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The chemistry of 3-cyanopyridine-2(1*H*)-chalcogenones

V P Litvinov

Contents

I.	Introduction	577
II.	Methods of synthesis	577
III.	Reactivity and chemical transformations	588
IV.	Applications	595
V.	Conclusion	595

Abstract. The data on the methods of synthesis and chemical properties of 3-cyanopyridine-2(1*H*)-chalcogenones published over the last 20 years are systematised and analysed. Special attention is given to the use of these compounds as building blocks in the synthesis of fused *O*,*N*,*S*-heterocycles. The bibliography includes 277 references.

I. Introduction

Pyridine derivatives and their fused analogues have been in the centre of attention of researchers over many years due to the high practical value of these compounds, in the first place, the unusually broad spectrum of biological activities. In a paper by Lukevits [1] devoted to the 150th anniversary of pyridine chemistry, it was noted that more than 10% of the 1500 therapeutic agents most popular to that period contain the pyridine ring in their active components. These include vitamins (B_3, B_6, PP), analgetics, analeptics, antiarrhythmic drugs, antiseptics, antidepressants, spasmolytics, neuroleptics, tranquilisers and other medicines manifesting diverse pharmacological activities. This is why the expediency of improving the existing methods and a search for novel methods for the construction of pyridine-containing substrates as 'building blocks' for organic synthesis leaves no doubt. The synthetic potential of such compounds revealed from the analysis of their structures and reactivities will enable the development of convenient, cost-effective and environmentally safe methods for the preparation of novel pyridine derivatives possessing valuable biological properties.

Recently, functionalised pyridinechalcogenones have become the subject of intensive studies in the chemistry of heterocyclic compounds. This particular class of substances presents both theoretical and practical interest. Pyridinechalcogenone derivatives are used, *inter alia*, as substrates in the preparation of a medicine Buspiron, which possesses antidepressant and analgetic activities and prevents narcotic dependence, and some novel types of calcium antagonists and antioxidants. In addition, these compounds can be used as models for the redox coenzymes NAD and NADP and as substrates for the synthesis of folic acid derivatives, vitamin B_6 and some other biologically active compounds. 3-Cyanopyridine-2(1*H*)-thione derivatives are used in the production of dyes, pigments, additives to fuels and lubricants, stabilisers for polymers and varnishes, acid – base indicators for titrimetric assays and as other important compounds.

The unfading interest in the chemistry of pyridinechalcogenones observed over the past two decades is reflected in numerous patents and papers that are partially systematised in the reviews [2 – 14] and numerous theses (see, *e.g.*, those presented over the past two years [15 – 19]).

The topicality of this line of research and the lack of comprehensive reviews on the state-of-the-art and future outlooks in heterocyclic chemistry served as a reason for preparing the present review. Here, an attempt is made at systematisation and analysis of modern data (predominantly those obtained in the past two decades) on the chemistry of 3-cyanopyridin-2(1*H*)-ones (thiones, selones).† These compounds contain, along with the nitrile group, an amide, a thioamide or a selenoamide group with the endocyclic nitrogen atom in the vicinal position and represent convenient synthons of a vast array of annelated heterocyclic systems (including those hardly obtainable by other methods). The main attention in the review is focused on the methods for the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones and their applications as building blocks in the synthesis of biologically active compounds. Aromatic, di- and tetrahydro-forms of these compounds, hydrated derivatives as well as enol tautomers are considered. The physicochemical properties and general regularities of the reactivities of this class of compounds have been discussed earlier (see, for example, Ref. 8) and are beyond the scope of the present review.

II. Methods of synthesis

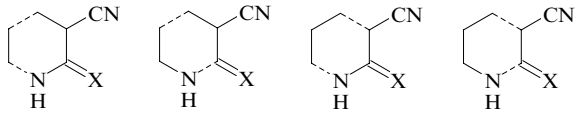
Systematisation of the methods for the synthesis of heterocyclic compounds is based on different principles (*e.g.*, type of reactants, reaction mechanisms, *etc.*). The formally logical retrosynthetic classification based on the topology of the bonds formed is especially popular. The formation of any heterocyclic system is represented as the formation of specific bonds in preformed structural blocks, which enables comparison and estimation of the value of each approach and the development of novel, hitherto

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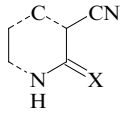
† According to the IUPAC Nomenclature, these compounds should be termed as 2-oxo(thioxo,selenoxo)-1,2-dihydropyridine-3-carbonitriles; however, in this work we shall adhere to the historic names.

unexplored trends. In the framework of this approach, all the methods for the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones are classified into six groups. Examples of methods for the introduction or modification of substituents in the preformed pyridine substrates and for cyclisation of a five-carbon fragment with formation of the N–C bond are few in number. Most of the data available refer to different methods for the synthesis of the pyridine ring from two fragments. Information on the cyclisation of three- and two-carbon fragments (3 + 2) is especially abundant as can be judged from the number of relevant papers. In this case, the formation of the N–C bond is accompanied by the formation of a new carbon–carbon bond, *viz*., C(5)–C(4) (structures **A** and **B**) or C(3)–C(4) (structures **C** and **D**).



A **B** **C** **D**

In addition to a small chapter devoted to the synthesis of the pyridine ring from three fragments (1 + 2 + 2) (structure **E**), some examples of the formation of the pyridine system based on ring transformation reactions are considered.



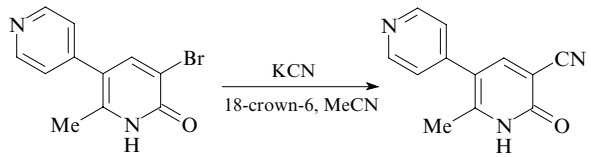
E

It is of note that the most promising procedures for the synthesis of pyridinechalcogenones based on cyclisation of several fragments are usually performed as one-pot synthesis. A chain of sequential conversions of functional groups, elongation of the carbon chain and its cyclisation without any additional reagent or a catalyst and without any change in the reaction temperature has got the name cascade heterocyclisation. Such a methodology of the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones has been discussed in detail.[2]

1. Introduction or modification of a substituent in a preformed pyridine substrate

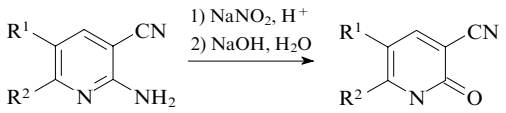
Introduction or modification of a substituent in a preformed pyridine substrate is the most direct approach to the synthesis of 3-cyanopyridine-2-chalcogenones. Only a few examples of this approach are known, since the starting compounds for such syntheses are difficult to obtain.

Thus substitution of the cyano group for the bromine atom was employed in a facile preparation of a phosphodiesterase inhibitor drug Milrinone (**1**). The reaction of 3-bromopyridin-2(1*H*)-one **2** with potassium cyanide in acetonitrile proceeds smoothly in the presence of 18-crown-6.[20]



2 **1**

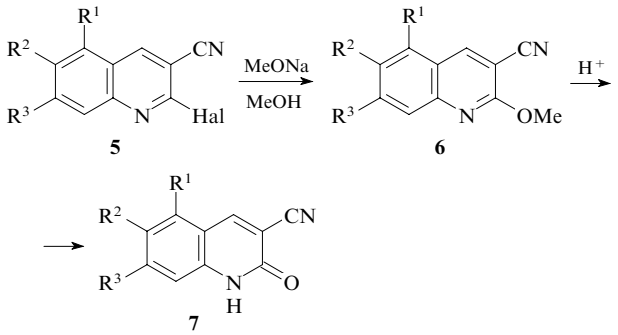
In some cases, the starting compounds contain a nitrile group in the pyridine (quinoline) ring. For example, 3-cyanopyridin-2(1*H*)-ones **3** were prepared from substituted 2-amino-3-cyanopyridines **4** by diazotisation and subsequent hydrolytic elimination of dinitrogen.[21,22]



4 **3**

R^1 = Ar, Het; R^2 = Alk, OAlk, SAlk, OPh.

Methoxylation of 3-cyano-2-haloquinolines **5** was used for an access to a broad series of 2-methoxy derivatives **6**; their acid hydrolysis resulted in 3-cyanoquinolinones **7**.[23–27]

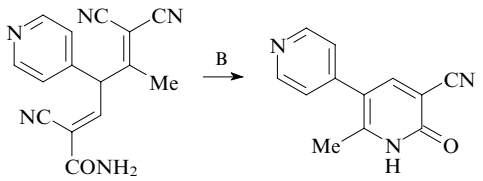


5 **6** **7**

R^1 = H, Alk, CN, NO_2, Hal; R^2 = H, Alk, Het, Hal, SO_3H; R^3 = Het.

2. Cyclisation of a five-carbon fragment with formation of the N–C(6) bond

Only one example of a conversion of an acyclic precursor (*viz*., polyfunctional alkene) into 3-cyanopyridin-2-one is documented. Synthesis of the aforementioned drug Milrinone (**1**) by cyclisation of tricyanohexa-1,4-dienamide **8** with elimination of malononitrile in EtOH in the presence of a base (B) (NaOH, Na_2CO_3 or EtONa) has been patented.[28] The yield of the target product was not indicated.



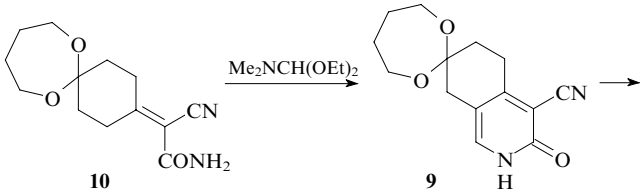
8 **1**

3. Synthesis of the pyridine ring from two fragments

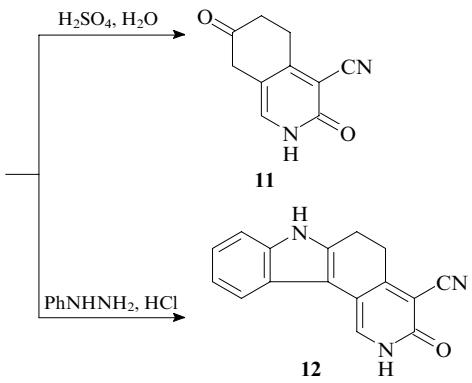
a. Cyclisation of four- and single-carbon fragments with formation of the N–C(6) and C(5)–C(6) bonds

The first, within the given classification, variant of the assembly of the 3-cyanopyridine-2-chalcogenone molecule from two fragments includes cyclisation of four- and one-carbon units. Such reactions result in the formation of the C(5)–C(6) and N–C(6) bonds of the pyridine ring. This approach is exemplified by a single type of reactions, *viz*., condensation of unsaturated cyanoamides with dimethylformamide acetal.

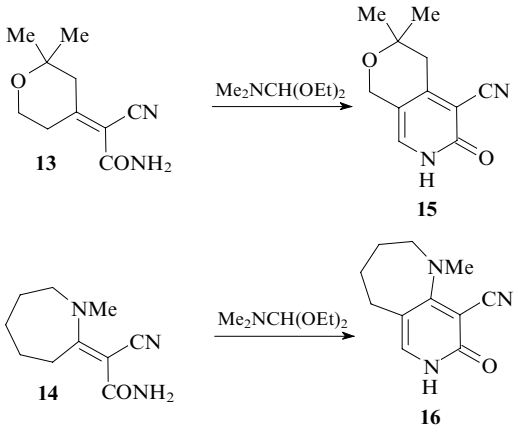
A non-trivial synthesis of tetrahydroisoquinolinone **9** from cyanoamide **10** and dimethylformamide diethyl acetal has been described.[29] This was converted into both isoquinolinedione **11** and pyrido[3,4-*c*]carbazole **12**.



10 **9**



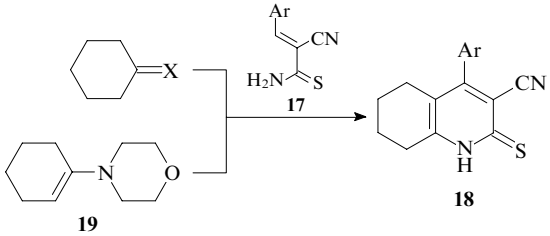
A similar reaction of cyanoamides **13** and **14** with dimethylformamide diethyl acetal was employed in the synthesis of pyrano[3,4-*c*]pyridin-3-one **15**[30] and pyrido[4,3-*a*]azepin-3-one **16**,[31] respectively:



b. Cyclisation of three- and two-carbon fragments with formation of the C(5) – C(4) and N – C bonds

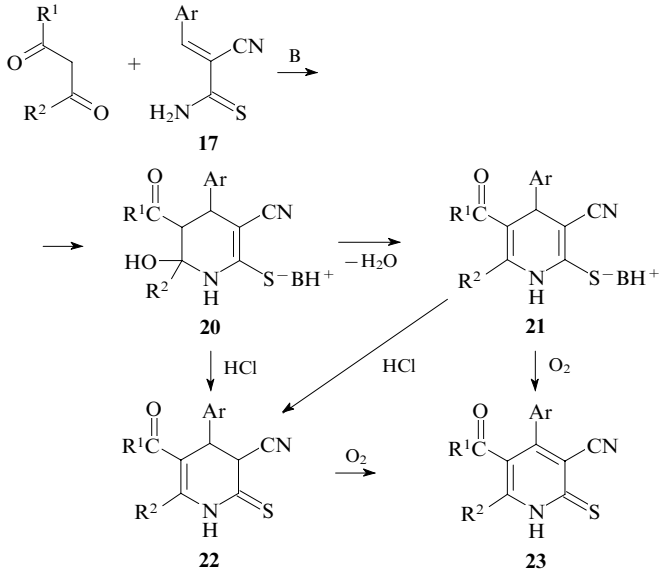
The construction of the pyridine molecule from two- and three-carbon fragments with simultaneous (or consecutive) formation of the C(4) – C(5) and N – C(6) bonds is often used in the synthesis of 3-cyanopyridine-2-chalcogenones. Arylmethylidene(cyano)-thioacetamides **17** are usually employed as the principal components to which a two-carbon fragment is attached.

Synthesis of tetrahydroquinolinethiones **18** from (thio)cyclohexanone or enamine **19** is the simplest example of such a reaction.[32] This is carried out in methanol at room temperature; the yields are 78% – 86 %.



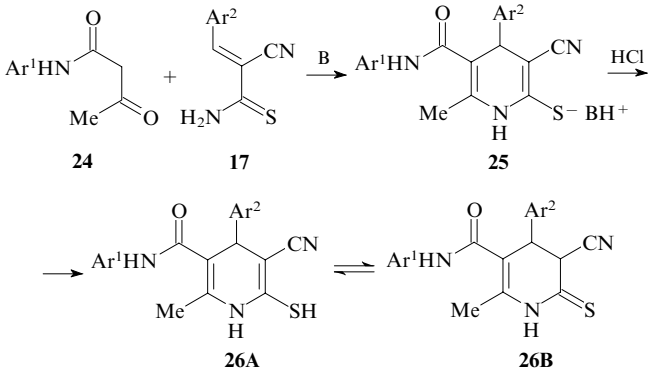
X = O, S; Ar = RC_6H_4 (R = H, 2-F, 4-F, 4-Cl, 4-Br, 4-MeO), 3-Py.

Diketones and the corresponding enamines react similarly with arylmethylidene(cyano)thioacetamides **17** to yield partially hydrogenated 3-cyanopyridine-2(1*H*)-thiones or their salts (Refs 11, 33 – 51). The intermediate thiolates **20** can be isolated; their subsequent dehydration results in 3-cyano-1,4-dihydropyridine-2-thiolates **21**. Upon acidification, the salts **20** and **21** are converted into 3-cyano-3,4-dihydropyridine-2-thiolates **22** which undergo dehydrogenation in solution to afford 3-cyanopyridine-2(1*H*)-thiones **23**. Enamines derived from diketones react with amides **17** in the absence of basic catalysts; the corresponding 1,4-dihydropyridine-2-thiolates are formed in high yields.

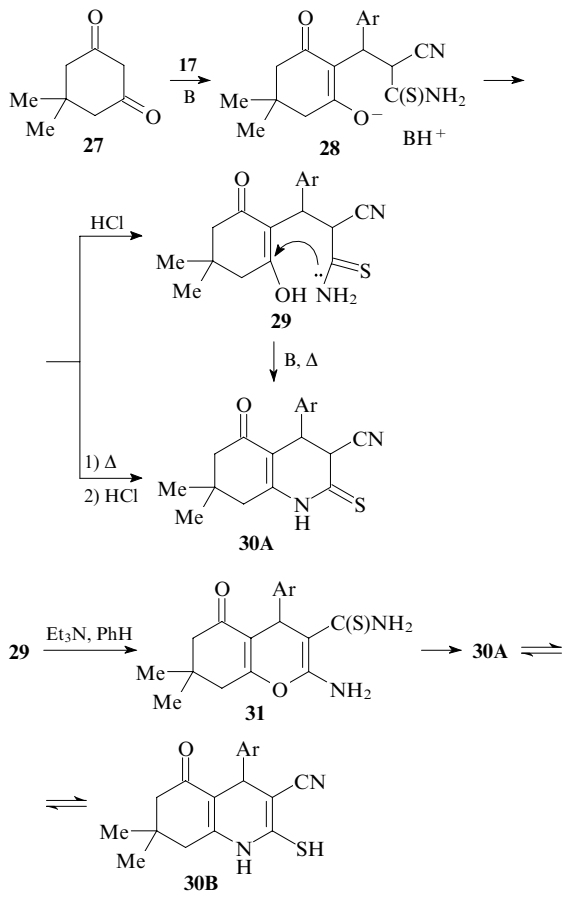


$R^1 = R^2$ = Alk.

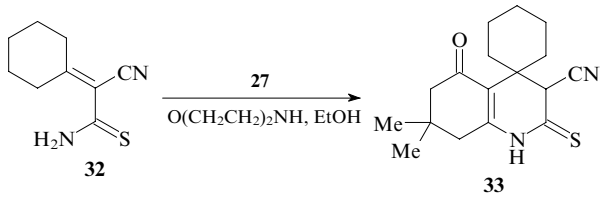
This type of reactions includes also the condensation of (het)arylmethylidene(cyano)thioacetamides **17** with acetoacetanilides.[52, 53] Amides **17** enter easily into the Michael reaction with anilides **24** due to the presence of an activated double bond; subsequent cyclisation yields 1,4-dihydropyridine-2-thiolates **25**. The latter are converted into thiols by treatment with HCl; in DMSO, thiols exist as a mixture of tautomers **26A** and **26B**.



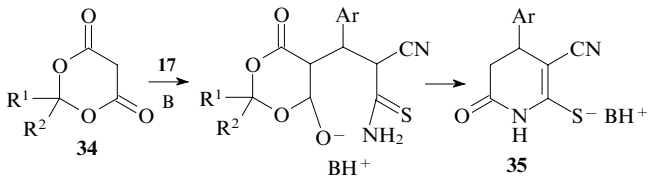
Cyclic 1,3-dicarbonyl compounds, in particular, dimedone, are also widely and successfully used in the synthesis of 3-cyanopyridine-2-chalcogenones (**27**). The use of dimedone made it possible to elucidate some peculiarities of the mechanism of its reaction with arylmethylidene(cyano)thioacetamides **17** (see, for example, Refs 7, 52, 54 and 55). In some cases, intermediate Michael adducts **28** were isolated as rather stable salts, which enabled studies of their properties. Thus acidification of salts **28** yielded compounds **29**; heating of the latter in the presence of organic bases (or direct heating of salts **28** with subsequent acidification) resulted in dihydropyridine-2-thiones **30A**. It is of note that compounds **29** are converted into substituted tetrahydro-4*H*-benzo[*b*]pyrans **31** in the presence of triethylamine. These represent the products of kinetic control, which are converted into thermodynamically controlled dihydropyridine-2-thiones **30A** existing in a tautomeric equilibrium with the thiol form **30B** in polar solvents (*e.g.,* ethanol).



Dimedone (**27**) was successfully used in the synthesis of spiro-fused 3-cyanopyridine-2(1*H*)-thione from cyclohexylidene(cyano)thioacetamide **32**. The reaction in ethanol in the presence of morpholine afforded 3,4,5,6,7,8-hexahydroquinoline-4-spiro-1′-cyclohexane-2(1*H*)-thione (**33**) in high yield.[52, 56]

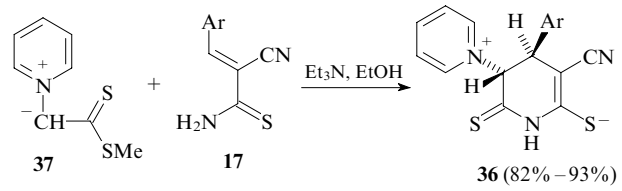


The reaction of arylmethylidene(cyano)thioacetamides **17** with Meldrum's acids **34** is an example of the use of other cyclic 1,3-diketones in the synthesis of pyridinechalcogenones by this method. This is carried out in ethanol in the presence of a base (*e.g.*, piperidine, *N*-methylmorpholine); under these conditions, 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates **35** are formed in 85% yields. If the reaction is carried out in benzene, the yields of the products drop down to 30%.[57]



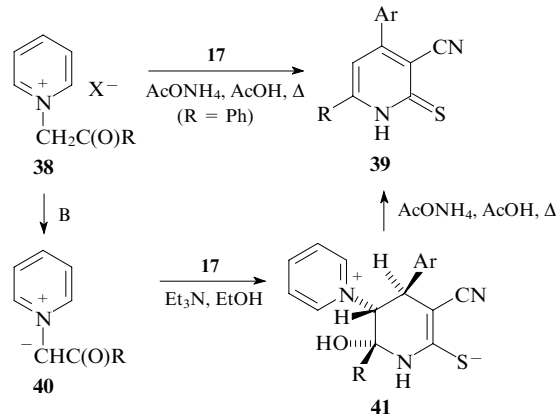
$R^1 = R^2 = Me$, $R^1 - R^2 = (CH_2)_5$; Ar = 2-ClC_6H_4, 4-BrC_6H_4.

Pyridinium ylides also play the role of two-carbon fragments.[58–66] Synthesis of *trans*-6-thioxo-1,4,5,6-tetrahydropyridine-2-thiolates **36** by the reaction of pyridinium ylide **37** with arylmethylidene(cyano)thioacetamides **17** can serve as an example.[51, 58, 59, 61]



Ar = 4-XC_6H_4 (X = HO, MeO, F, Cl, Br), 3-Py.

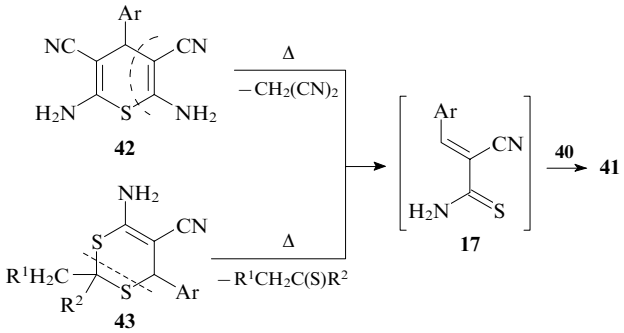
In this reaction, the effect of conditions on the nature of the products formed was observed. Thus heating of amides **17** with *N*-phenacylpyridinium salts **38** in the presence of ammonium acetate in acetic acid yielded 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones **39**.[58] However, reactions of pyridinium ylides **40** generated from the salts **38** with the same amides **17** in ethanol in the presence of triethylamine proceeded with high regio- and stereoselectivity and gave *trans,trans*-1,4,5,6-tetrahydropyridine-2-thiolates **41**.[62–64] The latter were converted into thiones **39** by heating in acetic acid in the presence of ammonium acetate.



R = Me, Ph, cyclo-C_3H_5; Ar = XC_6H_4 (X = H, 4-MeO, 4-NO_2, 2-F, 4-F, 4-Br), 3-Py.

Isoquinolinium ylides were also used in the synthesis of thiolates **41**.[63]

It is noteworthy that the three-carbon fragment (unsaturated thioamide) of the target pyridinechalcogenone is often cut out upon ring transformation of six-membered cyclic enaminonitriles, derivatives of 4*H*-pyran, 4*H*-thiopyran, 4*H*-selenopyran and 1,3-dithiacyclohexene.[7, 8, 32, 35, 54, 67–81] Thus it was found that heating of 4*H*-thiopyran **42** with pyridinium salt **38** results in the breakdown of the thiopyrane ring.[11] Subsequent reaction (formally, cross-ring transformation) of thioacetamide **17** and pyridinium ylide **40** formed thereupon yielded stable 1,4,5,6-tetrahydropyridine-2-thiolates **41**.

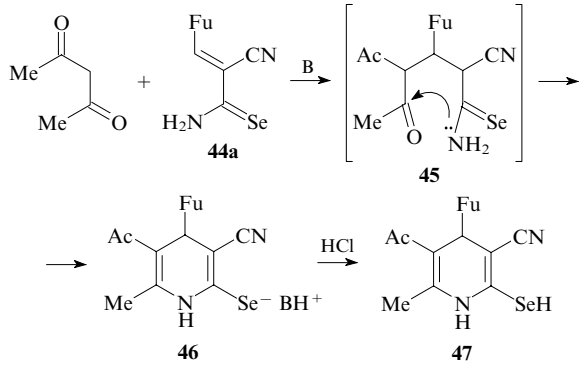


R^1, R^2 = Alk, $(CH_2)_n$; Ar = Ph, 3-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4.

The reaction of 1,3-dithiacyclohex-4-enes **43** with salt **38** proceeds in a similar manner. Upon elimination of a thioketone,[11]

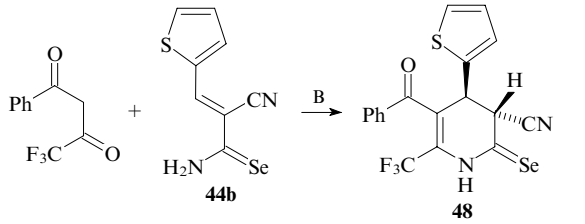
pyridinium ylides **40** react with *in situ* generated thioamides **17** to yield stereoselectively thiolates **41**.

The use of selenium analogues of thioamides **17** is documented. The reaction of acetylacetone with 2-furfurylidene(cyano)selenoacetamide **44a** affords, *via* the intermediate Michael adduct **45** and stable salt **46**, 5-acetyl-3-cyano-4-(2-furyl)-6-methyl-1,4-dihydropyridine-2-selenol (**47**) (yield 80%).[52, 82]

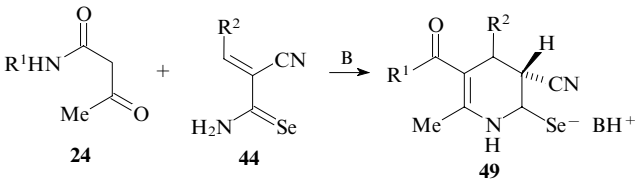


Fu is 2-furyl.

A method for the synthesis of *trans*-5-benzoyl-3-cyano-4-(2-thienyl)-6-trifluoromethyl-3,4-dihydropyridine-2(1*H*)-selone (**48**) was developed, which consists of treatment of benzoyltrifluoroacetone with 2-thienylmethylidene(cyano)selenoacetamide (**44b**) in the presence of *N*-methylmorpholine (yield 78%).[40]

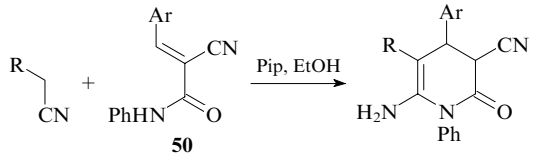


Condensation of hetarylmethylidene(cyano)selenoacetamides **44** with acetoacetanilide (**24**, R^1 = Ph) or acetoacetamide (**24**, R^1 = H) also occurs in a regioselective mode and yields 1,4-dihydropyridine-2-selenolates **49**.[83, 84]



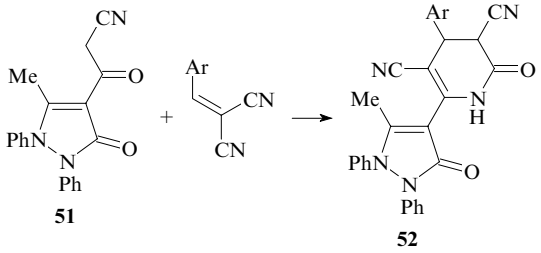
R^1 = H, Ph; R^2 = Het, B is morpholine.

In addition to the above-mentioned fragment CH–C(O), the role of a two-carbon component can be played by the CH_2CN group. Thus the reaction of anilides of cinnamic and other 3-aryl-2-cyanoacrylic acids **50** with this type of CH-acids was successfully used in the synthesis of 3,4-dihydropyridin-2(1*H*)-ones. These reactions are carried out in boiling ethanol in the presence of piperidine (Pip).[85]

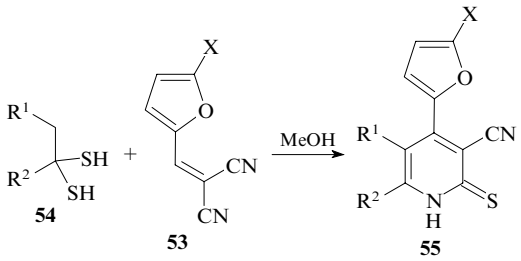


R = NC, EtO_2C, PhHNC(O), 4-ClC_6H_4C(O).

In conclusion, we mention some interesting examples of the use of unsaturated dinitriles as three-carbon and one-nitrogen atom donors for the pyridine ring. Reactions of dinitriles of the styrene type with 4-(cyanoacetyl)pyrazolinone **51** give substituted 3,4-dihydropyridine-2(1*H*)-thiones **52** in up to 75% yields.[86]

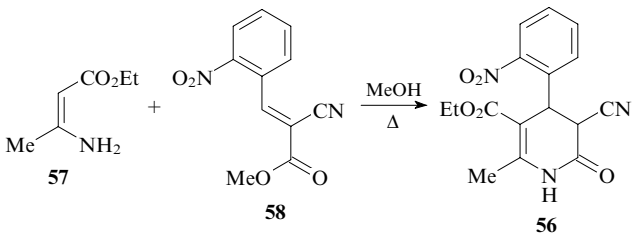


Reactions of substituted furfurylidenemalononitriles **53** with alicyclic and aliphatic *gem*-dithiols **54** were also reported.[68, 70] Contrary to benzylidenemalononitriles, these reactions directly yielded substituted tetrahydroquinolinethiones **55** rather than the corresponding 1,3-dithiacyclohexenes (see Section II.5).



R^1 = H, Me; R^2 = Me, Et; R^1–R^2 = $(CH_2)_n$ (n = 3–5); X = H, 2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$; B is morpholine,[68] Et_2NH.[70]

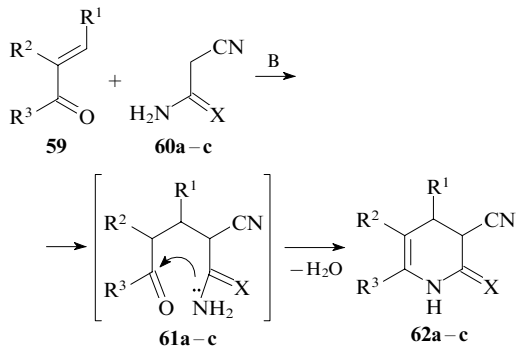
The synthesis of substituted pyridone **56** is the only example of construction of 3-cyanopyridine-2-chalcogenones from two- and three-carbon fragments; this involves the formation of the C(4)–C(5) and N–C(2) bonds. Nucleophilic addition of enamine **57** to unsaturated nitrile **58** yields the final product.[87]



c. Cyclisation of one- and three-carbon fragments with formation of the C(3)–C(4) and N–C bonds

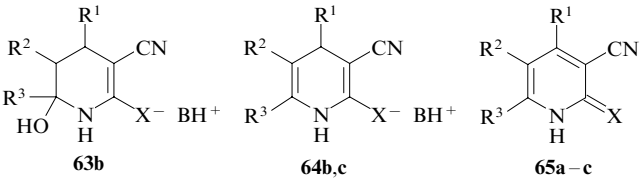
The construction of a pyridine system from two fragments with formation of the C(3)–C(4) and N–C(6) bonds is the most popular approach to the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones. Such conversions follow the cascade heterocyclisation mechanism and begin with the addition of 1,3-bis-nucleophile, *viz*., cyanoacetamide, its thio- or selenium derivative, to a three-carbon fragment. The role of the latter can be played by 1,3-bis-electrophiles, *e.g*., different forms of α,β-unsaturated carbonyl and 1,3-dicarbonyl compounds, such as aldehydes, ketones and their enols as ethers and salts, as well as by enamines and carboxylic acid derivatives (esters, amides, nitriles).

The majority of published data are devoted to the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones by the reaction of α,β-unsaturated carbonyl compounds **59** with cyano(thio,seleno)acetamides **60a**–**c**. This reaction occurs in the presence of organic bases as catalysts; the intermediate Michael adducts **61a**–**c** undergo cyclisation into 3-cyanodihydropyridine-2(1*H*)-chalcogenones **62a**–**c** in fairly high yields.



$R^1 - R^3$ = H, Alk, Ar, Het; X = O (**a**), S (**b**), Se (**c**); B is a base.

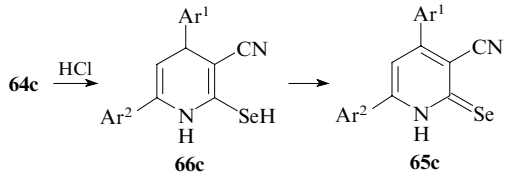
For the first time, this method was used for the preparation of 4,6-diaryl- (Refs 88 and 89) and 4-aryl-3-cyanopyridine-2(1*H*)-thiones.[90] Either stable intermediates, *viz*., salts **63** (for X = S), or salt derivatives of compounds **62,** *viz*., dihydropyridines **64** (for X = S, Se) or dehydrogenation products **65**, can be isolated depending on the reaction conditions and the nature of the reactants. In the course of isolation, compounds **61** (or **63**) are oxidised (dehydrogenated) by atmospheric oxygen into salts **64**.



In the reactions of cyanoacetamide (**60a**) with unsaturated (hetero)aromatic ketones **59** (R^1, R^3 = Ar, Het; R^2 = H), the Michael adducts (amides **61a**) can be isolated in a pure state.[91,92] Heating of the latter in acetic acid in the presence of ammonium acetate brings about their cyclisation into pyridones **62a**, which are further dehydrogenated into pyridones **65a**.

The reaction conditions and the nature of the base (catalyst) were varied in the synthesis of 3-cyanopyridine-2(1*H*)-thione derivatives (see, for example, Refs 93 – 98). Thus the use of sodium alkoxides in boiling alcohol afforded pyridinethiones **65b**,[89,99–101] while the use of an equimolar amount of an organic base (in ethanol at 20 °C) that served as both the catalyst and a stabilising reagent resulted in salts **63b** and **64b**.[90,93,95–98,102] Acidification of salts **64b** with hydrochloric acid afforded 3,4-dihydropyridine-2(1*H*)-thiones **62b**, which were oxidised by atmospheric oxygen to thiones **65b**.

The reaction of chalcones **59** (R^1, R^3 = Ar, R^2 = H) with cyanoselenoacetamide **60c** in the presence of excess *N*-methylmorpholine under similar conditions gave exclusively 1,4-dihydropyridine-2-selenolates **64c** (yield 90%).[52,103,104] Treatment of the latter with HCl afforded 1,4-dihydropyridine-2-selenols **66c**, which represent tautomers of dihydropyridine-2(1*H*)-selones **62c**; the latter are easily oxidised in the air into the corresponding pyridineselones **65c**.

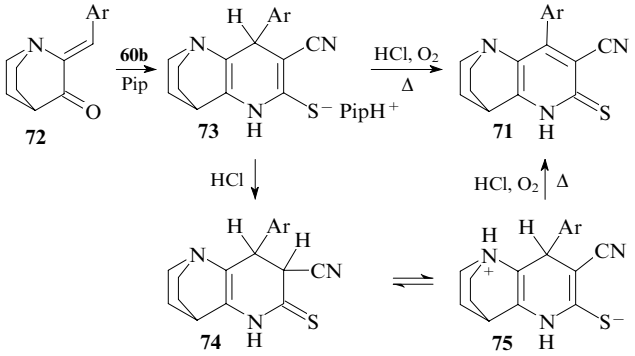


These data suggest that the nature of the substrate and the reagent should be taken into consideration in each particular case.

Examples of the synthesis of different 3-cyanopyridine-2-chalcogenone derivatives are given in Table 1. In all these cases, the role of the two-carbon component is played by cyano(thio, seleno)acetamide **60**, while a broad range of original 1,3-bis-electrophiles demonstrates the prospects of this approach. The versions of this reaction given in Table 1 are discussed below.

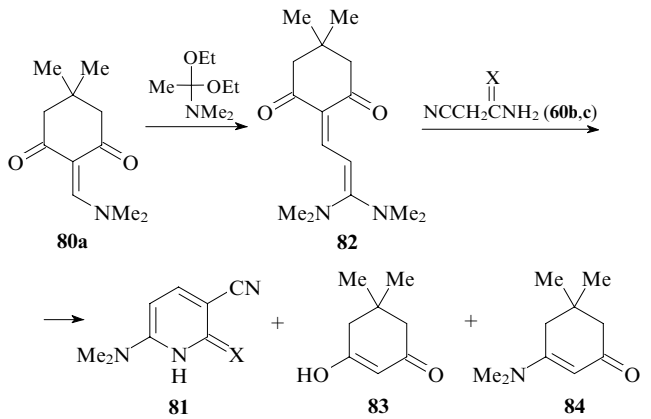
Hetero- and carbocycles (including steroids) can be annelated to α,β-unsaturated carbonyl fragments. No intermediate 3,4-dihydropyridines could be isolated in the reaction of cyclic unsaturated ketone **67** with cyanothioacetamide (**60b**) in methanol in the presence of sodium methoxide (see Table 1, entry 1).[105–108] However, the structurally similar isochroman-4-one **68** and amide **60a** gave 3-cyano-3,4-dihydroisochromano[3,4-*b*]pyridine-2(1*H*)-ones **69**, which were further dehydrogenated into compounds **70** (entry 2).[109]

Naphthyridinethiones **71** were prepared from 2-arylmethylidenequinuclidin-3-ones **72** and (cyano)thioacetamide (**60b**) (Table 1, entry 3).[110,111] After treatment with hydrochloric acid, the primary reaction products, *viz*., piperidinium 4-aryl-3-cyano-5,8-ethano-1,4,5,6,7,8-hexahydro-1,5-naphthyridine-2-thiolates **73**, were converted into 4-aryl-3-cyano-5,8-ethano-1,4,5,6,7,8-hexahydro-1,5-naphthyridine-2(1*H*)-thiones (**74**), which exist in a tautomeric equilibrium with betaines **75**. Heating of salts **73** or betaines **75** in ethanol in the presence of HCl resulted in their dehydrogenation and formation of compounds **71**.



Steroid derivatives **76** and **77** were obtained by similar reactions of ketones **78** and **79** with (cyano)thioacetamide **60b**;[112,113] in the former case, saponification of the acetoxy group took place (entries 4 and 5).

The three-carbon fragment used in the synthesis of pyridine-chalcogenones according to the (3 + 2)-scheme can represent a component of a more complex conjugated system. In such a case, compounds containing different functional groups are formed. For instance, dimethylaminomethylidenedimedone **80a** was employed in the synthesis of 3-cyano-6-dimethylamino-pyridine-2(1*H*)-chalcogenones (**81**).[114] Its reaction with *N*,*N*-dimethylacetamide diethyl acetal afforded diaminodienodione **82** in high yield. Reactions of the latter with cyanothio(seleno)- acetamides **60b**,**c** resulted in a mixture of pyridine **81** (entry 6), dimedone (**83**) and its derivative **84**.



Reactions of cyanoacetamides with cyclic and acyclic pentadien-3-ones also yielded cyanopyridinechalcogenone derivatives (see Table 1, entries 7 and 8). The reaction of dibenzylidenecyclopentanone **85** with thioamide **60b** in the presence of sodium

Table 1. Synthesis of 3-cyanopyridine-2-chalcogenone derivatives using cyanoacetamides $NCCH_2C(=X)NH_2$ (**60a**–**c**).

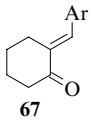
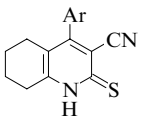
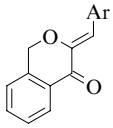
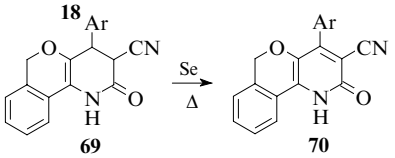
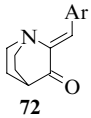
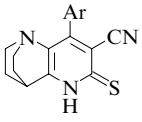
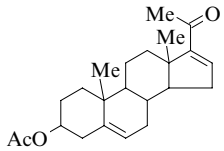
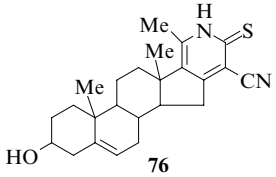
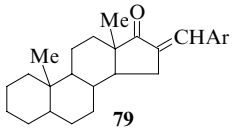
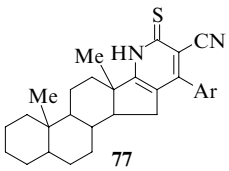
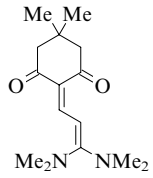
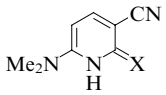
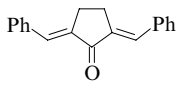
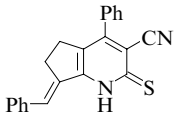
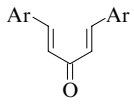
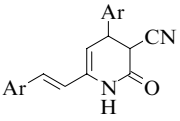
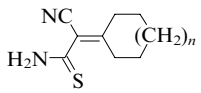
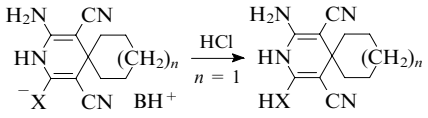
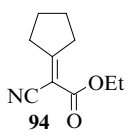
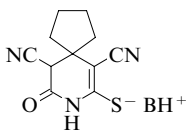
Entry	1,3-Bis-electrophile	X	Reaction conditions	Intermediates and products (yields)	Ref.
1	 **67**	S	MeONa, MeOH	 **18**	105–108
2	 **68**	O	Pip, EtOH, Δ	 **69** **70**	109
3	 **72**	S	Pip	 **71** (~65%)	110, 111
4	 **78**	S	EtONa, EtOH	 **76**	112, 113
5	 **79** Ar = Ph, 3-FC_6H_4, 2-Fu, 3-Py.	S	EtONa, EtOH	 **77**	112, 113
6	 **82**	S, Se	EtOH	 **81** X = S (76%), Se (43%).	114
7	 **85**	S	EtONa, EtOH, Δ	 **86** (79%)	83, 115
8	 **87**	O	170 °C in a sealed tube	 **88** (32%–37%)	116
9	 n = 1 (**32**), 0 (**92**).	S (n = 0, 1), Se (n = 1)	*N*-methylmorpholine (B), EtOH	 **89b**,**c**, **91** **90b**,**c** n = 1 (**89b**,**c**, **90b**,**c**), 0 (**91**).	52, 117–120
10	 **94**	S	*N*-methylmorpholine (B), EtOH	 **93** (72%)	121

Table 1 (continued).

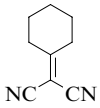
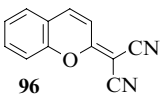
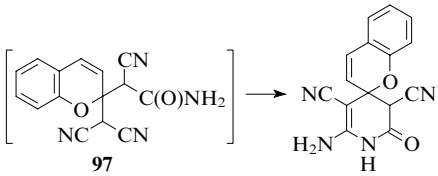
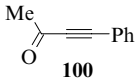
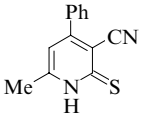
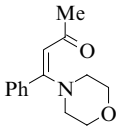
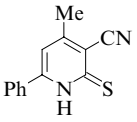
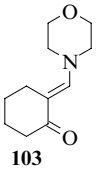
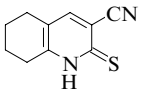
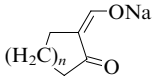
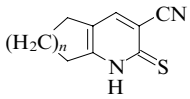
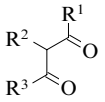
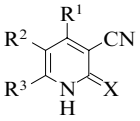
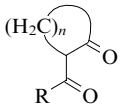
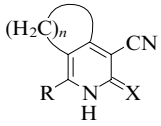
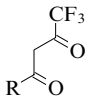
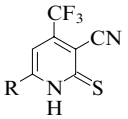
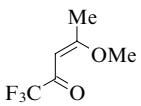
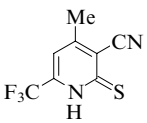
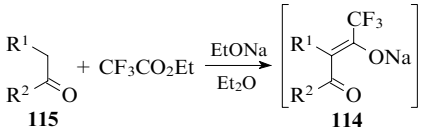
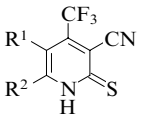
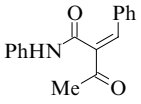
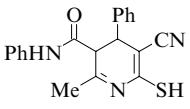
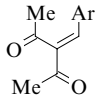
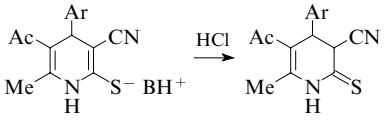
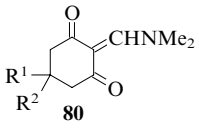
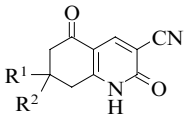
Entry	1,3-Bis-electrophile	X	Reaction conditions	Intermediates and products (yields)	Ref.
11	 **95**	Se	*N*-methylmorpholine, EtOH	**89c** ⟶ **90c**	52, 117–120
12	 **96**	O	Pip, Δ	 **97** **98**	86
13	 **100**	S	Et_3N	 **99** (34%)	122
14	 **101**	S	morpholine	 **102** (49%)	123
15	 **103**	S	AcOH, EtOH	 **104** (61%)	83
16	 n = 1, 4.	S	AcOH, EtOH, Δ	 n = 1 (**105**, 52%), 4 (**106**, 61%).	124
17	 **107** R^1, R^3 = Me, Ph; R^2 = H, Me.	S, Se	Et_3N, EtOH	 **65b**,**c**	34, 89, 125–127
18	 **108** n = 3, 4; R = Me, Et, Pr, Ph, Bn.	S, Se	Et_3N, EtOH	 **109**	93, 128, 129
19	 **112** R = Me, Ph, 2-thienyl.	S	Et_3N, EtOH, Δ	 **110** (90%)	53, 83, 130–134
20	 **113**	S	1) KOH, EtOH 2) **60b**, HCl	 **111** (90%)	53, 83, 130–134

Table 1 (continued).

Entry	1,3-Bis-electrophile	X	Reaction conditions	Intermediates and products (yields)	Ref.
21	 **115** **114** R^1, R^2 = H, Alk, Ar, Het.	S	AcOH, EtOH, Δ	 **110** (< 98%)	30
22	 **116**	S	Pip, EtOH	 **117**	45
23	 **118** Ar = 3-$NO_2C_6H_4$, 4-ClC_6H_4	S	Pip (B), EtOH	 **119** **120** (60% – 61%)	97
24	 **80** R^1 = H, Me; R^2 = H, Me, Ph.	O	NaOH, THF	 **121** (14% – 91%)	135

ethoxide at room temperature gave pyridine-2(1*H*)-thione **86** annelated with the cyclopentane ring.[83, 115] The reaction of acyclic symmetrical pentadienone **87** performed under more drastic conditions (heating of reactants at 170 °C in a sealed tube without a solvent) afforded substituted 3-cyano-3,4-dihydropyridin-2(1*H*)-ones **88**.[116]

Amides and esters of cycloalkylidenecyano(thio)acetic acid are also used as 1,3-bis-electrophiles in reactions with amides **60**. Thus the reaction of cyclohexylidenecyanothioacetamide **32** with cyanothio(seleno)acetamides **60b**,**c** in ethanol in the presence of *N*-methylmorpholine gave salts **89**, which were further converted into 6-amino-3,5-dicyano-1,4-dihydropyridine-4-spiro-1′-cyclohexane-2-thione (**90b**) or -selone (**90c**), respectively, upon treatment with HCl (entry 9).[52, 117–119] Similar spiro-fused 6-aminothiolates **91** were prepared from ethyl cyclopentylidenecyanothioacetamide (**92**);[120] 6-oxothiolates **93** were obtained from ethyl cyclopentylidenecyanoacetate (**94**) (entry 10).[121]

Mention should also be made of α,β-unsaturated nitriles, which, by virtue of their high availability and high reactivity, are widely employed in the synthesis of pyridinechalcogenones, of their spiro-fused derivatives, in particular. Thus compounds **89c** and **90c** were obtained from cyclohexylidenemalononitrile (**95**) and selenoacetamide **60c** (Table 1, entry 11).[52, 117–119] Refluxing of cyanoacetamide (**60a**) and dicyanomethylidenecoumarin **96** in ethanol in the presence of piperidine gave the adduct **97**, which underwent intramolecular cyclisation *in situ* into spiropyridinechalcogenone **98** (Table 1, entry 12).[86]

Regioselective syntheses of isomeric 3-cyano-4(6)-methyl-6(4)-phenylpyridine-2(1*H*)-thiones are documented.[122, 123] The isomer containing a phenyl group at position 4 (compound **99**) is formed in the reaction of (cyano)thioacetamide (**60b**) with acetylenic ketone **100** (entry 13). However, the reaction with enamino ketone **101** derived from alkyne **100** gave 6-phenylpyridinethione **102** (entry 14). Similarly, enamino ketone **103** gave tetrahydroquinolinethione **104** (example 15).[35]

1,3-Dicarbonyl compounds and their derivatives, *e.g.,* the above-mentioned enamino ketones **101** and **104**, are successfully employed in the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones. Reactions of cyanothioacetamide (**60b**) with sodium enolates of 2-formylcycloalkanones are known to yield pyridine-2(1*H*)-thiones **105** and **106** (Table 1, entry 16).[124] Reactions of 1,3-diketones **107** with cyanothio(seleno)acetamides (**60b,c**) gave high yields of substituted 3-cyanopyridine-2(1*H*)-thiones (**65b**) and -selones (**65c**) (entry 17).[34, 89, 125–127] In the presence of bases, a similar reaction of cyclic diketones **108** occurs with high regioselectivity and affords 4,5-polymethylene-3-cyanopyridine-2(1*H*)-thiones(selones) **109** (Table 1, entry 18).[93, 128, 129]

Different approaches to the synthesis of substituted isomeric trifluoromethylpyridine-2(1*H*)-thiones **110** (Table 1, entry 19) and **111** (entry 20) have been developed. These included the reaction of triofluoromethyl derivatives **112** with (cyano)-thioacetamide (**60b**) or the reaction of 4-methoxy-1,1,1-trifluoropent-3-enone (**113**) first with EtONa and then with amide **60b**.[53, 83, 130–134] The yields reach 90% in both cases.

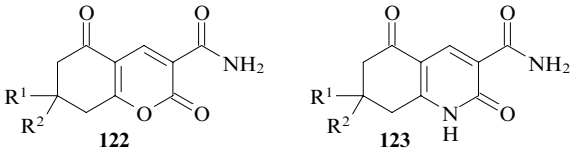
It is of note that the range of substituents in pharmacologically promising 3-cyano-4-trifluoromethylpyridine-2(1*H*)-thiones is limited by the availability of the starting 1,3-dicarbonyl compounds carrying a trifluoromethyl group. To overcome this limitation, it has recently been proposed to synthesise substituted 3-cyano-4-trifluoromethylpyridine-2(1*H*)-thiones **110** from sodium enolates of trifluoromethyl-1,3-diketones **114** (Table 1, entry 21).[30] The latter were prepared by coupling of methylene ketones **115** with ethyl trifluoroacetate; the free 1,3-diketone was introduced without isolation into the reaction with (cyano)thioacetamide (**60b**). The role of the starting methylene ketones was played by dialkyl-, alkylaryl-, hetaryl ketones and five–eight-membered cycloalkanones; in some cases, the yields of pyridinethiones **110** reached 98%.[17]

The reaction of (cyano)thioacetamide (**60b**) with 3-benzylideneacetoacetanilide (**116**) was studied.[45] It was thiol **117** that was the condensation product (Table 1, entry 22), although no such prototropic tautomer is known for other compounds of this series.[8]

The reaction of 3-arylideneacetylacetone **118** with amide **60b** in ethanol in the presence of piperidine yielded thiolates **119**;

treatment of the latter with HCl resulted in their conversion into thiones **120** possessing neurotropic activity (entry 23).[97]

Reactions of 2-dimethylaminomethylidenecyclohexane-1,3-diones **80** with cyanoacetamide (**60a**) in THF in the presence of NaOH yielded a mixture of quinolinecarbonitriles **121** (entry 24) and benzopyrancarboxamides **122**.[135] Only quinoline-3-carboxamides **123** were obtained in high yields upon change in the solvent (refluxing of the reaction mixture in absolute ethanol).

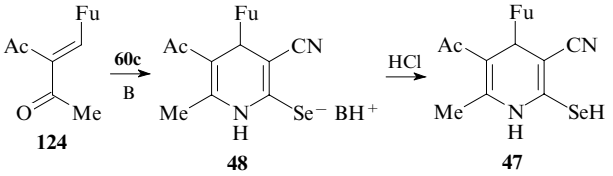


122 **123**

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

Thus, numerous examples of the use of cyano(thio,seleno)-acetamides in the synthesis of 3-cyanopyridinechalcogenones listed in Table 1 illustrate the versatility of this approach.

In some cases, the same compounds can be prepared by varying the reactants. For example, the reaction products of acetylacetone with 2-furfurylidenecyanoselenoacetamide **44a** considered above (see Section II.3.b) were also synthesised under mild conditions (abs. EtOH, 20 °C) from 2-furfurylideneacetylacetone (**124**) and (cyano)selenoacetamide (**60c**) in the presence of *N*-methylmorpholine.[52,82] Ethyl benzylidene- and 2-furfuryl-ideneacetoacetates react similarly with amide **60c**.[52,136–138]

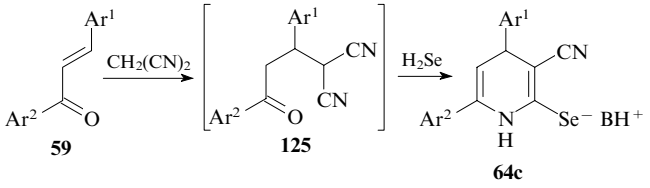


124 **48** **47**

3,5-Dicyano-6-oxo-1,4,5,6-tetrahydropyridine-4-spiro-1′-cyclopentane-2-thiolate (**93**) is formed in the reaction of cyclopentylidene(cyano)thioacetamide **92** with amide **69b** (see Table 1) or ethyl cyanoacetate.[121]

Reactions of bis-nucleophiles with bis-electrophiles were described in the foregoing sections. However, each of the reactants undergoing cyclisation to give the pyridine system can simultaneously contain electrophilic and nucleophilic sites. In this case, the role of a two-carbon fragment is played by CH-acids (*e.g.*, malononitrile, ethyl cyanoacetate, acetoacetanilide, *etc.*).

Several examples of the use of malononitrile in the formation of the pyridine ring have been described. Reactions of chalcones **59** with malononitrile yield δ-keto dinitriles **125**, which give selenolates **64c** upon treatment with hydrogen selenide. The latter can further be converted into compounds **65c** and **66c** (see above).

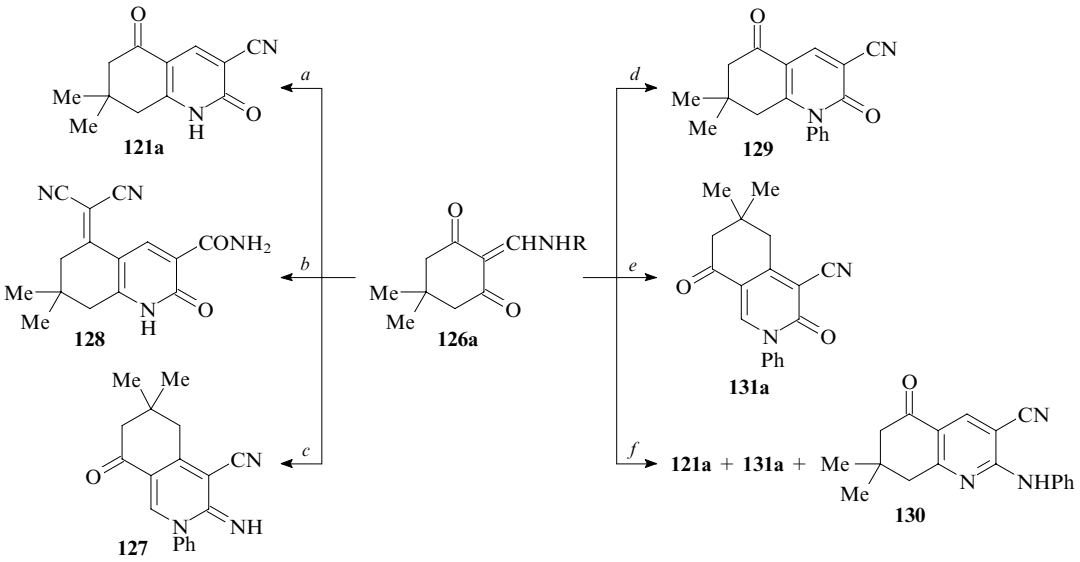


59 **125** **64c**

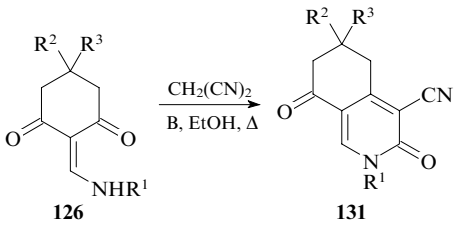
The synthesis of hydrogenated 3-cyanoquinolin-2-ones by the reaction of malononitrile with 2-aminomethylidenecyclohexane-1,3-diones was studied in detail. It is of note that the direction of this reaction strongly depends on the reactant ratio and the nature of the catalyst and the solvent. Thus refluxing of 2-anilinomethylidene-5,5-dimethylcyclohexane-1,3-dione (**126a**) with an equimolar amount of malononitrile in ethanol in the presence of KOH gave 3-cyano-7,7-dimethyl-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (**121a**)[139,140] (Scheme 1), while the reaction in the presence of a two-fold excess of malononitrile yielded 4-cyano-3-imino-6,6-dimethyl-2-phenyl-2,3,5,6,7,8-hexahydroisoquinolin-8-one (**127**) under identical conditions.[139,141] The reaction with a two-fold excess of malononitrile and piperidine as a catalyst in ethanol afforded 3-carbamoyl-5-dicyanomethylidenequinolin-2-one (**128**),[139] while the reaction in DMF in the presence of KOH resulted in *N*-phenyl-substituted 3-cyanoquinolin-2-one **129**.[142] With equimolar amounts of the reactants in the presence of an excess of morpholine, compounds **121a, 130** and **131a** were obtained in yields of 46%, 25% and 17% , respectively.[114] In the absence of a catalyst, this reaction yielded exclusively quinolinone **121a**.

Reactions of compounds **126** bearing other substituents with a small excess of malononitrile were carried out by 1-hour refluxing in ethanol in the presence of catalytic amounts of morpholine to yield exclusively isoquinolinones **131**.[114]

Scheme 1



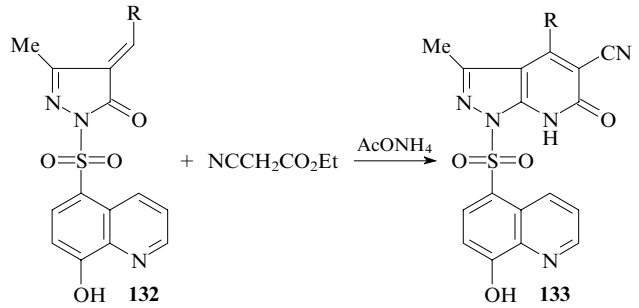
(*a*) $CH_2(CN)_2$ (1 equiv.), KOH, EtOH, Δ; (*b*) $CH_2(CN)_2$ (2 equiv.), KOH, EtOH, Δ; (*c*) $CH_2(CN)_2$ (2 equiv.), Pip, EtOH; (*d*) $CH_2(CN)_2$ (2 equiv.), KOH, DMF; (*e*) $CH_2(CN)_2$ (excess), morpholine (cat.), EtOH, Δ, 1 h; (*f*) $CH_2(CN)_2$ (1 equiv.), morpholine (excess), EtOH, Δ, 1 h.



126 **131**

R^1 = Me, Ph; R^2, R^3 = H, Me, Ph; B is morpholine.

Let us consider a non-trivial example of a reaction of 5-hetarylsulfonyl-8-hydroxyquinolines **132** with ethyl cyanoacetate in the presence of ammonium acetate, which afforded a new heterocyclic system **133**.[143]

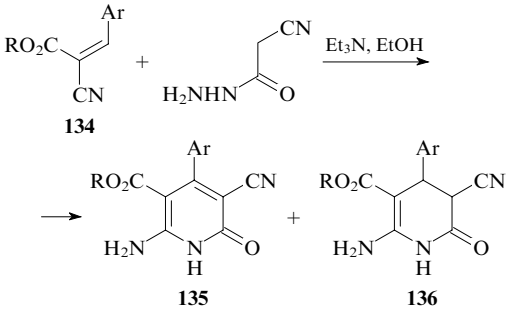


132 **133**

R = Alk.

A method for the synthesis of 3,4-dihydropyridine-4-spiro-1′-cyclohexane-2(1*H*)-thione by the reaction of amide **32** with acetoacetanilide in ethanol in the presence of *N*-methylmorpholine (yield 87%) has been described.[52, 144]

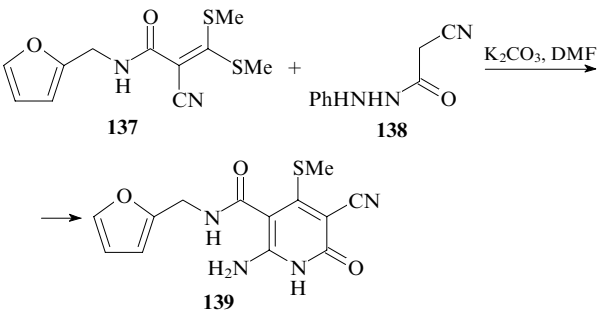
Alkylarylidenecyanoacetates **134** reacted with cyanoacetohydrazide in boiling ethanol in the presence of triethylamine or piperidine to give pyridones **135** in > 80% yields.[145] However, at room temperature this reaction gave, along with pyridones **135**, 3,4-dihydropyridin-2(1*H*)-ones **136**.[146–148]



134 **135** **136**

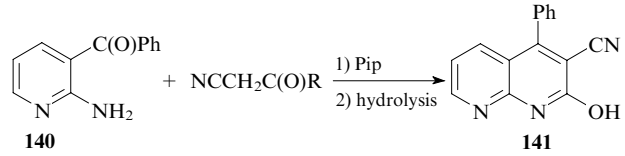
Ar = 4-XC_6H_4 (X = H, Me, Cl, NO_2).

The reaction of *N*-furfurylacrylamide **137** with *N*′-phenylcyanoacetohydrazide **138** gave functionalised 3-cyanopyridone **139**.[149]



137 **138** **139**

In all the above-cited reactions of the pyridine ring closure, the N–C(6) bond was formed along with the C(3)–C(4) bond. However, there is only one example of the formation of the N–C(2) bond, *viz*., condensation of 2-amino-3-benzoylpyridine (**140**) with cyanoacetic acid derivatives. Subsequent hydrolysis gives 3-cyano-2-hydroxy-1,8-naphthyridine **141**.[150]



140 **141**

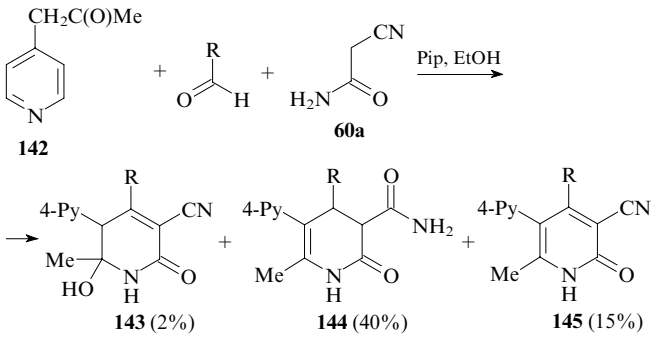
R = NH_2, OMe, OEt.

Thus, this method for the preparation of 3-cyanopyridine-2-chalcogenones is represented by the largest number of examples. Presumably, it is the most efficient approach to the synthesis of this class of compounds.

4. Synthesis of the pyridine ring from three fragments

Among other approaches to the synthesis of pyridine chalcogenones, multicomponent condensations (cascade heterocyclisation) have recently gained increasing popularity. For example, three-component condensation (1 + 2 + 2), which consists of reactions of aliphatic, aromatic or heteroaromatic aldehydes with 1,3-dicarbonyl compounds and cyano(thio,seleno)acetamides **60a–c**, is often used in the synthesis of substituted 3-cyanopyridine-2(1*H*)-thiones.[7, 8, 17, 22, 125, 151–154] In this section, aldehydes and isatins are considered as examples of one-carbon fragments, while substituted acetone, malononitrile and pyridinium ylides, as fragments forming the C(5)–C(6) bond in the pyridine ring. In all these cases, cyanoacetamides **60a**,**b** were used as nitrogen, C(2) and C(3) sources.

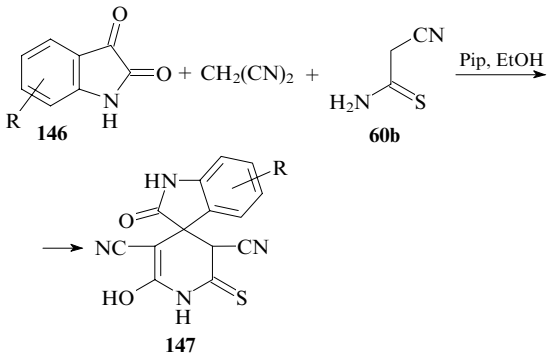
Thus condensation of 4-pyridylacetone (**142**) with aldehydes and cyanoacetamide (**60a**) gave a mixture of pyridones **143–145**, which were separated by crystallisation.[155]



142 **60a** **143** (2%) **144** (40%) **145** (15%)

R = Ar, Het.

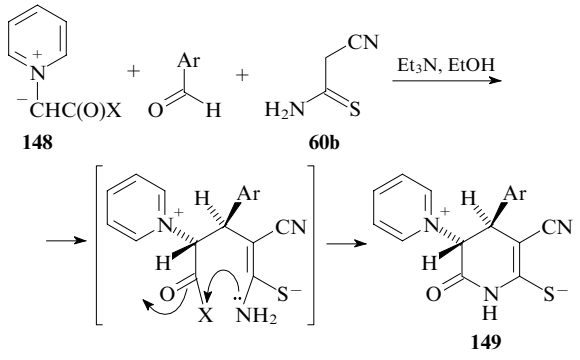
Substituted isatins **146** reacted with malononitrile and (cyano)thioacetamide **60b** in ethanol in the presence of piperidine. This afforded spiro derivatives **147**, which represent the hydrolysis products of the intermediate 6-iminopyridine-2-thiones and which are difficult to prepare by other methods.[156]



146 **60b** **147**

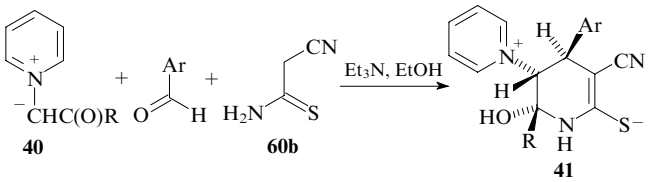
As is known, pyridinium ylides generated *in situ* from quaternised pyridines are widely and successfully employed in organic

synthesis,[155–158] particularly for the preparation of substituted 3-cyanopyridine-2(1*H*)-thiones. Simple procedures for their synthesis were developed on the basis of the three-component coupling methodology.[17, 51, 58–62, 64–66, 159–163] Thus reactions of pyridinium ylides **148** with aromatic aldehydes and cyanothioacetamide (**60b**) in ethanol in the presence of triethylamine proceeded in a regio- and stereoselective manner and afforded hydrogenated *trans*-4-aryl-3-cyano-5-pyridiniumpyridine-2-thiolates **149** in high yields.[51, 58–61]



X = NH_2, OAlk; Ar = 4-YC_6H_4 (Y = HO, MeO, F, Cl, Br), 3-Py.

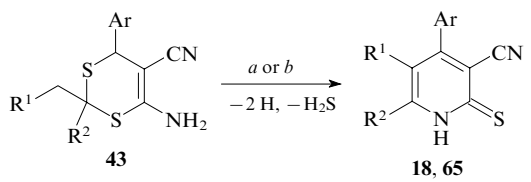
The synthesis of the aforementioned thiolates **41** (see Section II.3.b) was also accomplished using three-component condensation of pyridinium ylides **40**, (cyano)thioacetamide (**60b**) and aromatic aldehydes.[58, 64, 160]



R = Me, Ph, cyclo-C_3H_5; Ar = XC_6H_4 (X = H, 4-MeO, 4-NO_2, 2-F, 4-F, 4-Br), 3-Py.

5. Ring transformation reactions

The formation of the pyridine ring from other heterocycles represents a non-trivial approach to the synthesis of 3-cyanopyridine-2(1*H*)-thiones. Originally, this method was used for the preparation of pyridines annelated with a five- or six-membered ring at positions 5 and 6.[67, 69] Thus 4-amino-6-aryl-5-cyano-1,3-dithiacyclohex-4-enes **43** spiro-fused with cycloalkanes [$R^1-R^2 = (CH_2)_n$, n = 3, 4] were used in the synthesis of the corresponding 5,6-polymethylene-3-cyanopyridine-2(1*H*)-thiones **18**. This transformation occurs upon short-term heating of the reactants in pyridine or DMF (conditions *a*). This reaction follows a complex mechanism [71] and is accompanied by a loss of two hydrogen atoms and H_2S. Later, this reaction was extended [72] to non-spirocyclic 1,3-dithiacyclohex-4-enes **43** (R^1 = H, Me; R^2 = Me), which underwent ring transformation into pyridinethiones **65** upon heating in methanol or DMF in the presence of a base [diethylamine or morpholine (conditions *b*)]. The yields were moderate in all cases.

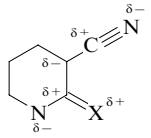


R^2 = Me: R^1 = H, Me (**65**); $R^1-R^2 = (CH_2)_n$ (n = 3, 4) (**18**);
Ar = RC_6H_4 (R = H, 2-F, 4-F, 4-Cl, 4-Br, 4-MeO), 3-Py.

Thus, the above-cited examples of the construction of 3-cyanopyridine-2-chalcogenone derivatives demonstrate the high promise in the development of novel approaches to their synthesis, on the one hand, and enable the prediction of novel trends in this branch of heterocyclic chemistry, on the other hand.

III. Reactivity and chemical transformations

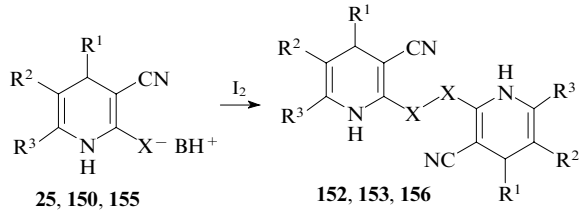
Chemical properties of 3-cyanopyridine-2-chalcogenones have been the subject of intensive studies over the last 15–20 years. Their main fragment [NC−C−C(X)N−] contains four nucleophilic and two electrophilic sites.



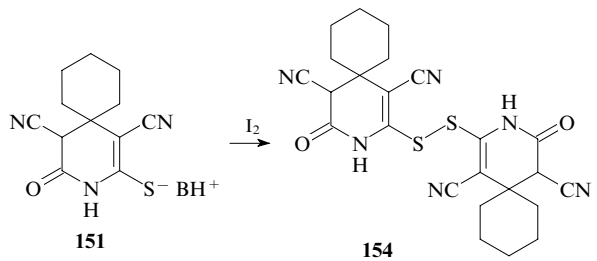
Two vicinal reactive functional groups (the nitrile group and the thio(seleno)amide group incorporating an endocyclic nitrogen atom) possess different properties: addition reactions are characteristic of the former, while the latter reacts with electrophilic reagents. The interest in such systems is caused by two main reasons: the possibility of their transformations into functionalised pyridines possessing valuable characteristics and their use as building blocks in the synthesis of fused heterocycles. 3-Cyanopyridine-2-chalcogenones are promising synthons for complex heterocyclic systems containing a pyridine fragment, *e.g.,* furo(pyrazolo, thieno, selenopheno)pyridines, pyridothienopyridines, pyridothienopyrimidines and other annelated heterocycles manifesting a broad range of biological activities. The chemical transformations of some 3-cyanopyridine-2-chalcogenones are described below. The primary attention is given to reactions of partially hydrogenated derivatives with halogens and alkylating reagents as well as to heterocyclisation reactions. Dehydrogenation reactions were considered in the previous section in relation to discussion of the methods for the synthesis of these compounds.

1. Reactions with halogens

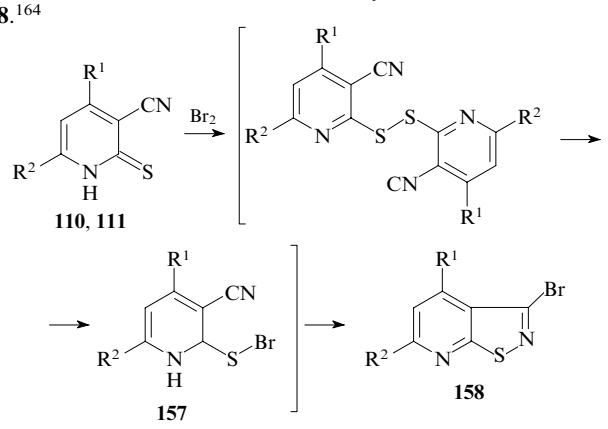
Reactions of some thiolates with elemental iodine have been studied.[52, 72, 151] It was found that treatment of salts **25** and **150** and the spiro-fused 6-oxothiolate **151** with iodine in ethanol in the presence of alkali afforded the corresponding disulfides **152**–**154** in high yields together with small amounts of dehydrogenation products. Such disulfides are usually formed upon oxidation of the corresponding thiones by atmospheric oxygen. Similarly, selenolate **155** gave diselenide **156**.



X = S: R^1 = 2-ClC_6H_4, R^2 = NC, R^3 = H_2N (**150**, **153**);
R^1 = 2-ClC_6H_4, 2-Fu; R^2 = PhNHC(O), R^3 = Me (**25**, **152**);
X = Se, R^1 = 2-ClC_6H_4, R^2 = EtO_2C, R^3 = Me (**155**, **156**).



Bromination of trifluoromethyl-substituted 3-cyanopyridine-2(1*H*)-thiones **110** and **111** also proceeded *via* the corresponding disulfides. However, under the reaction conditions the latter were converted into bromides **157**, which cyclised into isothiazoles **158**.[164]



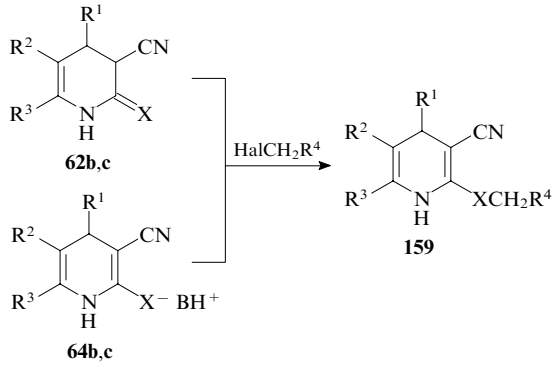
110, **111** **157** **158**

$R^1 = CF_3$, $R^2 = Me$ (**110**); $R^1 = Me$, $R^2 = CF_3$ (**111**).

2. Alkylation

Numerous recent publications on the reactivities of 3-cyanopyridine-2(1*H*)-chalcogenones deal with different aspects of alkylation of sulfur- and selenium-containing derivatives. Reactions with alkylating reagents may involve two nucleophilic sites due to ambident character of the HN–C(X) fragment (X = S, Se) of these heterocycles. As a rule, reactions with alkyl halides and activated halides (α-halogenocarbonyl compounds) in the presence of bases involve the chalcogen atom.

Numerous studies have shown (see, for example, Refs 7, 15, 43, 48, 50–52, 103–106, 165–176) that the alkylation of 3,4-dihydropyridinechalcogenones **62b**,**c** or their salts **64b**,**c** with alkyl halides is regioselective and results in 2-alkylthio(seleno)-1,4-dihydropyridines **159**.

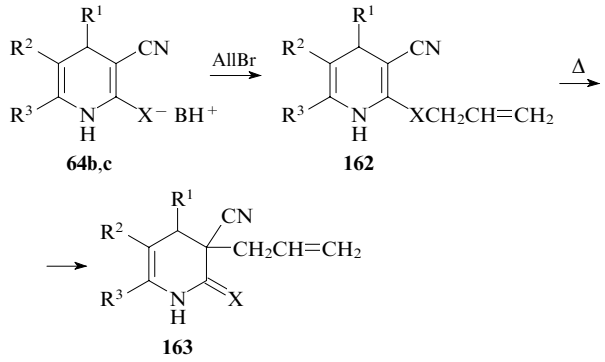


62b,**c** **64b**,**c** **159**

R^1, R^2, R^3 = H, Alk, Ar, Het; R^4 = Alk; X = S, Se;
B is *N*-methylmorpholine.

Reactions of betaines **41** with alkyl halides in ethanol or DMF (in the absence of bases) gave 6-alkylthiotetrahydropyridine salts **160**.[47, 51] However, heating of betaines **41** with allyl bromide in ethanol and subsequent prolonged storage of the reaction mixture at room temperature gave a [3,3]-sigmatropic rearrangement product, *viz*., compound **161** as a mixture of two epimers (Scheme 2).

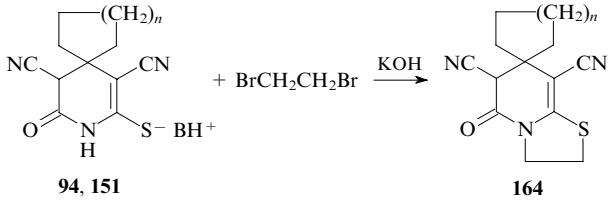
A [3,3]-sigmatropic rearrangement of 2-allylthio(seleno)-1,4-dihydropyridines **162** into 3-allyl-3,4-dihydropyridinechalcogenones **163** also occurred in the alkylation of salts **64b**,**c** with allyl bromide.[7, 52, 57, 120, 136, 177–179] However, in contrast with analogous transformations of aromatic allyloxy(thio)pyridines and -quinolines,[180–182] this reaction was regiospecific: the yields of compounds **163** reached 98%.



64b,**c** **162** **163**

R^1, R^2, R^3 = H, Alk, Ar; X = S, Se.

A convenient method for the synthesis of hitherto unknown spiro-fused heterocyclic systems (6,8-dicyano-5-oxo-2,3,6,7-tetrahydro-5*H*-thiazolo-[2,3-*a*]pyridine-7-spiro-1′-cycloalkanes, **164**) has been developed.[52, 118, 121, 183] It includes alkylation of thiolates **94** and **151** with 1,2-dibromoethane in DMF at room temperature.

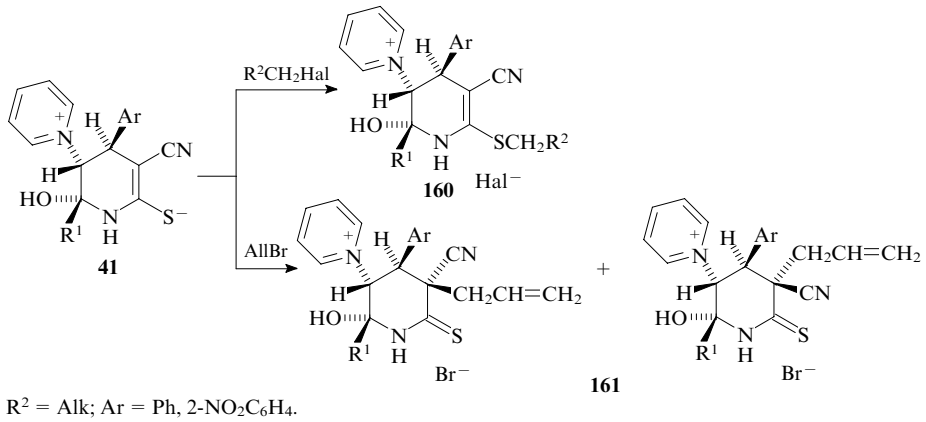


94, **151** **164**

n = 1 (**94**), 2 (**151**).

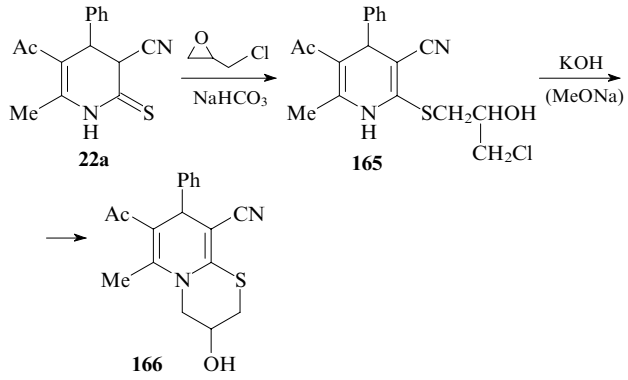
Reaction of sulfide **22a** with epichlorohydrin yielded thione **165**, which underwent cyclisation into pyridothiazine **166** upon treatment with ethanolic KOH or MeONa.[184]

Scheme 2

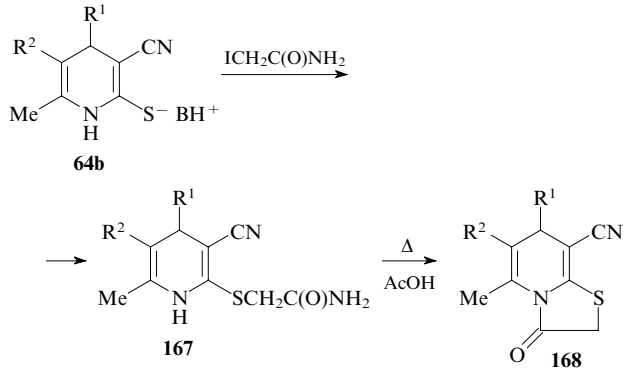


41 **160** **161**

R^1, R^2 = Alk; Ar = Ph, 2-$NO_2C_6H_4$.

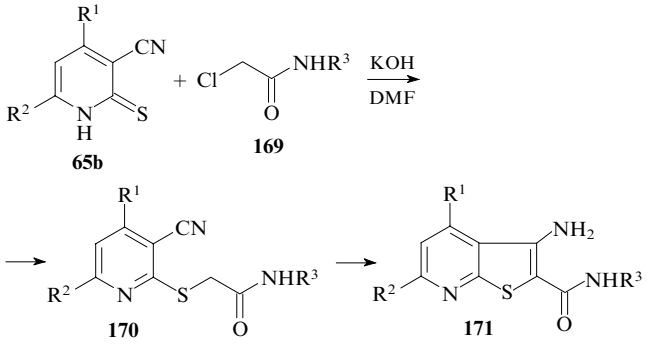


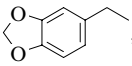
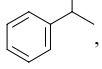
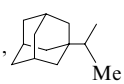
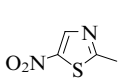
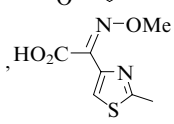
Haloacetic acid derivatives (amides and chlorides) were also studied as alkylating agents. Thus salts **64b** (R^3 = Me) reacted with iodoacetamide in ethanol to give sulfides **167**. The latter underwent intramolecular cyclisation into 3-oxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridines **168** upon refluxing in acetic acid. The yields depended on the nature of the substituent at position 4 of the pyridine ring: for R^1 = 4-Py, the yields were 70% – 85%, while its replacement by the aryl substituent (R^1 = 4-ClC_6H_4) resulted in a significant reduction of the product yield (down to 25%).[185]



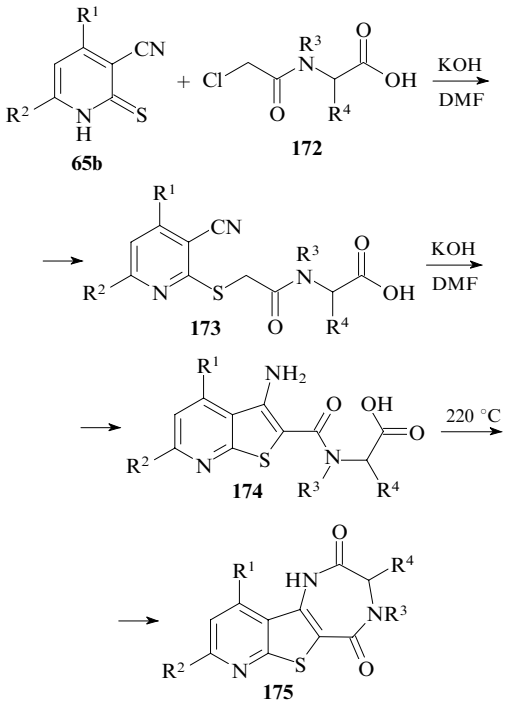
R^1 = 4-Py, 4-ClC_6H_4; R^2 = Ar, Het.

N-Substituted chloroacetamides **169** are currently successfully employed as alkylating agents in the synthesis of novel 3-cyanopyridine-2(1*H*)-thiones.[164] A broad range of such derivatives were obtained by condensation of chloroacetyl chloride with pharmacologically active amines (*e.g.*, α-phenylethylamine, remantadine, *etc*.). Chloroacetamides **169** reacted with pyridinethiones **65b** in DMF or EtOH in the presence of KOH. Both compounds **170** and the respective intramolecular cyclisation products (substituted thienopyridines **171**) were obtained in high yields.



R^1, R^2 = Alk, Ar, Het; R^3 = Pr^i, cyclo-C_3H_7, Bn, $X_nC_6H_{5-n}$ (X = 4-F, 3-F_3C, 3,4-$(MeO)_2$, 3,4-OCH_2O); , , , , , .

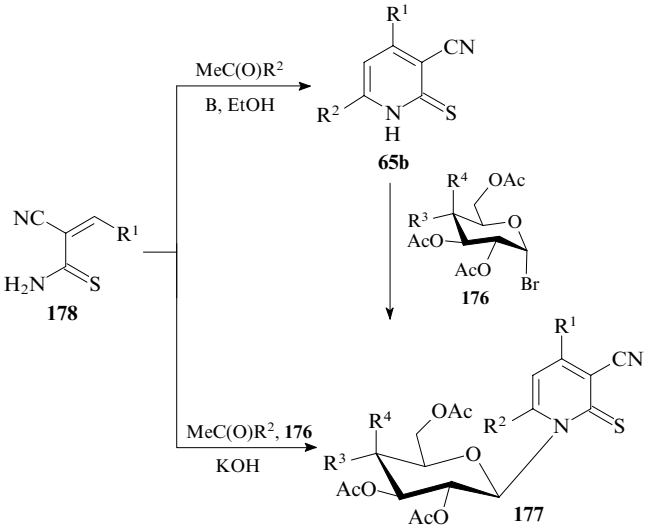
The alkylation reaction was used for the introduction of α-amino acid fragments into 3-cyanopyridine-2(1*H*)-thiones.[16] Thus chloroacetamides **172** prepared by condensation of chloroacetyl chloride with amino acids reacted with pyridinethiones **65b** to give the alkylation products **173**. The latter cyclised under the reaction conditions into thienopyridines **174** analogous to the above-mentioned compounds **171**. However, thienopyridines **174** contained an ω-carboxy group at position 2 rather than the carbamide group, which enabled their intramolecular cyclisation into 4-dihydro-1*H*-pyrido[3′,2′:4,5]thieno[2,3-*e*][1,4]diazepine-2,5-diones **175** upon heating.



R^1, R^2 = Alk, Ar, Het; R^3 = H: R^4 = H, Me, Pr^i, Bn; $R^3 - R^4$ = $(CH_2)_3$.

1-Bromomethylcarborane can also be used as an alkylating agent.[186, 187]

All the reactions of 3-cyanopyridine-2(1*H*)-thiones with the above-considered electrophilic agents involve the chalcogen atom (sulfur or selenium); the alkylation at the nitrogen atom of the pyridine ring was described in only few cases (see Refs 188 – 190). This can be explained in terms of the hard and soft acids and bases theory. Whereas soft electrophiles react at the sulfur atom, reactions with harder reagents involve the nitrogen atom. In the presence of aqueous KOH, 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -galactopyranosyl bromides **176** react with cyanopyridinechalcogenones **65b** to yield *N*-glycosides **177**. The latter can be prepared in one step starting from cyanothioacetamides **178**, glycosyl bromides **176** and ketones.[190]



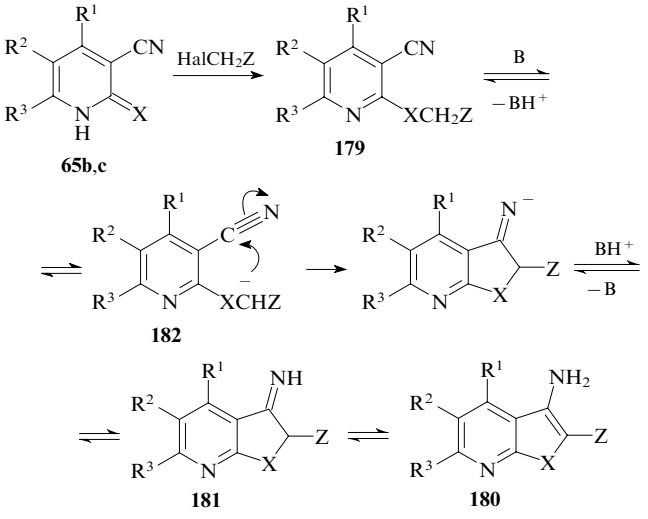
R^1, R^2 = Me, Et, Ph; R^3 = H, R^4 = OAc; R^3 = OAc, R^4 = H.

For other aspects of alkylation reactions of pyridinechalcogenones, see Refs 3, 5, 7 and 8.

3. Heterocyclisation

In addition to the aforementioned studies of chemical properties of pyridinechalcogenones, heterocyclisation of their functional derivatives is of the greatest interest as one of the most promising approaches to the synthesis of fused heterocyclic systems containing a pyridine fragment (see, for example, Refs 7, 20–22, 52, 83, 105, 108, 167, 173, 176, 178, 191–200).

Thus the Thorpe–Ziegler cyclisation of 2-alkylthio(seleno)-3-cyanopyridines **179** prepared by alkylation of 3-cyanopyridine-2-chalcogenones (**65**) in DMF or ethanol in the presence of a base gives thieno(selenopheno)-[2,3-*b*]pyridines **180**. The reaction mechanism can be presented by the following sequence:[11,201]



R^1, R^2, R^3 = Alk, Ar, Het; X = S, Se;
Z is an electron-withdrawing group.

It was found that the equilibrium between the tautomeric forms **180** ⇌ **181** is virtually completely shifted towards the amine **180**. The electron-withdrawing effect of the substituent Z, which determines the stability and the concentration of the carbanion **182**, is the rate-limiting factor of this cyclisation. The following order of activities of substituents Z was empirically established:[8,11] NO_2 > ArC(O) > CN > CO_2Alk > $C(O)NH_2$ > H.

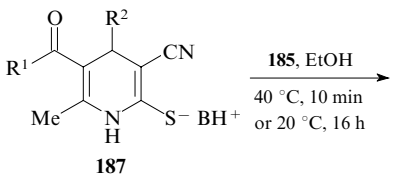
The substituent Z that imparts sufficiently high CH-acidity on the SCH_2Z fragment of compound **179** and stabilises anion **182** usually represents a π-acceptor; only one example of a reaction involving a σ-withdrawing group (the carborane fragment) is documented.[187]

The cyclisation is usually carried out in the presence of bases; acid catalysis is used less often. Systems KOH–EtOH, K_2CO_3–EtOH, EtONa–EtOH, K_2CO_3–DMF, less often Na_2CO_3–EtOH, MeONa–EtOH, KOH–EtOH–H_2O, AcONa–EtOH (abs.), Et_3N–EtOH, K_2CO_3–Me_2CO, Et_3N–dioxane, Et_3N–DMSO, are generally employed. Bases are used in both stoichiometric and catalytic amounts. Spontaneous formation of thienopyridines in the alkylation of thiones **65b** in the presence of equimolar amounts of the base has been observed in some cases; no intermediate products could be isolated. As a rule, the reaction is carried out at room temperature, although in some cases heating can be required. There are some examples of cyclisation in boiling ethanol[202,203] or under phase-transfer catalysis conditions with Bu_4NBr used as the catalyst.[204,205]

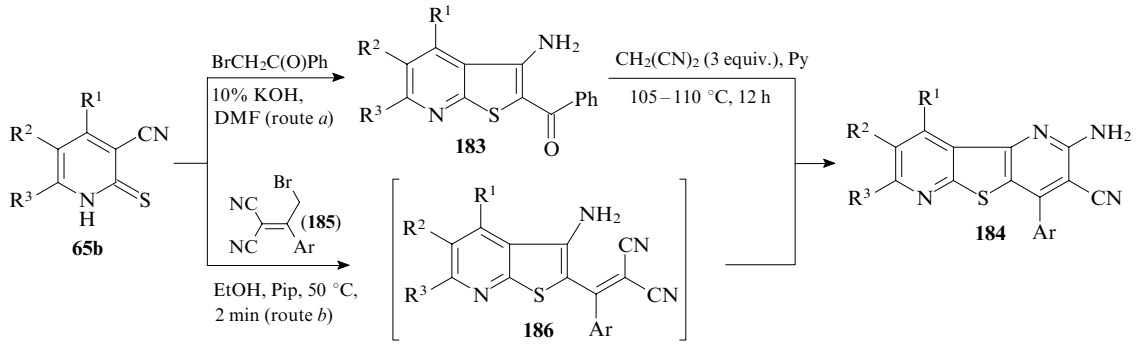
It is of note that the synthesis of thienopyridines is most often based on the cyclisation of 2-alkylthio-3-cyanopyridines that are conventionally prepared from 3-cyano-pyridine-2(1*H*)-thiones **65b** (or the corresponding thiolates) and an alkylating agent containing an electron-withdrawing substituent in the α-position relative to the halogen atom. This can also be achieved by multicomponent cascade heterocyclisation, which allows an access to pyridinechalcogenones from simple and readily available acyclic precursors in a one-pot procedure.[2] This strategy served as a basis for the synthesis of thienopyridines and related systems, *e.g.*, derivatives of quinoline, isoquinoline, benzo[*b*]quinoline, pyrano- and thiopyranopyridines, benzothiopyranopyridine, pyridopyridines (naphthyridines) and other fused heterocycles; the bibliography on the subject includes over 170 references (see the monograph [199]).

Among numerous examples of this synthesis, special mention should be made of a successful solution of the problem of construction of substituted pyridothienopyridines which is based on the cascade conversions of some 3-cyanopyridine-2(1*H*)-thione derivatives.[206,207] On the whole, this type of heterocyclisation has a number of advantages over classical Friedlander annelation, since cascade reactions proceed faster and under less drastic conditions and ensure high yields of target products in one step. Thus the alkylation of thiones **65b** is accompanied by the Thorpe ring closure resulting in thienopyridines **183**; prolonged refluxing of the latter in the presence of the excess of malononitrile affords tricyclic Friedlander cyclocondensation products, *viz.*, compounds **184** (route *a*, yields 67%–75%). Compounds **184** can be prepared in 2 min from the same cyanopyridinethiones **65b** and 2-aryl-3-bromo-1,1-dicyanopropenes **185** (route *b*, yields 57%–95%); in the latter case, the intermediate thienopyridine **186** is not usually isolated from the reaction mixture, but is subjected to cyclisation *in situ* (Scheme 3).

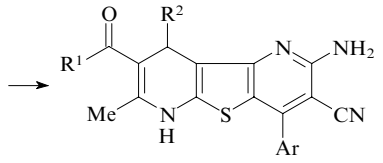
Later, the approach based on the use of bromides **185** was used in the synthesis of other dipyridothiophenes.[208,209] For the first time, thiolates **187** were used as starting materials for the synthesis of 6,9-dihydropyrido [3′,2′:4,5]thieno[3,2-*b*]pyridines **188**. It is of note that in this case the cascade heterocyclisation occurs spontaneously in the absence of a basic catalyst.[208]



Scheme 3



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

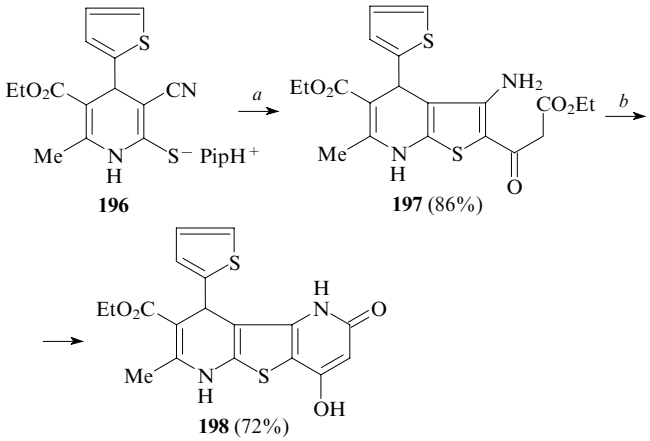


188 (41%–82%)

R^1 = EtO, Me; R^2 = 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 2-thienyl;
Ar = 4-BrC_6H_4.

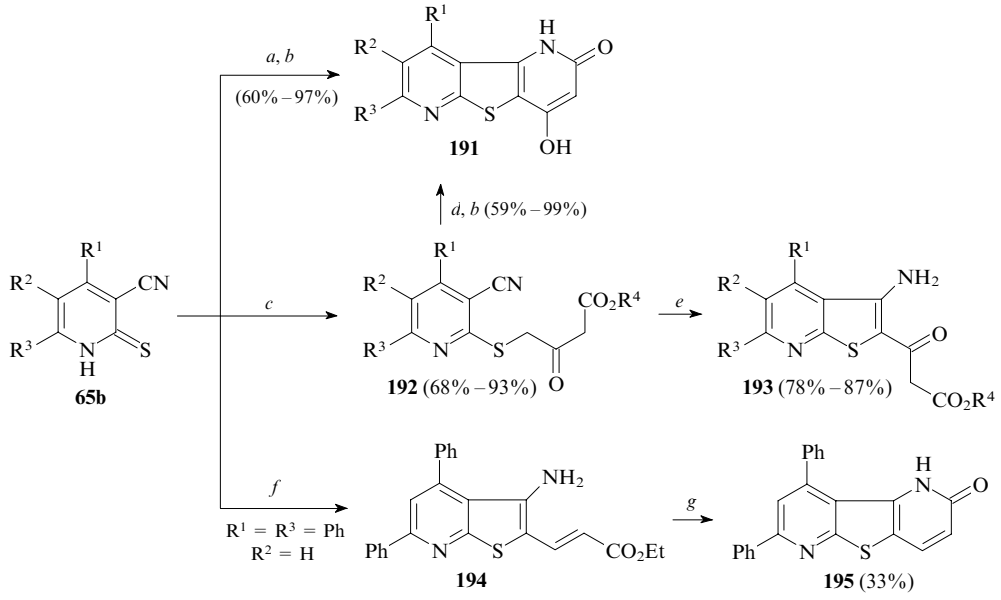
Among other alkylating agents used in heterocyclisation reactions that yield fused thienopyridine derivatives, alkyl γ-chloroacetoacetates **189** [17, 210–213] and ethyl 4-bromocrotonate are worthy of mention (**190**).[177, 208] Some aspects of the use of compounds **189** and **190** in the synthesis of heterocycles are detailed in the review.[214] The cascade heterocyclisation of substituted pyridine-2(1*H*)-thiones **65b** and γ-chloro β-oxo esters **189** in boiling ethanol in the presence of KOH or EtONa is the most efficient procedure for the preparation of dipyridothiophenes **191**. If the reaction is carried out under mild conditions, the intermediates, *i.e.,* pyridine **192** and thieno[2,3-*b*]pyridine **193**, can be isolated; they easily cyclise in the presence of bases into the target products **191**.[211] Thienopyridine **194** prepared by the reaction of thione **65b** (R^1 = R^3 = Ph, R^2 = H) with crotonate **190** was similarly converted into dipyridothiophene **195** (Scheme 4).[177]

The reaction of piperidinium 1,4-dihydropyridine-2-thiolate **196** with the ester **189** (Alk = Et) gave the thienopyridine derivative **197**; the latter was converted into the corresponding dipyridothiophene **198** in good yield under more drastic conditions.[211]



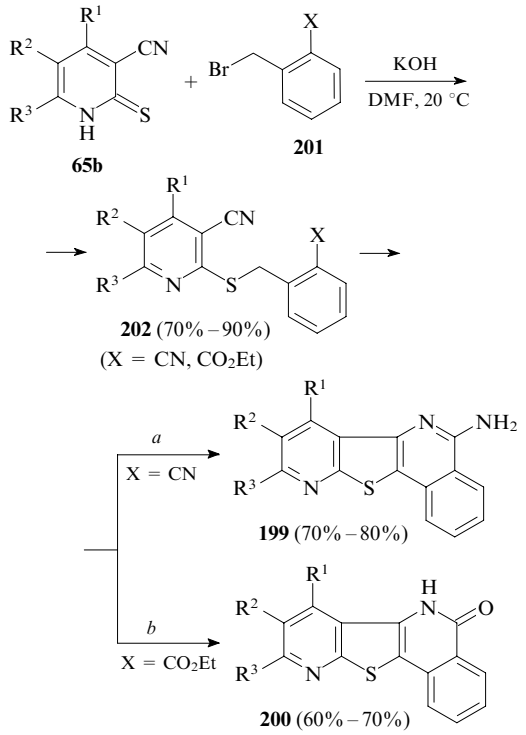
(*a*) **189**, KOH, EtOH, 40 °C; (*b*) (1) KOH, EtOH, Δ, 5 min; (2) 10% HCl.

Scheme 4



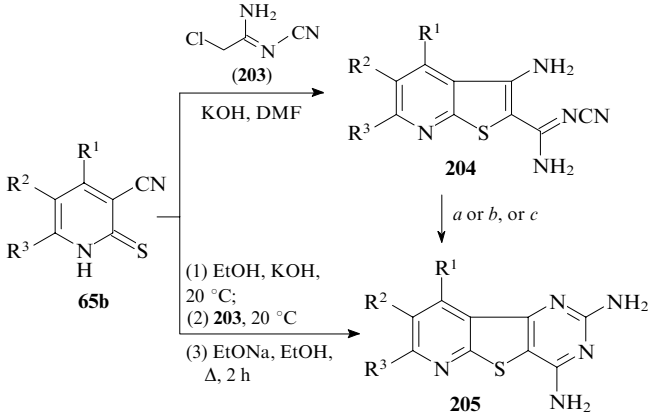
(*a*) $ClCH_2C(O)CH_2CO_2Alk$ (**189**) (R^4 = Et, Pr^i), KOH or EtONa, EtOH, Δ; (*b*) 10% HCl; (*c*) 189, 10% KOH, DMF; (*d*) KOH or EtONa, EtOH, Δ; (*e*) Et_3N, EtOH, Δ; (*f*) $BrCH_2CH{=}CHCO_2Et$ (**190**), KOH or EtONa, EtOH; (*g*) HCl, MeOH, Δ, 8 h;
R^1, R^2, R^3 = H, Alk, Ar, Het.

The cascade synthesis of pyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinolines **199** and **200** was accomplished using *o*-bromomethylbenzoic acid derivatives **201** as convenient precursors.[215,216] This reaction is carried out either as a one-pot procedure or with isolation of intermediate benzylthiopyridines **202**.



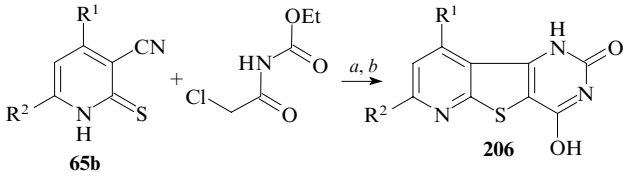
(*a*) KOH, DMF, Δ; (*b*) Bu^{t}OK, DMF, Δ; R^1, R^2, R^3 = Alk, Ar, Het.

Two approaches to the synthesis of tricyclic pyridothienopyrimidine systems were developed. Reactions of 3-cyanopyridine-2(1*H*)-thione derivatives **65b** with *N*-cyanochloroacetamidine (**203**) afforded thienopyridines **204**,[173,208,217,218] which underwent cyclisation into pyridothienopyrimidines **205** (yields 60% – 90%) under the action of basic or acidic catalysts. These compounds can also be synthesised directly from thiones **65b** and chloride **203**.



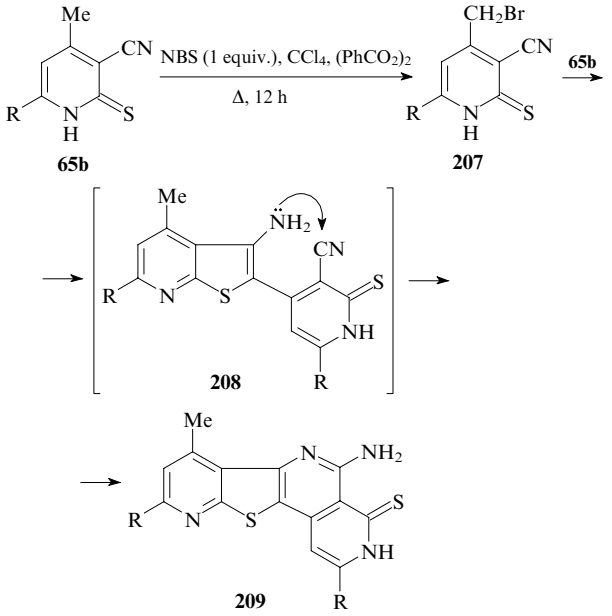
(*a*) EtONa, EtOH, Δ, 6 h; (*b*) 35% HCl, MeOH, 0.5 – 12 h;
(*c*) Ac_2O, Δ, 6 h;
R^1 = 4-$MeOC_6H_4$, 4-FC_6H_4, 2-$NO_2C_6H_4$, 2-thienyl;
R^2 = MeCO, EtO_2C; R^3 = Me.

The second approach, *viz.*, condensation of pyridinethiones **65b** with *N*-(ethoxycarbonyl)chloroacetamide, was used in the synthesis of pyridothienopyrimidines **206**.[17,213]



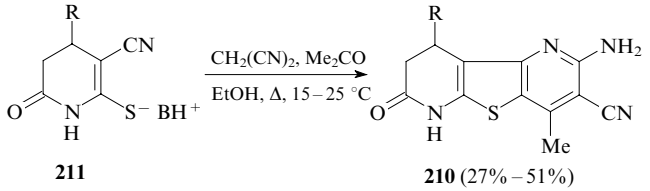
(*a*) EtONa, EtOH – DMF (1 : 1), Δ, 2 h; (*b*) 10% HCl, 20 °C;
R^1 = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$; R^2 = Ph, 2-thienyl.

A non-trivial procedure for the synthesis of fused thienoazines has been proposed.[219] It included radical bromination of pyridinethiones **65b** (R^1 = Me, R^2 = H) affecting the 4-methyl group with formation of bromides **207**. Reaction of the latter with the starting thiones first yielded intermediates **208** and then tetracyclic systems **209** containing annelated thienopyridine and naphthyridine fragments.



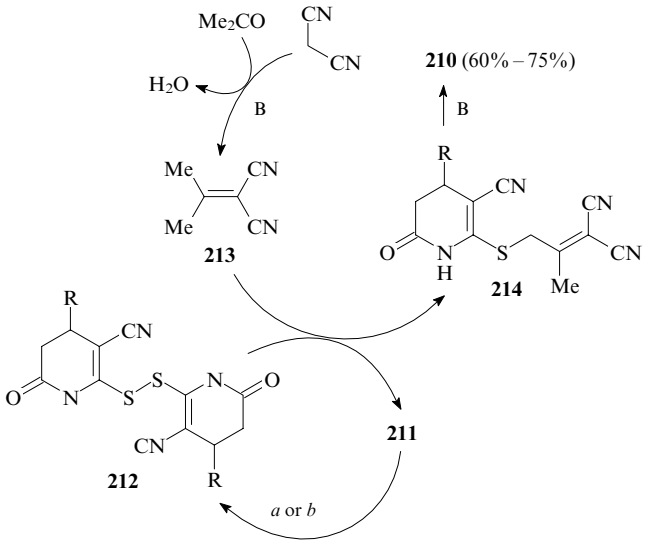
R = Me, Ph; NBS is *N*-bromosuccinimide.

Of note is the multicomponent approach to the synthesis of substituted 6,7,8,9-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines **210** based on the reaction of pyridinethiolates **211**, with malononitrile and acetone.[16,220 – 223]



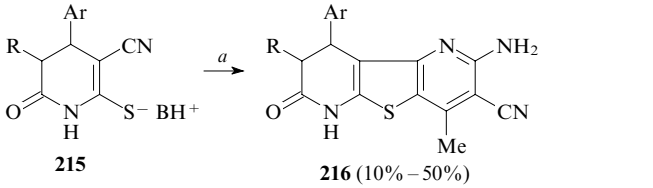
R = Ar, Het; B = *N*-methylmorpholine.

The following reaction mechanism has been proposed:[16,223,224] the starting pyridinethiolate **211** is oxidised by atmospheric oxygen to the corresponding bis(2-pyridyl) disulfide **212**, which reacts with an anion derived from isopropylidenemalononitrile **213** generated *in situ* from malononitrile and acetone resulting in the cleavage of the S – S bond and the formation of dicyanoallyl sulfide **214** and thiolate **211**. The latter undergoes reoxidation into the disulfide, while compound **214** cyclises into dipyridothiophene **210**. The feasibility of this reaction mechanism was confirmed by the independent synthesis of compounds **210** from disulfides **212** formed upon mild oxidation of thiolates **211**. In the latter case, the target products were obtained with the highest yields (60% – 75%).



B is *N*-methylmorpholine; R = Ar, Het;
(*a*) O_2, EtOH, (*b*) I_2, EtOH – H_2O, 24 h (90% – 100%).

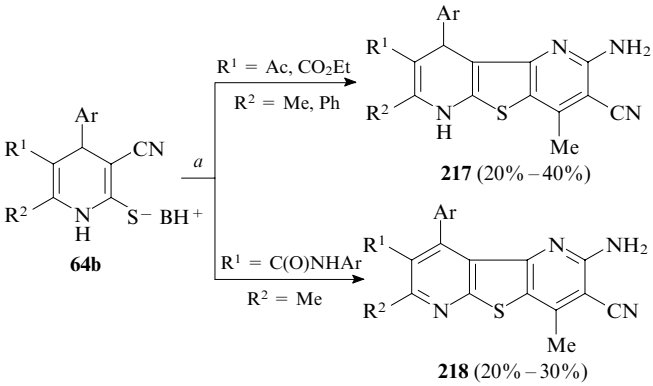
A similar reaction of thiolates **215** and **64b** with malononitrile and acetone in boiling EtOH afforded partially hydrogenated pyridothienopyridines **216** and **217** or their dehydrogenated derivatives **218**.[222] Under analogous conditions, hexahydroquinoline-2-thiolates **219** yielded hexahydropyridothienoquinolines **220**.



215

216 (10% – 50%)

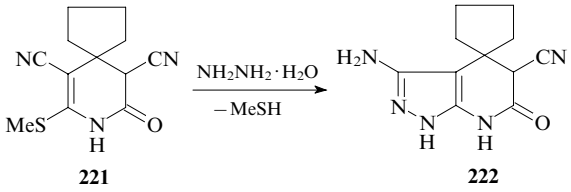
R = CO_2Me, CO_2Et



R = H, Me.

(*a*) $CH_2(CN)_2$, Me_2CO, EtOH, Δ.

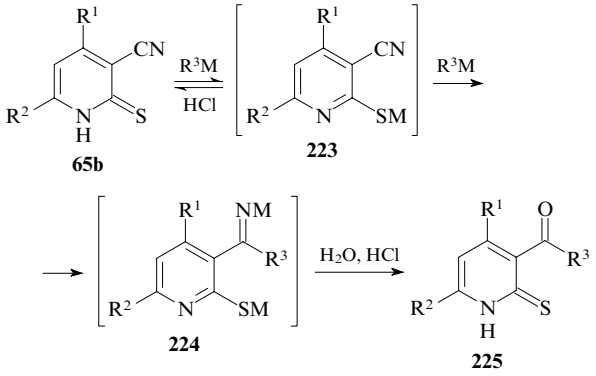
Heterocyclisation of pyridinechalcogenones under the action of 1,2-bis-nucleophiles was carried out. Thus the reaction of spiro-fused 2-(methylthio)tetrahydropyridone **221** with hydrazine hydrate in ethanol gave 3-amino-5-cyano-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine-4-spiro-1′-cyclopentane (**222**) (Refs 52, 88, 120, 121).



221 **222**

4. Other transformations of 3-cyanopyridine-2(1*H*)-chalcogenones

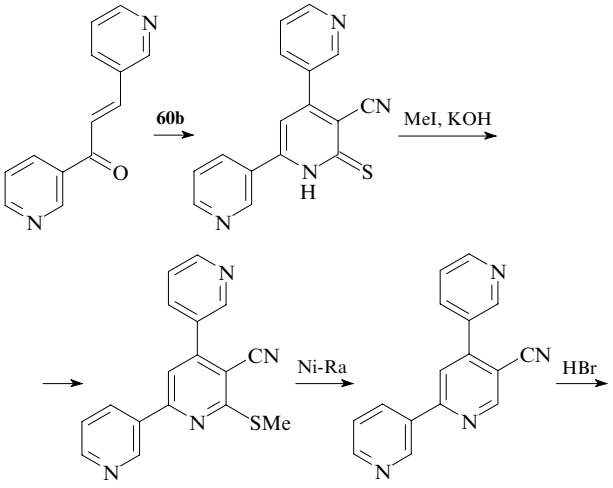
Other chemical transformations of 3-cyanopyridine-2(1*H*)-chalcogenones *e.g.,* hydrolysis of the nitrile group, reaction with organometallic compounds, *etc*., have been described earlier and are not considered in this review. Suffice it to mention the recently studied reaction of 3-cyanopyridine-2(1*H*)-thiones **65b** with n-butyllithium and methylmagnesium iodide in ether, which occurs *via* intermediates **223** and **224** to yield ketones **225**.[225, 226]

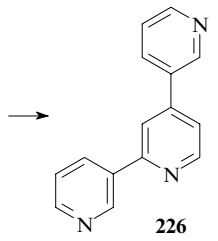


R^1 = H, Me; R^2 = Me, Pr^n, Bu^n, Bu^i, n-C_5H_{11}; R^3 = Me, Bu^n; M = Li, MgI.

Recently, the attention of investigators has been focused on the reduction of the nitrile group in 3-cyanopyridine-2(1*H*)-thiones and their 2-methylthio derivatives. This reaction can be used for the preparation of aminomethyl- and formyl-substituted pyridines, the promising building blocks for the synthesis of novel fused heterocycles. Catalytic hydrogenation with Raney nickel and reduction with complex metal hydrides [*e.g*., lithium aluminium hydride, lithium triethoxyaluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride] were studied. It was found that either the reduction of the nitrile group or the cleavage of the C – S bond took place depending on the reaction conditions and the nature of the catalyst.[19, 227 – 230]

The use of Raney nickel in the synthesis of nicotelline **226**, a minor alkaloid of the tobacco plant, has been described.[64, 83, 231]

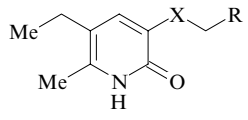




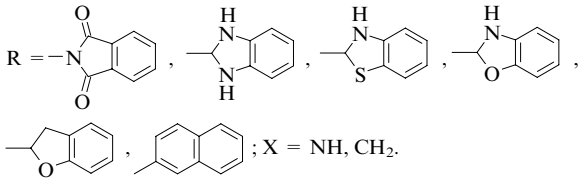
226

IV. Applications

It is known [8, 232–238] that 3-cyanopyridine-2(1*H*)-thiones are used in the commercial production of dyes, pigments, additives to fuels and lubricants, acid-base indicators for titrimetric analysis [233] and other industrially important substances. Considerably more attention is given to the biological activities of pyridinechalcogenone derivatives. In the first place, this concerns the cardiotonic effect of a vast majority of compounds of this series (Refs 34, 169, 181, 184, 239–260). Some of them were found to possess cardiovascular, coronary and pronounced vasodilatory activities.[261, 262] Other biological activities of this class of compounds include analgetic and antihypertensive activities,[117, 170, 247] antianaphylactic,[108, 192, 193] ionotropic,[249] antidiabetic,[263] diuretic and sodium-diuretic activities,[150] as well as antioxidant,[169, 170, 264, 265] antiviral,[20, 105, 196, 266] antiinflammatory [109, 167] and antimicrobial activities.[105–108, 143, 267, 268] Some of these derivatives are potent tranquilisers,[269–273] antiallergic drugs for treatment of bronchial asthma,[269] antihepatitis agents,[50] *etc*. Special attention is given to the detection, among pyridones **227**, of inhibitors of reverse transcriptase of human immunodeficiency virus (HIV-1).[194, 245, 270–277]



227



Pyridinechalcogenones formed the basis for the development of biodegradable agrochemicals,[172] plant growth regulators, pesticides and herbicides.[23, 52, 91, 103, 104, 150] Other applications of cyanopyridinechalcogenone derivatives are also known (see Refs 3, 5, 8 and references cited therein).

V. Conclusion

The development of novel chemo-, regio-, stereo- and enantioselective methods for the synthesis of multifunctional carbo- and heterocycles possessing valuable properties among which pyridine derivatives occupy a special position is one of the major problems of the synthetic organic chemistry of the 21st century. In this context, the development of synthetic procedures and investigations into reactivities of 3-cyanopyridine-2(1*H*)-chalcogenones as versatile building blocks acquire special importance. Such compounds found wide application in the synthesis of miscellaneous heterocyclic systems containing an annelated pyridine ring.

The analysis of the data on the methods for the synthesis, chemical behaviour and synthetic potentials of 3-cyanopyridine-2(1*H*)-chalcogenones has made it possible to outline the prospects of this branch of heterocyclic chemistry and to highlight the most promising trends of research in this area. Based on these data, one can expect further successful escalation of studies aimed at the development of novel approaches to the synthesis of fused *O*,*N*,*S*-heterocycles possessing a broad range of valuable properties on the basis of pyridinechalcogenones.

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