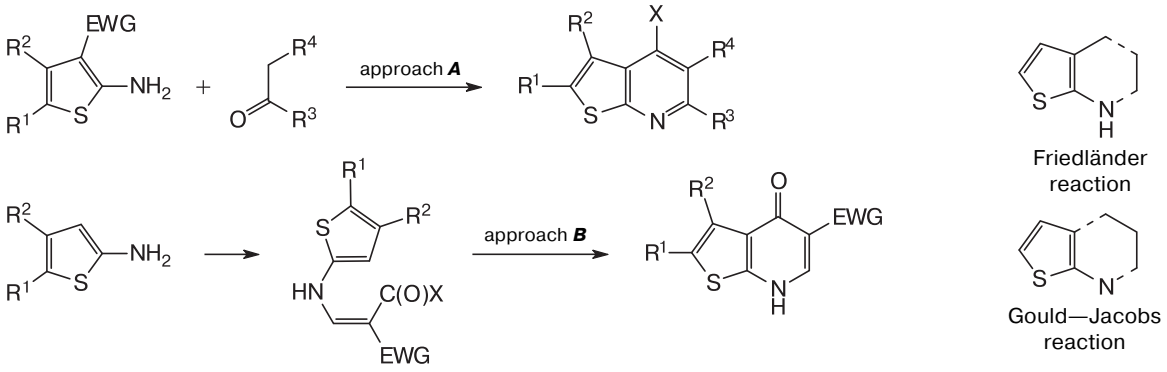
The interest in this method for constructing the thieno[2,3-*b*]pyridine system is explained by the availability of the starting 2-aminothiophenes, which are easily obtainable from carbonyl compounds, sulfur, and methylene active nitriles under the Gewald reaction conditions. Certain aspects of the transformation of 2-aminothiophenes into thienopyridines have been considered in recent reviews devoted to the chemistry of Gewald's thiophenes.[153—155]

In most cases, 2-aminothiophenes can be converted to thienopyridines by two fundamentally different methods, which suggest the construction of the pyridine ring either by the Friedländer reaction and related transformations (Scheme 34, approach ***A***) or by the Gould—Jacobs reaction (approach ***B***).

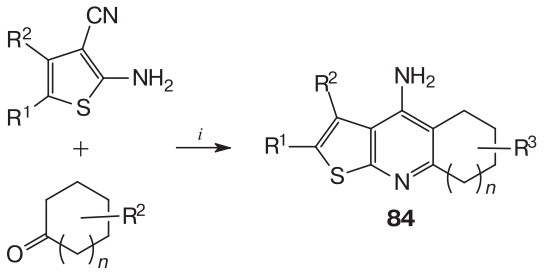
The Friedländer synthesis was used to obtain thienopyridines **84**, the structural analogs of tacrine **85**, which are acetylcholinesterase inhibitors (Scheme 35).[156—161] The search for new compounds in this series is due to the fact that tacrine, being one of the few drugs efficient in the treatment and therapy of Alzheimer's disease, has a pronounced hepatotoxic effect.[162] The reaction of ketones with 2-amino-3-cyanothiophenes is usually catalyzed by acids: TsOH and $AlCl_3$,[156,157,160] $Yb(OTf)_3$,[158] $BF_3 \cdot Et_2O$ and $ZnCl_2$,[159] $POCl_3$.[161] It should be noted that thiophene analogs of tacrine exhibit low inhibitory effect[161] or even complete absence of activity.[157] Molecular modeling results show that the lone pairs of the sulfur atom hinder efficient interaction with the acetylcholinesterase binding site.[157]

The Friedländer reaction takes place under a wide variety of conditions. Thus, thiophene **86** can react with

Scheme 34

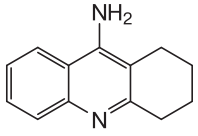


Scheme 35



n = 0—2

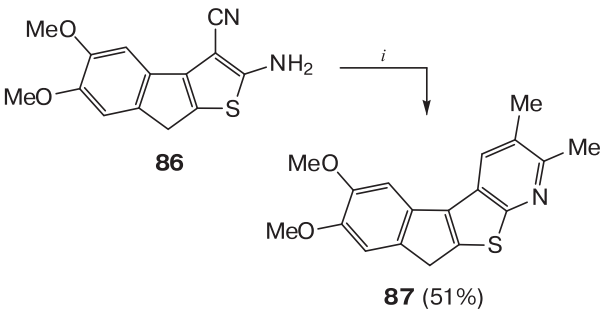
Reagents: *i.* acid catalysis, $ClCH_2CH_2Cl$.



85 tacrine

various ketones under solvent-free conditions (in the melt) in the presence of anhydrous $ZnCl_2$, as exemplified by the synthesis of tetracyclic product **87** (Scheme 36).[163]

Scheme 36

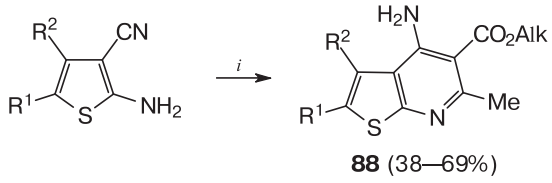


Reagents and conditions: *i.* MeC(O)Et, $ZnCl_2$, solvent-free, 120—130 °C, 2 h.

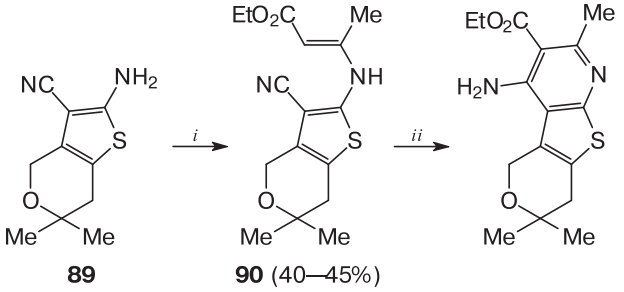
The reaction of Gewald′s 2-aminothiophenes with ethyl acetoacetate is less unambiguous. Under $SnCl_4$-catalysis conditions, thienopyridines **88** were isolated[164—168] in moderate yields (Scheme 37). However, in the presence of TsOH thienopyran **89** gave[18] only β-enamino ester **90**, which was further cyclized by treatment with EtONa. It is interesting to note that structural analog **91** reacts with ethyl acetoacetate in a different way: in the presence of EtONa, only a mixture of linear tautomeric condensation product is formed, which do not cyclize even under harsh conditions. In contrast, the reaction in refluxing AcOH gives thienopyridine **92**.[18]

The decisive role in the choice of the route for the reaction of 2-aminothiophene-3-carbonitriles with ketones is played by the catalyst. Thus, only Friedländer products are formed in the presence of Brønsted acids (TsOH or polyphosphoric acid).[93] When Lewis acids ($AlCl_3$ or $ZnCl_2$) are used, trace amounts of thienopyrimidines **94** were also found among the reaction products.[169] The latter are products of the competing tandem Pinner—Dimroth reaction and subsequent photooxidation and become the major reaction products under EtONa catalysis (Scheme 38).

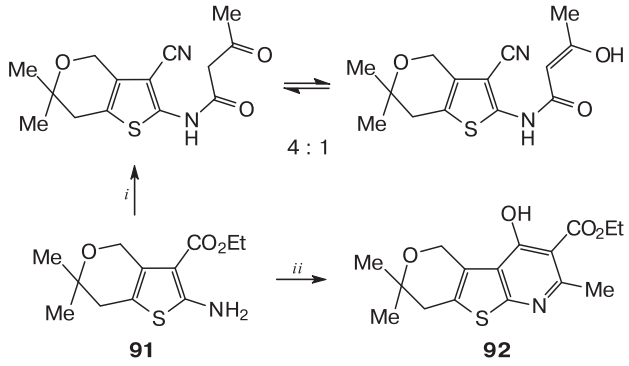
Scheme 37



Reagents and conditions: *i.* $MeC(O)CH_2CO_2Alk$, $SnCl_4$, toluene, reflux.



Reagents and conditions: *i.* $MeC(O)CH_2CO_2Et$, TsOH, EtOH; *ii.* EtONa.

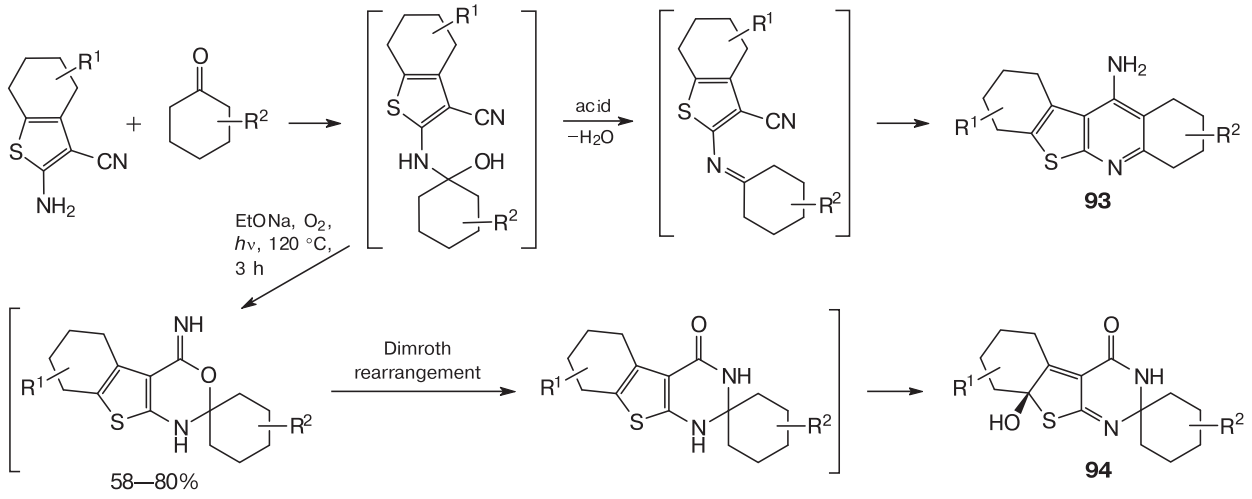


Reagents and conditions: *i.* $MeC(O)CH_2CO_2Et$, EtONa, EtOH; *ii.* $AcCH_2CO_2Et$, AcOH, reflux.

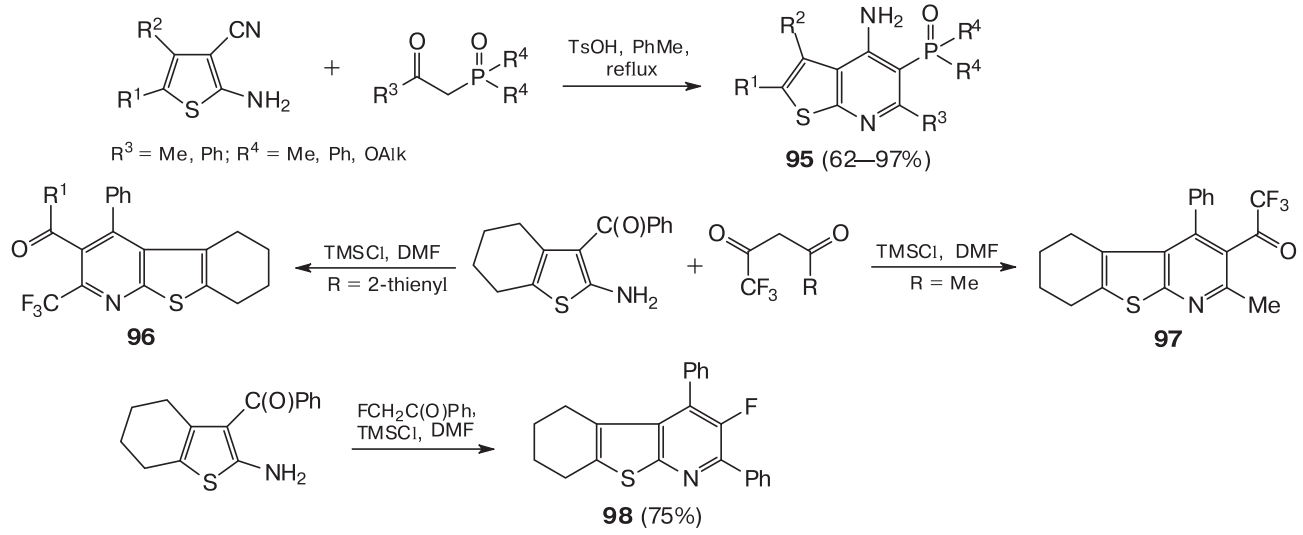
In the Friedländer reaction with Gewald′s thiophenes β-ketophosphonates,[170,171] heterocyclic ketones and 1,3-diketones,[172] methylene active nitriles (under basic catalysis conditions),[173,174] and α-haloketones[175] can react instead of ketones or ethyl acetoacetate. Synthesis of phosphonates **95**[170] and fluorinated thienopyridines **96**, **97**,[172] and **98**[175] are some examples (Scheme 39).

The reaction is tolerant to a wide range of substituents in the starting reagents, which makes it possible to obtain thienopyridines with relatively labile substituents. For example, the reaction of thienylboronate **99** and cyclohexanone gives[176] thienoquinoline **100** in almost quantitative yield (Scheme 40).

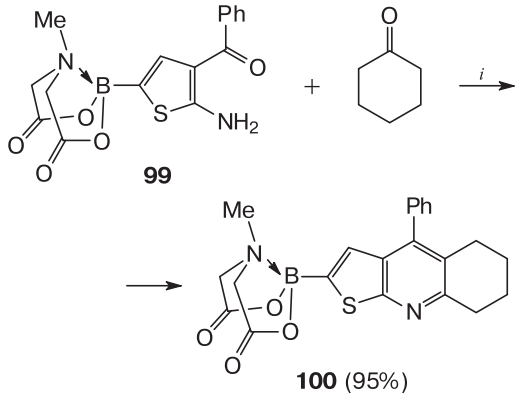
Scheme 38



Scheme 39



Scheme 40



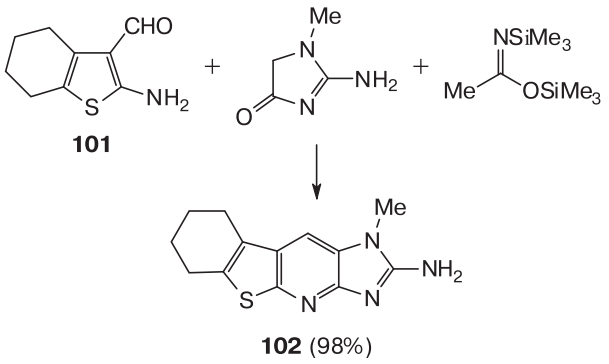
Reagents and conditions: *i*. TMSCl, DMF, 100 °C.

2-Aminothiophenes can also be involved into the Friedländer reaction with less active carbonyl compounds. Thus, aldehyde **101** quantitatively reacts with creatinine to form compound **102**.[177] Creatinine was activated by converting to the corresponding *O*-silylenolate using bis(trimethylsilyl)acetamide, which also turned out to be a suitable solvent (Scheme 41).

A convenient modification of the Friedländer reaction is an approach involving preliminary acylation of 2-amino thiophenes and the subsequent treatment of the resulting *N*-(2-thienyl)acetamides (for example, **103**)[178] with strong bases (Scheme 42).[18,178—183] The following bases can be used for cyclization at the last stage: Et_3N,[183] NaH,[178] $KN(SiMe_3)_2$, Pr^iNLi,[179] and EtONa.[18,180—182]

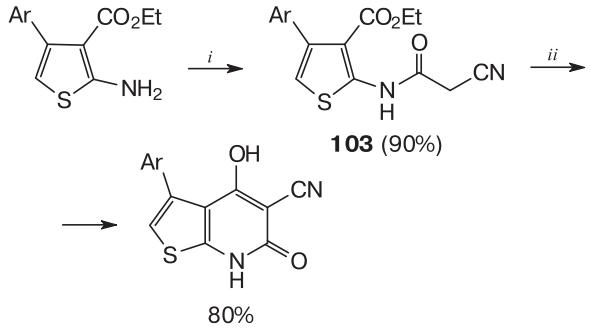
A similar approach was used[184] to obtain thienopyridine **104**, which exhibited moderate cytotoxicity. The key

Scheme 41



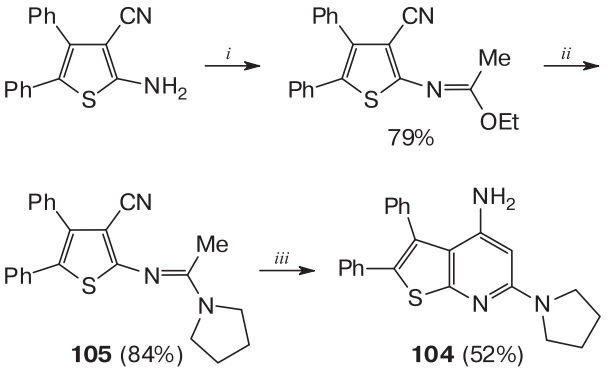
Reagents and conditions: 1) 140 °C, 2 h; 2) 1 *M* HCl; 3) 2 *M* NaOH.

Scheme 42



Reagents and conditions: *i*. $NCCH_2CO_2H$, PCl_5, CH_2Cl_2, Et_3N; *ii*. NaH, THF, reflux.

Scheme 43

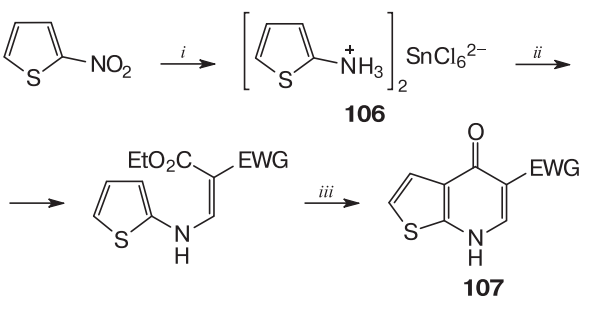


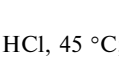
Reagents and conditions: *i*. $MeC(OEt)_3$, reflux, 5 h; *ii*. pyrrolidine, ~20 °C, 5 h; *iii*. $NaNH_2$, toluene, reflux, 5 h.

step in the synthesis is the intramolecular cyclization of acetamidine **105** on treatment with sodium amide (Scheme 43).

Synthesis of thienopyridines by the Gould—Jacobs reaction (see Scheme 34, approach ***B***) are based on the procedure[185] described in 1977 by Khan and Guarçoni. They proposed the approach that involved the reduction of 2-nitrothiophene with tin in hydrochloric acid followed by the reaction of bis(2-thienylammonium) hexachlorostannate **106** with ethoxymethylidene derivatives of methylene active esters and thermal cyclization. This scheme is still used today with minor variations.[186—189] 4,7-Dihydrothienopyridin-4-ones **107** obtained by this method (Scheme 44) are important intermediates in the synthesis of biologically active thienopyridines showing a wide spectrum of activity.

Scheme 44

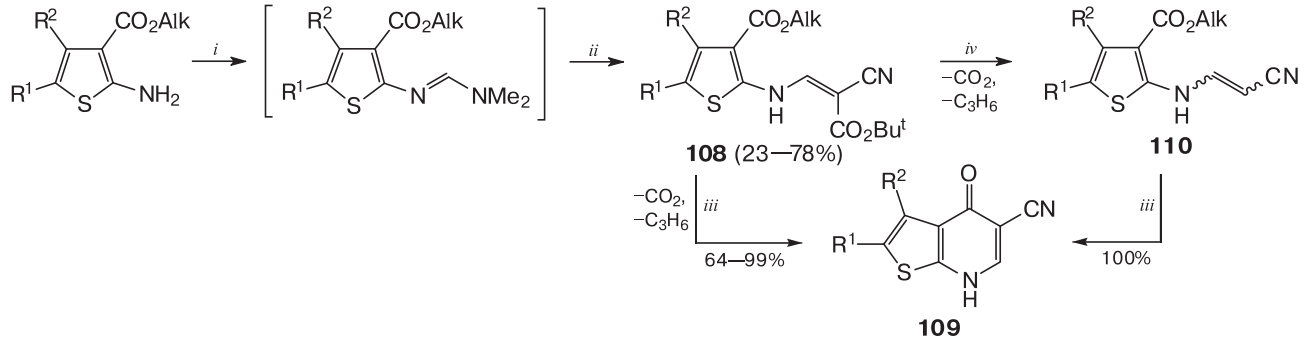


Reagents and conditions: *i*. Sn, HCl, 45 °C; *ii*.  , pyridine, 40—50 °C; *iii*. Ph_2O or Dowtherm, reflux (250 °C).

However, this approach has a number of significant disadvantages. Commercially available 2-nitrothiophene almost always contains an impurity of 3-nitrothiophene (~10—20%) and therefore requires additional purification; substituted 2-nitrothiophenes are poorly available, which significantly limits the variability of possible products, while the method itself is not atom-economical and produces a large amount of tin-containing waste.[190] In addition, the yield of hexachlorostannate **106** is usually low, while free 2-aminothiophene is unstable; therefore, after alkalization of salt **106**, the product should be used in the reaction immediately.[185] In this regard, a more convenient approach was developed,[190,191] which suggests the use of Gewald´s 2-aminothiophenes as the starting compounds. The key step in the synthesis is the thermolysis of *tert*-butyl esters **108**, which is accompanied by elimination of isobutylene and cyclization to form thieno[2,3-*b*]pyridines **109** in high yields. Under milder conditions, intermediate enaminonitriles **110** can be isolated as a mixture of (*E*)- and (*Z*)-isomers (1 : 1) (Scheme 45).

An alternative approach[192] to 4,7-dihydrothienopyridin-4-ones consists in the conversion of Gewald´s thiophenes to aminomethylidenemalonates **111**. The latter can be subjected to regioselective cleavage of the ester group bonded to the thiophene ring. Under the Gould—Jacobs reaction conditions, further decarboxylation and cyclization occur to give compounds **112** (Scheme 46).

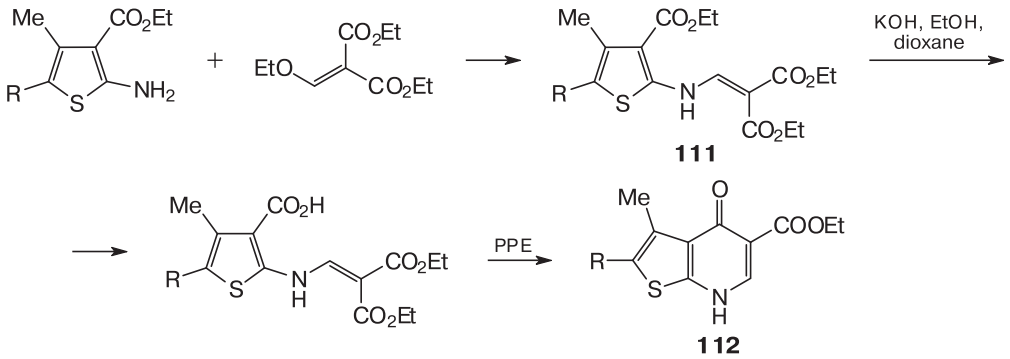
Scheme 45



Alk = Me, Et; R^1 = H, Me, Et, Bn, Ph; R^2 = H, Me, Pr^i, Ar

Reagents and conditions: *i*. $(MeO)_2CHNMe_2$, 100 °C, 2 h; *ii*. $NCCH_2CO_2Bu^t$, Bu^tOH, 2—8 days; *iii*. Ph_2O, 255 °C, 2 h; *iv*. Ph_2O or $Cl_2C_6H_4$, 180 °C.

Scheme 46

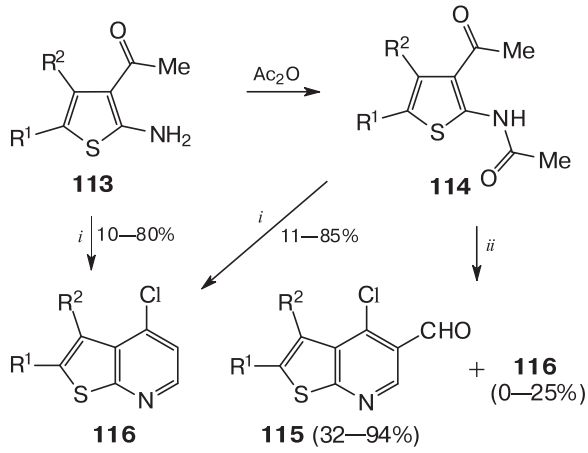


R = H, Br, Ar

In addition to the above general approaches, a number of specific methods to prepare thienopyridines from 2-aminothiophenes have been described. Thus, functionalized thienopyridines can be synthesized using the Vilsmeier—Haack reaction.[193,194] Treatment of products **114**, obtained by acetylation of 3-acetyl-2-aminothiophenes **113**, with the Vilsmeier´s reagent at 65 °C gave 4-chloro-3-formylthienopyridines **115** in 32—94% yields, which contain an admixture (0—25%) of deformylation products **116**.[193] A higher temperature and a longer reaction time favor the preferrable formation of compounds **116**. The latter were also obtained directly from 3-acetyl-2-aminothiophenes **113** under similar conditions[194] (Scheme 47).

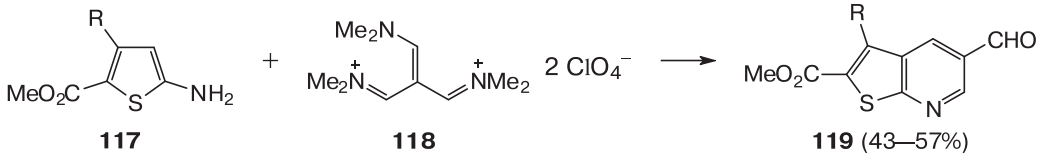
The thienopyridine system can be constructed using a methodology similar to the Combes reaction, namely, the reaction of 3-unsubstituted 2-aminothiophenes with 1,3-dicarbonyl reagents or their precursors. For example, thiophenes **117** react[195] with vinamidinium salt **118** to give aldehydes **119**, while their reaction with acyl-

Scheme 47



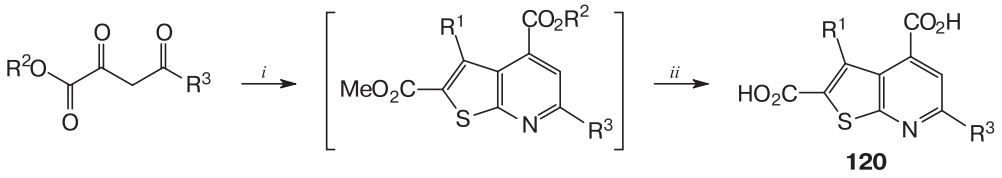
Reagents and conditions: *i*. $POCl_3$, DMF, 100 °C, 20—24 h; *ii*. $POCl_3$, DMF, 65 °C, 4—5 h.

Scheme 48



R = H, Me

Reagents and conditions: MeONa, MeOH, reflux, 12 h.



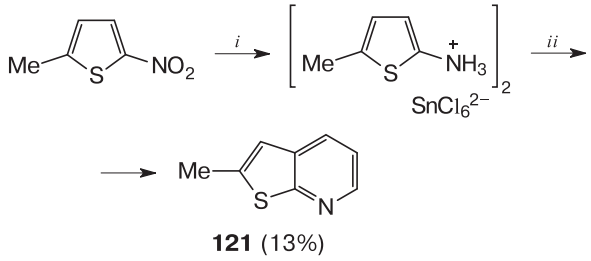
R^1 = H, Me; R^2 = Me, Et; R^3 = Me, Ar, *cyclo*-Pr

Reagents: *i*. **117**, Me_3SiCl, DMF; *ii*. 1) LiOH, MeOH, 2) KOH, Pr^iOH.

pyruvates[196] followed by alkaline hydrolysis gives dicarboxylic acids **120** (Scheme 48).

The reaction of 2-amino-5-methylthiophene with malonic dialdehyde diacetal in the presence of $ZnCl_2$ results in 2-methylthieno[2,3-*b*]pyridine **121** in a low 13% yield[197] (Scheme 49).

Scheme 49

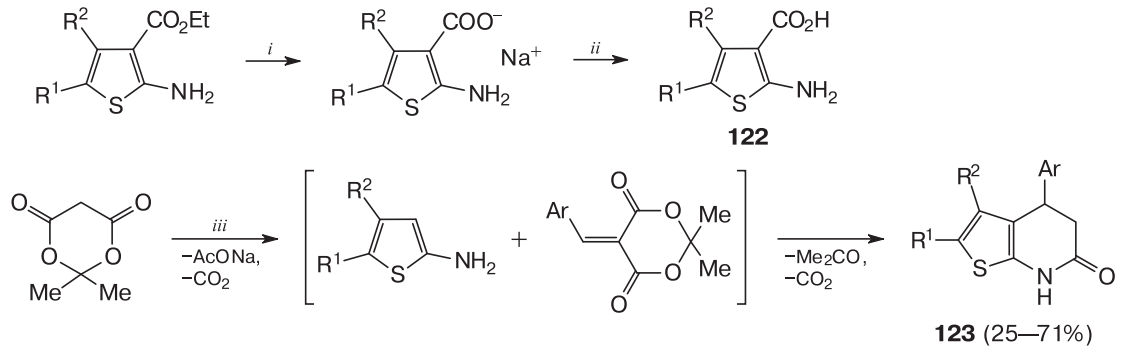


Reagents and conditions: *i*. Sn, HCl; *ii*. $(MeO)_2CHCH_2CH(OMe)_2$, $ZnCl_2$.

It is obvious that the possibilities for the synthesis of thienopyridines by the reaction between 1,3-dinucleophile (C—C—N) and 1,3-dielectrophile (C—C—C) are limited by the availability of dinucleophilic reagents, 3-unsubstituted 2-aminothiophenes. This limitation can be overcome by the *in situ* generating amino thiophenes through decarboxylation of 2-aminothiophene-3-carboxylic acids **122**, which are readily available by hydrolysis of the corresponding Gewald's thiophenes. Such an approach is exemplified by the synthesis[198,199] of tetrahydrothienopyridines **123** (Scheme 50).

2-Aminobenzo[*b*]thiophenes **124** can be obtained by the Curtius rearrangement of commercially available thiophenecarbonyl azides with subsequent hydrolysis. Amines **124** react[200] with 1,3-dielectrophiles, fluorine-containing 1,3-diketones or perfluorobenzaldehyde to form fused thienopyridines **125** and **126** (Scheme 51).

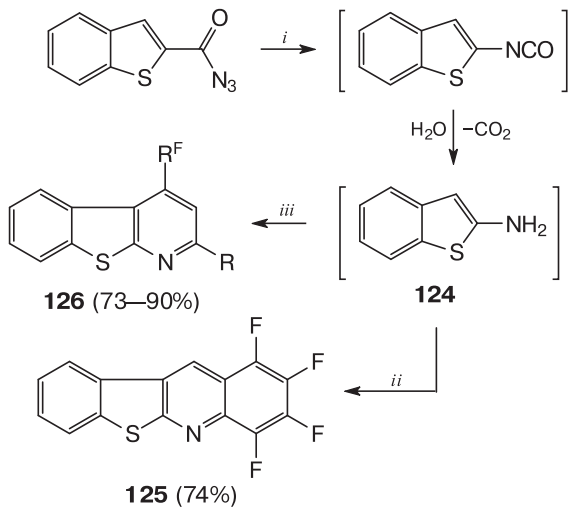
Scheme 50



R^1, R^2 = H, Br, Ar

Reagents and conditions: *i*. NaOH, EtOH (aq.), *ii*. HCl; *iii*. ArCHO, **122**, AcOH, EtOH, reflux.

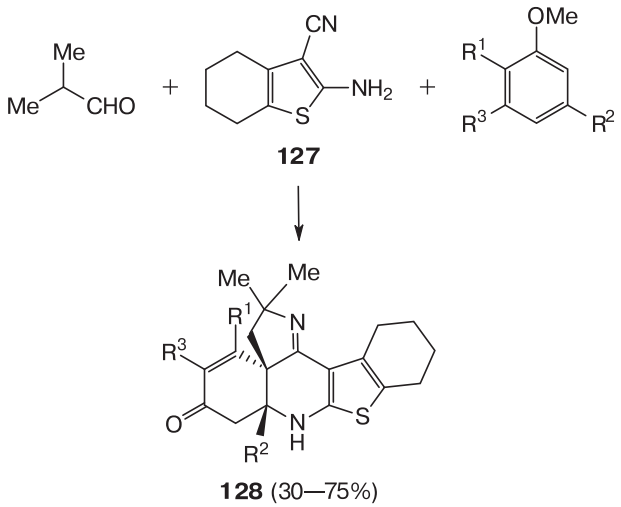
Scheme 51



Reagents and conditions: *i*. AcOH, DMF, reflux, 2—3 h; *ii*. C_6F_5CHO, AcOH, DMF; *iii*. $R^FC(O)CH_2C(O)R$, AcOH, DMF.

Recently, an unusual condensation of 1-methoxynaphthalene (or substituted anisoles) with isobutyral and 2-aminothiophene-3-carbonitrile (**127**) in sulfuric acid was described.[201] The products of this cascade reaction are polyfused thienopyridines **128** (Scheme 52).

Scheme 52

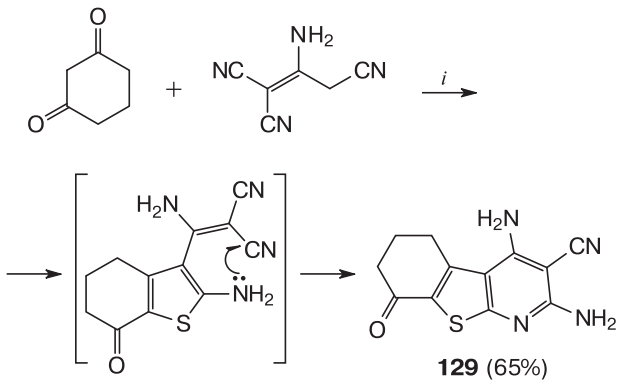


$R^1 + R^3$ = benzo, R^2 = H; R^1—R^3 = H, Alk

Reagents and conditions: 94% H_2SO_4, 5—25 °C, 30 min.

Typically,[202] the Gewald reaction with malononitrile dimer as the methylene active compound leads to the corresponding 2-amino thiophenes. However, in some cases, the process proceeds more deeply and gives products of further intramolecular 6-*exo*-*dig*-cyclization, as was shown by the example of obtaining compound **129** (Scheme 53).[203]

Scheme 53



Reagents and conditions: *i*. S_8, Et_3N, dioxane, reflux, 2 h.

An interesting method has been proposed[204] for the preparation of poorly available thieno[2,3-*b*]pyridine-6-carbonitriles with the possibility of varying substituents at positions 4 and 5. Thus, the reaction of Gewald´s amino thiophenes **130** with Appel´s salt leads to 2-cyanothieno-[2,3-*d*]-1,3-oxazin-4-ones **131**. The latter react smoothly with donor dienophiles with the CO_2 elimination and the pyridine ring closure (Scheme 54).

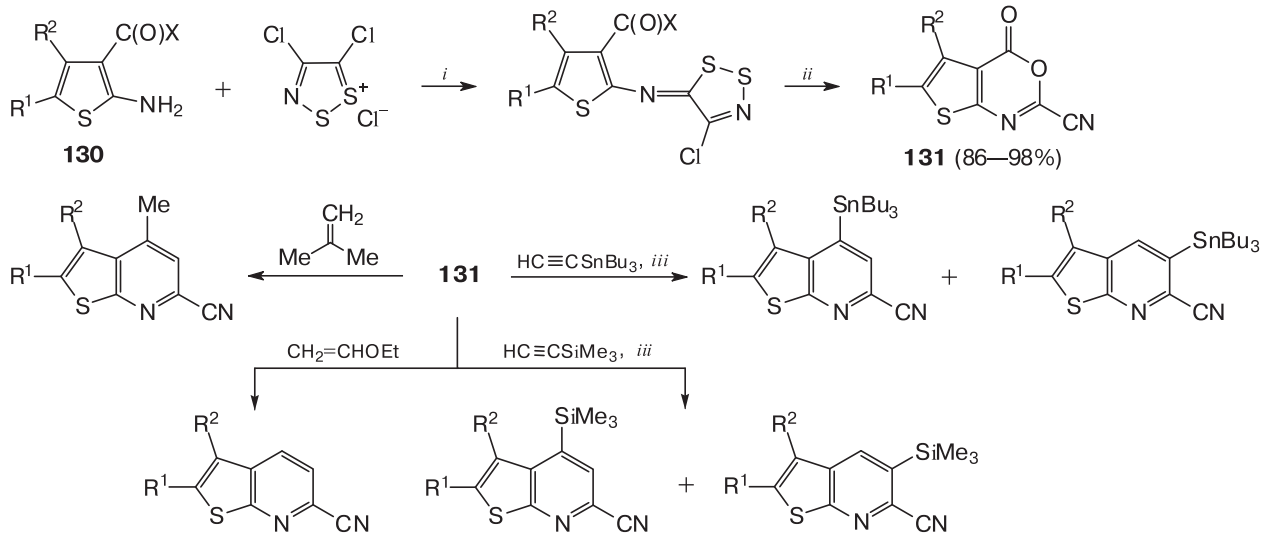
As shown[205] by the synthesis of compound **132**, simple thieno[2,3-*b*]pyridine derivatives can be obtained by an approach based on the conversion of carboxylic acid *N*-(2-thienyl)amides into *N*-(2-thienyl)alkynylimines and further tandem desilylation/cycloisomerization in the presence of chloro(cyclopentadienyl)bis(triphenylphosphine) ruthenium complex (Scheme 55).

Compounds **133** available from 2-nitrobenzothiophene are amine photobase generators and upon exposure to visible light (405 nm) decompose with elimination of free amine.[206] Benzo[4,5]thieno[2,3-*b*]quinoline-11-carbonitrile (**134**) is a by-product formed by the photolysis of the protecting group (Scheme 56).

3-Acetyl-2-(phenylamino)thiophenes **135** can be converted into the corresponding enaminoketones by the reaction with DMF dimethyl acetal (Scheme 57), which under the synthesis conditions undergo an intramolecular S_NVin reaction with the thienopyridine ring closure.[207,208] An alternative approach to 4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine system[209] involves the intramolecular condensation of enamino ketone **136** induced by NaH as key ring forming step.

Recently,[210] the possibility of obtaining benzothienopyridine derivatives **137** from 3-bromo-2-nitrothiophene was shown. The reaction includes a Negishi cross-coupling of 3-bromo-2-nitrothiophene with alkenylzinc

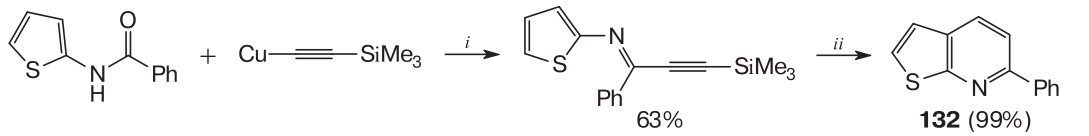
Scheme 54



R^1 = Et, R^2 = H; $R^1 + R^2 = (CH_2)_4$, X = OH, NH_2

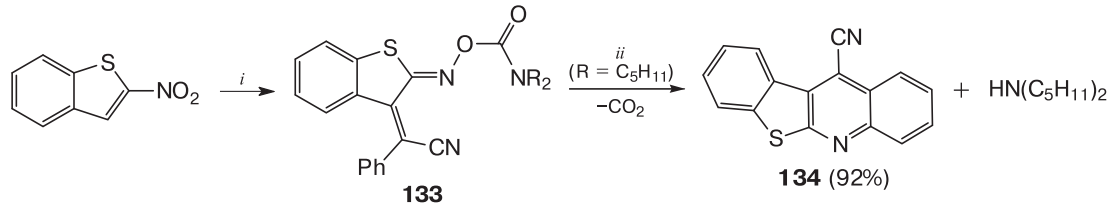
Reagents and conditions: *i*. CH_2Cl_2, pyridine, ~20 °C, 30 min; *ii*. $ZnCl_2$, PrCN, reflux; *iii*. benzene, reflux.

Scheme 55



Reagents and conditions: *i*. CH_2Cl_2, $(CF_3SO_2)_2O$, 2-chloropyridine, THF, –78 °C; *ii*. $CpRu(PPh_3)_2Cl$, SPhos, NH_4PF_6, toluene, 105 °C.

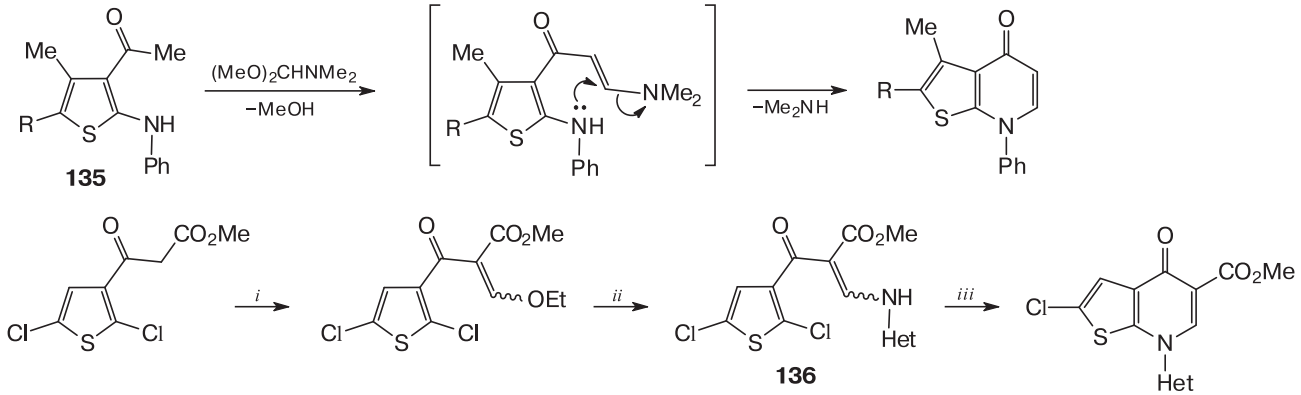
Scheme 56



R = C_5H_{11}, Bn, R + R = morpholino

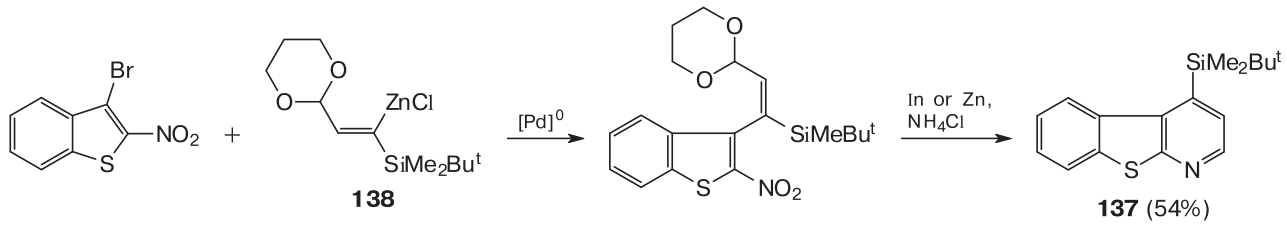
Reagents and conditions: *i*. 1) BnCN, KOH, MeOH; 2) $ClC(O)NR_2$, NaH, THF; *ii*. *hv* (405 nm), MeCN, 30 min.

Scheme 57



Reagents and conditions: *i*. $HC(OEt)_3$, Ac_2O, 135—140 °C; *ii*. $HetNH_2$, $HCCl_3$, 50 °C, 24 h; *iii*. NaH, THF, 62—65 °C, 2—3 h.

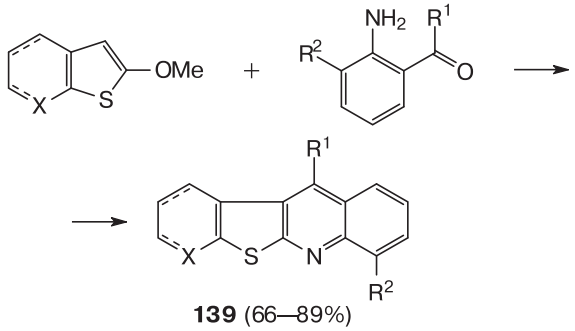
Scheme 58



chloride **138** and subsequent reductive cyclocondensation (Scheme 58).

Fused thienopyridines **139** can be prepared by the $InBr_3$-catalyzed coupling of 2-methoxythiophenes or 2-methoxybenzothiophenes with *ortho*-amino ketones (Scheme 59).[211] The reaction is tolerant to some functional groups and gives good yields of the target products, although it requires relatively harsh conditions.

Scheme 59



R^1 = Me, Ph; R^2 = H, OH; X = CH, Me

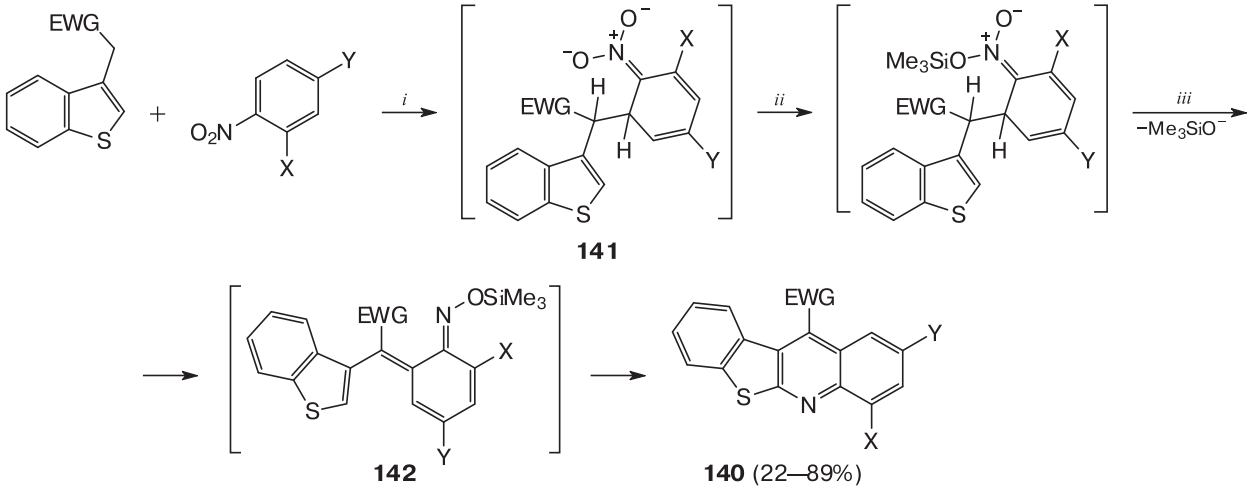
Reagents and conditions: $InBr_3$ (5 mol.%), Ar, PhCl, 110—130 °C, 24 h.

Tetracyclic products **140** can be synthesized by the recently proposed method,[212] which involved the reaction of thiophenes bearing a methylene active group at the C(3) atom with substituted nitrobenzenes, subsequent silylation of the formed Janovsky σ-complex **141**, and cyclization of intermediate **142** (Scheme 60). The reaction proceeds under mild conditions, but the yields of thienopyridines **140** vary within a wide range.

4. Construction of thienopyridine system with the simultaneous formation of the pyridine and the thiophene rings

A number of new methods describing the construction of the pyridine and thiophene rings from acyclic precursors within a single synthetic stage were reported recently. For example, a multicomponent one-pot synthesis of thienopyridines **143** from acetoacetanilides, cyanothioacetamide, aldehydes, and alkylating agents $HalCH_2EWG$ in the presence of bases was described.[213,214] The most likely intermediates of the process are *S*-alkyl derivatives of

Scheme 60

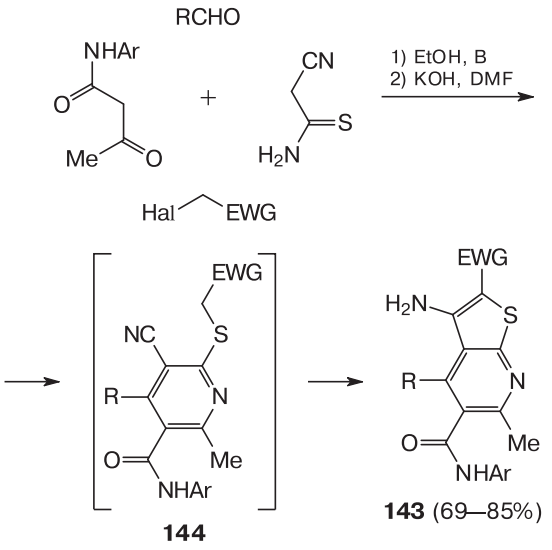


EWG = CN, SO_2Ph; X = H, Cl; Y = Hal, SPh

Reagents and conditions: *i*. Bu^tOK, Et_3N, THF, −70 °C; *ii*. Me_3SiCl, −65→~20 °C, 24 h; *iii*. Me_3SiCl, Et_3N.

nicotinonitriles **144** (Scheme 61). Oxidation of the 1,4-dihydropyridine system probably precedes the Thorpe—Ziegler closure of the thiophene ring. This method allows one to obtain libraries of functionally substituted thienopyridine derivatives in good yields.

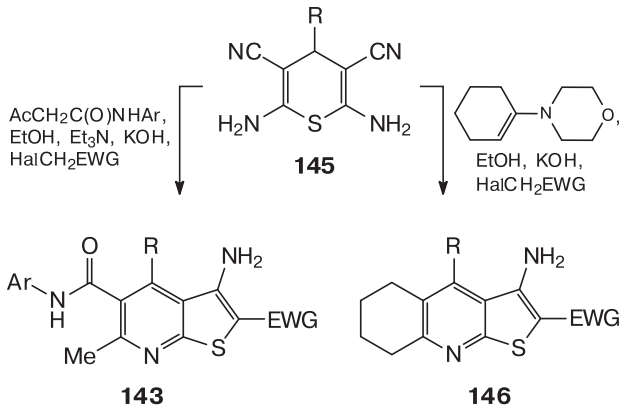
Scheme 61



B = *N*-methylmorpholine, Et_3N

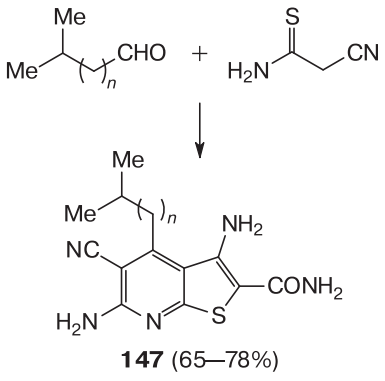
Recyclization of 4*H*-thiopyrans **145** upon the reaction with acetoacetanilides[215] or 1-(morpholino)cyclohexene[216,217] in the presence of alkylating agents leads to thienopyridines **143** or thienoquinolines **146** (Scheme 62).

Scheme 62



Thienopyridines **147** were isolated[218] in 65—78% yields as a result of the successive reactions of aliphatic aldehydes with cyanothioacetamide, malononitrile, and chloroacetamide in the presence of bases (Scheme 63). Synthesis of a library of structurally similar thienopyridines from malononitrile was reported.[219] Thus, treatment of a solution of malononitrile in ethanol with hydrogen sulfide in the presence of catalytic amounts of Et_3N and subsequent successive addition of the corresponding aldehyde, malononitrile, DMF, an alkylating agent, and an alkali gives thienopyridines **148** in good yields (65—83%) (Scheme 64). The authors of the works[218,219] suggest that thiopyrans **145** are the most probable intermediates in the described processes, which in some cases can be isolated and characterized.

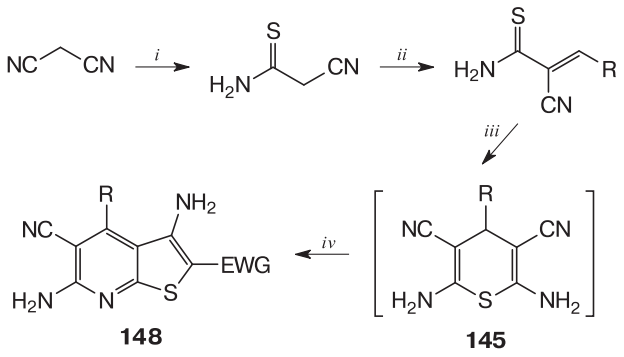
Scheme 63



n = 1, 2

Reagents and conditions: 1) EtOH, morpholine; 2) $NCCH_2CN$, reflux, 1 h; 3) $ClCH_2C(O)NH_2$, KOH.

Scheme 64

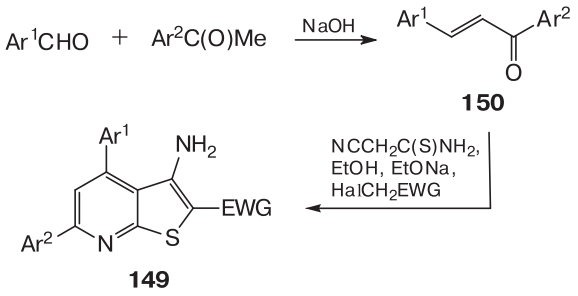


R = Et, Ar, Het; EWG = C(O)Ar, CONHAr, CO_2Alk

Reagents and conditions: *i*. H_2S, Et_3N, EtOH, 10 °C; *ii*. RCHO; *iii*. $H_2C(CN)_2$, 4—6 h; *iv*. 1) 10% KOH, DMF, 24 h; 2) $HalCH_2EWG$, 10% KOH.

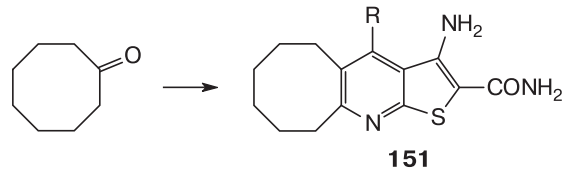
A multicomponent synthesis of 4,6-diarylthieno[2,3-*b*]-pyridines **149** by successive treatment of chalcones **150** with cyanothioacetamide, bases, and alkylating agents was proposed[220] (Scheme 65). Chalcones **150**, in turn, can also be generated *in situ* from the corresponding aldehydes and acetophenones in a one-pot process.[221]

Scheme 65



Compounds **151** interesting as inhibitors of eEF2 kinase were synthesized[222] in a one-pot procedure from cyclooctanone, the corresponding aldehyde, cyanothioacetamide, and α-bromoacetamide (Scheme 66).

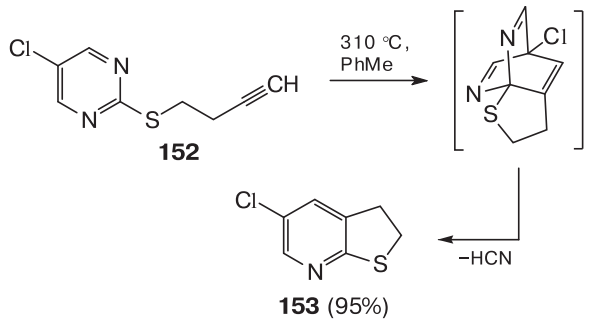
Scheme 66



Reagents and conditions: 1) RCHO, KOH (2 equiv.), MeOH, reflux 3 h; 2) $NCCH_2C(S)NH_2$, MeOH (3 equiv.), reflux; 3) $BrCH_2CONH_2$, MeONa, reflux.

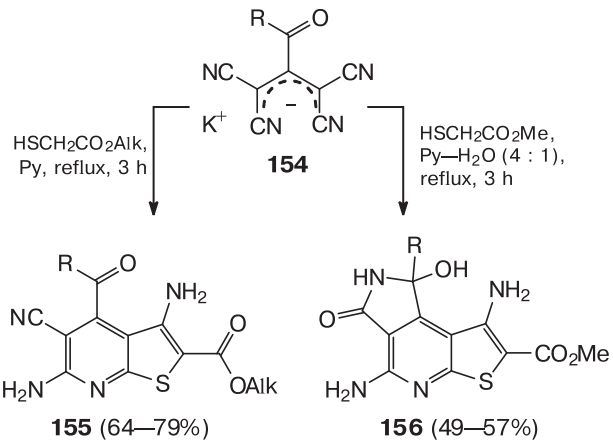
A method for obtaining the products of the intramolecular inverse electron-demand Diels—Alder reaction, pyrimidine derivatives, in a flow reactor has been described.[223] In particular, this method was used to convert compound **152** to 2,3-dihydrothienopyridine **153** (Scheme 67).

Scheme 67



Potassium 2-acyl-1,1,3,3-tetracyanopropenides **154** readily react with thioglycolates in refluxing pyridine to give highly functionalized thienopyridines **155** in yields up to 79%.[224] It is interesting to note that in 80% aqueous pyridine this reaction leads to pyrrolo[3,4-*d*]thieno[2,3-*b*]-pyridines **156**, apparently due to partial hydrolysis of one of the nitrile groups (Scheme 68).[225]

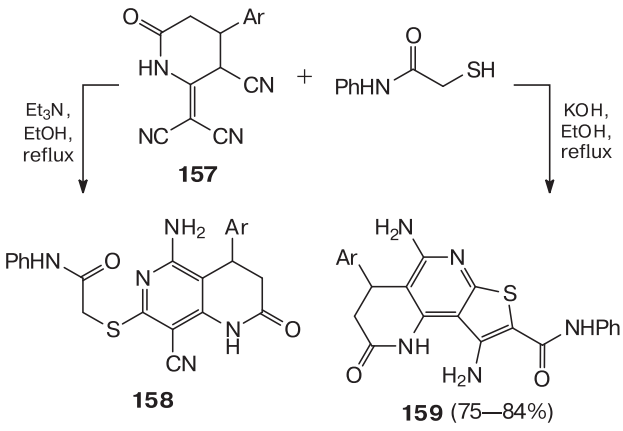
Scheme 68



Alk = Me, Et; R = Ar, Het

Depending on the conditions, 2-(dicyanomethylene)-piperidines **157** react[226] with α-mercaptoacetanilide to form either 1,6-naphthyridines **158** or, when using a stronger base, thieno[2,3-*h*][1,6]naphthyridines **159** (Scheme 69).

Scheme 69



Conclusion

The above data array on the methods for constructing the thieno[2,3-*b*]pyridine system demonstrates the most current trends in this field of heterocyclic chemistry. First of all, it can be noted that the variety of the presented strategies and approaches of the synthesis reflects the interest of researchers and indicates the practical importance of thieno[2,3-*b*]pyridines. In general, based on this analysis, one can predict further fruitful growth in research on the chemistry of thienopyridine and related systems. At the same time, it should be noted the uneven depth of study and popularity of synthesis methods, as well as a large percentage of works exploiting already conventional approaches to the synthesis (first of all, this is the Thorpe—

Ziegler cyclization, Gould—Jacobs and Friedländer syntheses based on 2-aminothiophenes). At the same time, there are a number of insufficiently studied approaches representing local *terra incognita* in the chemistry of heterocyclic compounds. These areas include insufficiently explored issues of directed functionalization of the thienopyridine system, obtaining molecules with desired properties, promising for pharmaceutical and agrochemical use. Methods focused on the simultaneous construction of the thiophene and the pyridine fragments from acyclic precursors demonstrate great synthetic potential.[227] Here, we should especially note the potential of readily available reagents, such as cyanothioacetamide,[228—230] malononitrile dimer,[202] as well as a number of other low-molecular-weight polyfunctional compounds.

This work was financially supported by the Russian Foundation for Basic Research and Krasnodar region (Project No. 19-43-230007 r_a). V. V. Dotsenko is grateful to the Ministry of Education and Science of the Russian Federation for financial support (Project No. 0795-2020-0031).

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Received October 17, 2019;
in revised form March 23, 2020;
accepted July 22, 2020