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Cyanothioacetamide: a polyfunctional reagent with broad synthetic utility

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The review integrates and analyzes the published data on the chemical reactivity of α-cyanothioacetamide, a convenient starting compound for the preparation of activated alkenes, functionally substituted pyrans, thiopyrans, pyridines, thiophenes, pyrroles, quinolines, isoquinolines, pyrimidines, thienopyrroles, pyrazolopyridines, pyridothienopyrimidines and pyrimidothienodiazines. The relatively small α-cyanothioacetamide molecule has several reaction centres. Nucleophilic reactions of the methylene group are covered most extensively, including the Thorpe reaction; reactions with diazonium salts, azides, iso(thio)cyanates and nitroso compounds; nucleopilic substitution; Knoevenagel condensation; Michael reaction; and multicomponent syntheses. Separate parts of the review are devoted to nucleophilic reactions involving the thiocarbonyl and amino groups and electrophilic reactions involving thiocarbonyl and nitrile groups. The focus is on the publications of the last 15 years.
The bibliography includes 350 references.

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1. Introduction

α-Cyanothioacetamide (**1**) has been recognized as a unique polyfunctional reagent with large synthetic potential since it was first prepared. It proved to be convenient for the synthesis of many nitrogen and sulfur compounds, mainly heterocycles. The heterocycles thus obtained are often structural fragments of natural molecules; also, numerous biologically active products have been found among them. Despite the large number of studies on the application of α-cyanothioacetamide and its derivatives for the synthesis of nitrogen heterocycles,[1 – 8] there is still no review summarizing its synthetic potential. Here, we arranged the literature data according to the key reaction step.

The small α-cyanothioacetamide molecule contains as many as four nucleophilic sites, namely, the amino group, the sulfur atom, the nitrile nitrogen atom and the carbanion formed from the methylene group, and two electrohilic sites, namely, the nitrile and thioamide carbon atoms. Most publications deal with the use of this reagent as a CH acid,

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Current research interests: organic fluorine compounds, heterocyclic compounds, chemistry of organic sulfur compounds, multicomponent reactions, homogeneous catalysis.

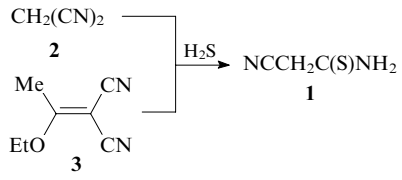
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that is, address reactions that start with the nucleophilic attack by α-cyanothioacetamide on electrohilic sites of other molecules, mainly C-electrophiles. The participation of the nitrile nitrogen atom as the nucleophile in the key reaction step is barely known. Formally, proton addition that catalyzes electrohilic reactions of the nitrile group can be regarded as such a step (see below, Section 6).

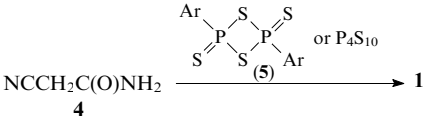
α-Cyanothioacetamide was obtained for the first time in 1956 by E.G.Howard [9] by the reaction of malononitrile (**2**) with hydrogen sulfide at room temperature in absolute ethanol with triethanolamine as the catalyst (Scheme 1). Apart from the method of syntheses, the patent [9] covered the fungicidal activity against the phytophthora root rot of tomatoes with the absence of toxicity. Later, Schmidt and Kubitzek [10] used a picoline–ethanol mixture as the solvent and the catalyst for this reaction. In 1962, McCall [11] proposed a method for the synthesis of this compound from substituted 2-(1-ethoxyethylidene)malononitrile (**3**) and hydrogen sulfide in ethanol with triethylamine as the catalyst (65% yield). The same researcher obtained α-cyanothioacetamide in 45% yield from malononitrile and hydrogen sulfide in ethanol in the presence of a catalytic amount of triethylamine (see Scheme 1).[11]

Scheme 1



α-Cyanothioacetamide is also formed upon the replacement of oxygen in the cyanoacetamide (**4**) molecule by sulfur on treatment with either Lawesson's reagent (**5**) [12] in THF at 20 °C or P_4S_{10} in ethanol on refluxing for 4 h,[13] the product yields being 71% and 30%, respectively (Scheme 2).

Scheme 2



Ar = Ph, 4-$MeOC_6H_4$

2. Nucleophilic reactions of the methylene group

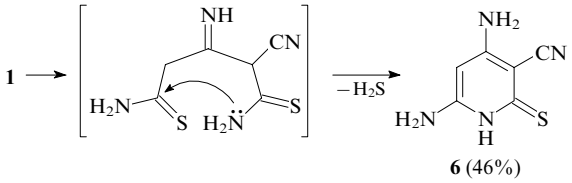
α-Cyanothioacetamide is mainly used in chemical reactions as a C-nucleophile. The most widely encountered reactions include the Thorpe, Knoevenagel and Michael reactions and nucleophilic vinylic substitution (S_NVin).

2.1. Thorpe reaction

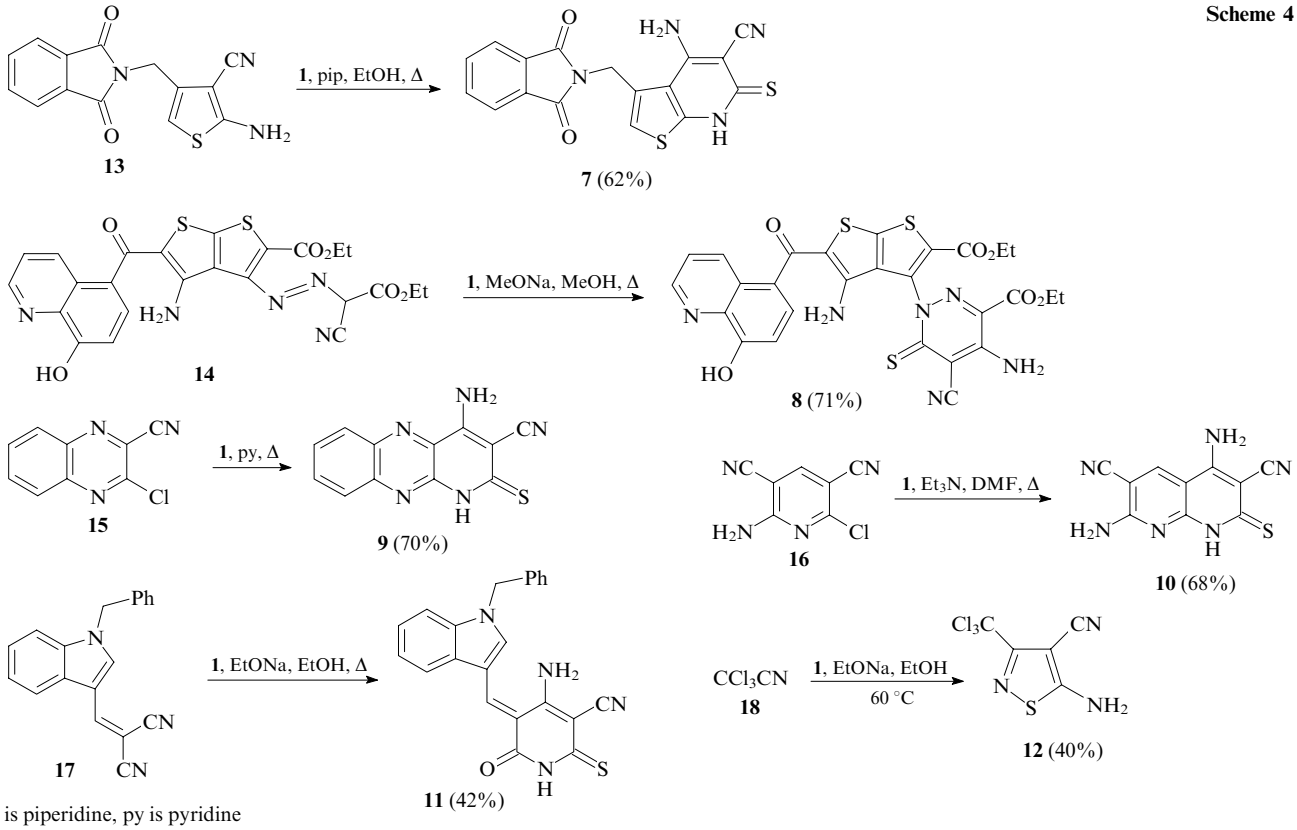
α-Cyanothioacetamide undergoes the Thorpe dimerization in ethanol at 20 °C in the presence of piperidine to give pyridinethione **6** (Scheme 3).[14]

Codimerization of α-cyanothioacetamide with other organic compounds containing a cyano group also does not stop after the formation of adducts, but ends in the formation of various heterocycles — substituted thie-

Scheme 3



Scheme 4

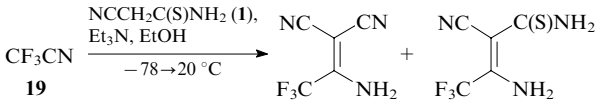


pip is piperidine, py is pyridine

no[2,3-*b*]pyridine (**7**),[15] pyridazine (**8**),[16] pyrido[2,3-*b*]quinoxaline (**9**),[17] 1,8-naphthyridine (**10**),[18] pyridone (**11**)[19] and isothiazole (**12**).[20] The nature of the products depends on the set of substituents present in the reactants, which include thiophene (**13**), thieno[2,3-*b*]thiophene (**14**), quinoxaline (**15**), pyridine (**16**) and indole (**17**) derivatives. In the case of trichloroacetonitrile (**18**), the reaction follows a somewhat different pathway, which is attributable to the oxidative behaviour of compound **18** (Scheme 4).

If chlorine is replaced by fluorine (the oxidative behaviour is absent in this case), linear products of trifluoroacetonitrile (**19**) codimerization, namely, substituted acrylonitriles **20** and **21**, can be obtained (Scheme 5).[21]

Scheme 5

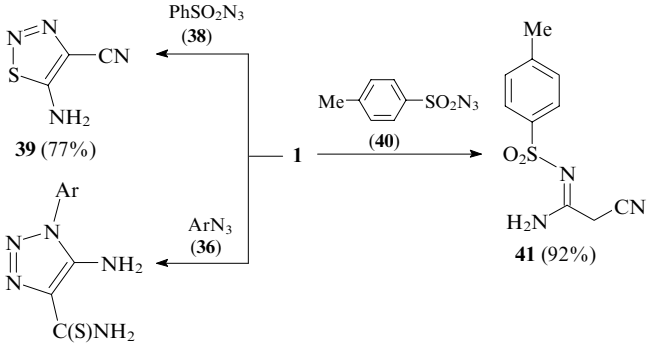


2.2. Reactions with diazonium salts, azides, iso(thio)cyanates and nitroso compounds

As the azo component, α-cyanothioacetamide readily undergoes azo coupling reaction with diazonium salts (for example, compounds **22**–**28**) in refluxing ethanol in the presence of AcONa to give respective hydrazones **29**,[22] **30**[23] and **31**[24] and also fused nitrogen heterocycles **32**,[25] **33**,[26] **34**[27] and **35a**,**b** (Scheme 6).[28]

The reaction of α-cyanothioacetamide with aryl azides **36** in methanol catalyzed by MeONa affords substituted 1,2,3-triazole **37**.[29] Benzenesulfonyl azide (**38**) reacts with CH-acid **1** at 20 °C in pyridine to afford thiadiazole **39**.[30] At the same temperature, but without a solvent, *p*-toluenesulfonyl azide (**40**) was converted to azomethine **41** (Scheme 7).[31]

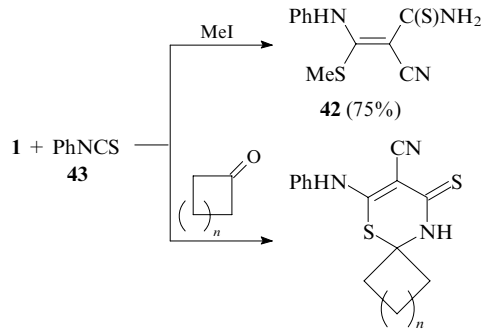
Scheme 7



Ar = Ph, 4-MeC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$

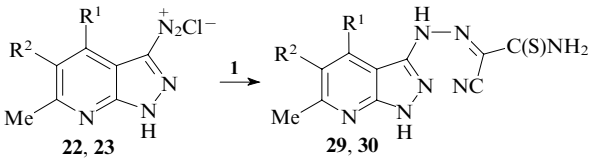
Substituted acrylonitrile **42** is formed upon the reaction of α-cyanothioacetamide with phenyl isocyanate (**43**) and methyl iodide on heating in ethanol in the presence of NaOH.[32] The replacement of methyl iodide by cycloalkanones in this reaction, together with the use of DMF as the solvent in the presence of AcOH and microwave irradiation

Scheme 8

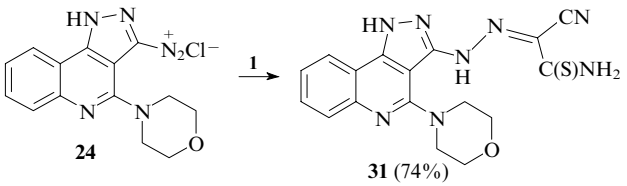


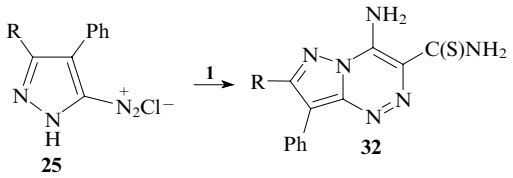
n = 1–4

Scheme 6

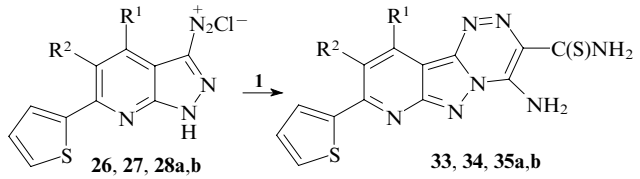


22, **29**: R^2 = H: R^1 = 4-ClC$_6$H$_4$ (55% yield), 2-Fu (89%);
23, **30**: R^2 = EtO$_2$C: R^1 = 4-BrC$_6$H$_4$ (88%), 4-Me$_2$NC$_6$H$_4$ (95%);
Fu is furyl





R = H (50% yield), Me (54%)



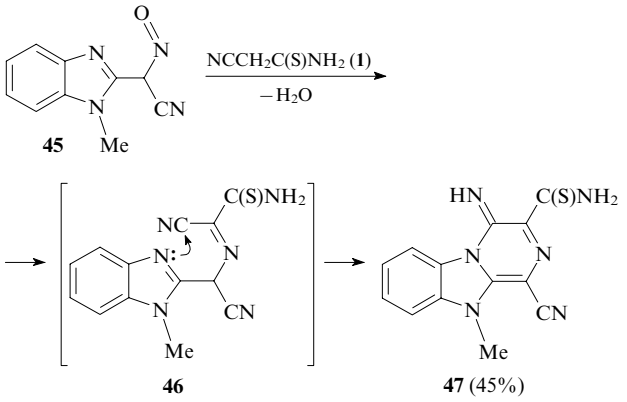
Compounds	R^1	R^2	Product yield (%)
26, **33**	CF_3	H	85
27, **34**	C_6H_4OMe-4	H	81
28a, **35a**	1-Naph	CO_2Et	90
28b, **35b**	2-Naph	CO_2Et	91

Naph is naphthyl

results in the preparation of spiro thiazine systems **44** (Scheme 8).[33]

Benzimidazole derivative **45** containing a nitroso group is condensed with compound **1** in refluxing ethanol in the presence of Et_3N to give intermediate azomethine **46**, which undergoes intramolecular cyclization to system **47** (Scheme 9).[34]

Scheme 9

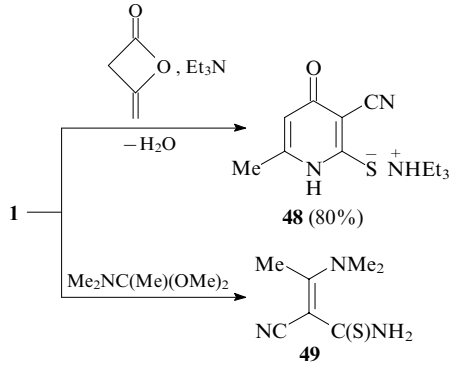


2.3. Nucleophilic substitution

In the reactions of nucleophilic substitution involving α-cyanothioacetamide, hydroxy(alkoxy), amino(alkylamino, arylamino) and mercapto(methylthio) groups and chloride anions can act as nucleofuges. The final products of these reactions are mainly various heterocycles, mainly pyridine derivatives.

The acylation of CH acid **1** with diketene in 1,4-dioxane at 0–10 °C leads to salt **48**.[35] *N*,*N*-Dimethylacetamide dimethylacetal reacts with α-cyanothioacetamide at 20 °C to give substituted but-2-enethioamide **49** (62% yield).[36, 37] The use of methanol as the solvent in this reaction decreases the yield of compound **49** down to 50% (Scheme 10).[37]

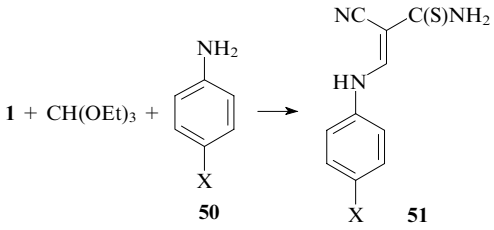
Scheme 10



The formylation of cyanothioacetamide with triethyl orthoformate in the presence of equimolar amounts of aromatic amines **50** proceeding on heating without a solvent furnishes enaminothioamides **51** (Scheme 11).[38, 39]

The reactions of α-cyanothioacetamide with activated alkoxyethylenes proceed very easily and give various products in good yields. However, the direct products of nucleophilic vinylic substitution (S_NVin) are rarely isolated. As a

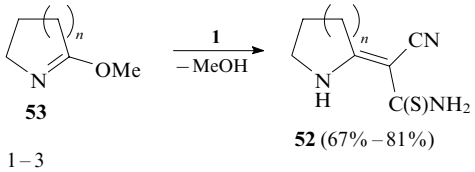
Scheme 11



X	Yield (%)	Ref.
H	90	38
	78	39
Et	85	38

rule, they undergo intramolecular cyclization under the reaction conditions to give nitrogen heterocycles. The amino group of thioamide **1** serves as the source of nitrogen. An example of isolation of the S_NVin products — 2-cyanocrotonic acid thioamides **52** — formed in the reaction of imidates **53** with α-cyanothioacetamide on refluxing the reaction mixture in DMF has been reported (Scheme 12).[40]

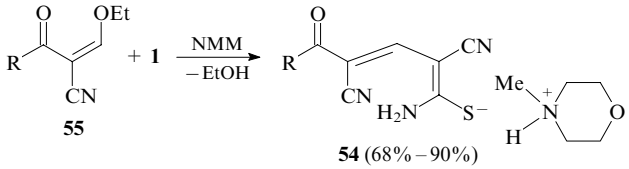
Scheme 12



n = 1–3

The direct products of the S_NVin reaction — salts **54** — can be isolated when ethoxyalkenes **55** are used and the synthesis is carried out under mild conditions (ethanol, 20 °C) (Scheme 13).[41, 42]

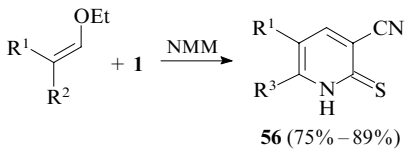
Scheme 13



R = EtO, PhNH, 2-MeC_6H_4NH; NMM is *N*-methylmorpholine

In most of these reactions, salts **54** are intermediates because of intramolecular cyclization, which takes place to give functionalized 4-unsubstituted pyridinethiones **56** (Scheme 14).[41–48]

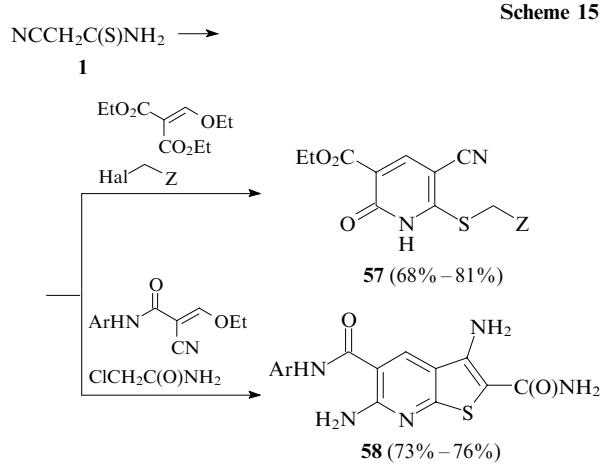
Scheme 14



R^1 = H, Ac, CN, $C(O)CF_3$, Bz, 2-thenoyl, C(O)NHPh; R^2 = $C(O)CF_3$, CN, $C(O)CO_2Et$, Ac; R^3 = NH_2, CF_3, Me, CO_2Et

The involvement of alkyl halides as the third component of the S_NVin reaction allows the one-pot synthesis of functionalized 2-alkylthio-substituted pyridones **57**. When α-chloroacetamide is used as the alkylating agent in this condensation, thieno[2,3-*b*]pyridines **58** are obtained (Scheme 15).[42]

Scheme 15

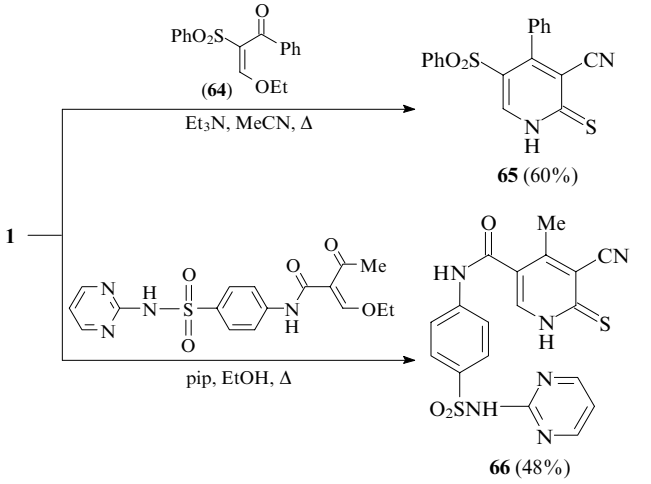


Hal = Cl, Br, I; Z = H, Et, Pr^n, Ar′C(O), Ar′NHC(O), $CH_2{=}CH$; Ar = 4-MeC_6H_4, 4-BrC_6H_4

If allyl bromide is taken as the alkylating agent in the above process, the reaction of α-cyanothioacetamide with ethoxymethylidenemalonate carried out at room temperature in the presence of EtONa and EtOH followed by treatment of the reaction mixture with $KOH-H_2O$ proceeds by an unusual route to give pyrido[2,3-*d*]pyrimidine **59**, the formation of which can be interpreted in the following way. The Michael addition of CH acid **1** to S_NVin reaction intermediate **60** gives adduct **61**, which cyclizes with elimination of diethyl malonate to afford substituted pyridine **62**. The latter undergoes the S_NVin reaction with ethoxymethylidenemalonate, resulting in the formation of fused heterocycle **63**; this product is doubly alkylated at the SH groups to give the final structure **59**, which has been isolated as a side product. The expected pyridone **57** (Z = $CH_2{=}CH$) is formed as the major product (Scheme 16).[49]

In some cases, the reactions of functionalized alkoxyalkenes with α-cyanothioacetamide do not follow the S_NVin pathway. First, the Knoevenagel condensation takes place with the participation of the carbonyl group of the initial 1-acyl-2-alkoxyalkene **64** and then the intramolecular S_NVin reaction occurs, giving rise to 6-unsubstituted pyridine-2-thiones **65**[50] and **66** (Scheme 17).[51]

Scheme 17

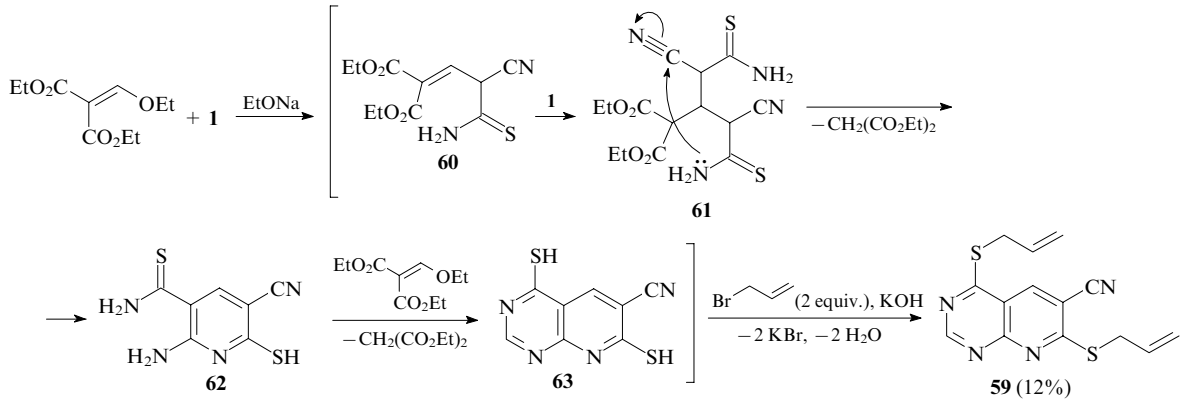


The nucleophilic displacement of the SH group occurs in the Gewald reaction of α-cyanothioacetamide, elemental sulfur and diamides **67** in refluxing ethanol in the presence of EtONa. The reaction affords bis(pyrrolethiones) **68** containing tetrasubstituted five-membered heterocycles (Scheme 18).[52]

The displacement of the methylthio group at the sp^2-hybridized carbon atom by α-cyanothioacetamide proceeds, most often, in refluxing ethanol in the presence of base catalysts. However, the reaction rarely stops after the formation of the substitution product. This pathway is implemented if there is no way for intramolecular cyclization. Benzo[*cd*]indolinium iodide **69** reacts with CH acid **1** in refluxing absolute ethanol in the presence of Et_3N to give (*Z*)-2-(benzo[*cd*]indol-2(1*H*)-ylidene)-2-cyanoethanethioamide (**70**) (Scheme 19).[53]

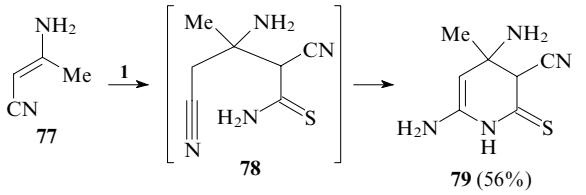
In all other cases, the S_NVin reactions end in the formation of heterocycles. Their nature depends on the set of substituents in the starting alkenes **71a**–**c**, **72**. The reactions give the sodium salts of 4-methylthio-substituted pyridine-2-thiol (**73**)[54, 55] and pyrimidine -4-thiol (**74**),[56] and also 2-mercaptopyridine **75**[57, 58] and partly hydrogenated pyrrolo[1,2-*c*]imidazoles **76** (Scheme 20).[59]

Scheme 16



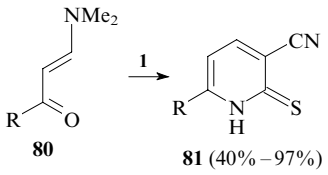
In most S_NVin reactions of α-cyanothioacetamide and enamines, substitution of the amino group takes place. There is a known example in which the primary amino group is preserved, *i.e.*, only the first step takes place, that is, the nucleophilic addition of CH acid **1** to 3-aminocrotonitrile (**77**) on refluxing in 1,4-dioxane. Actually, this is the Michael reaction, which is followed by intramolecular cyclization of the resulting adduct **78** to substituted dihydropyridinethione **79** (Scheme 21).[60]

Scheme 21



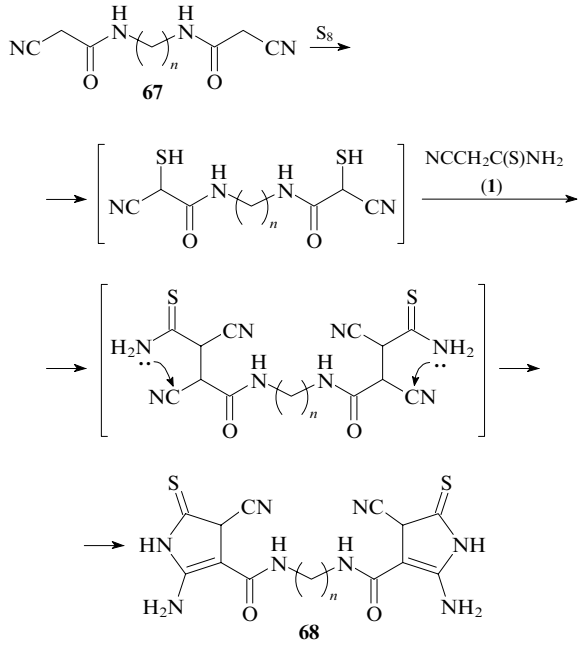
β-Enaminoketones **80** reacts with CH acid **1** by the S_NVin mechanism to give 4,5-unsubstituted pyridines **81**. The reaction occurs in refluxing ethanol in the presence of AcOH,[61] on refluxing in AcOH in the presence of $AcONH_4$,[62,63] on heating in DMF to 50 °C in the presence of Bu^tONa [64] and on refluxing in ethanol in the presence of 1,4-diazabicyclo[2.2.2]octane.[65–68] The highest product yield was attained for R = 3,4-$Cl_2C_6H_3$, while the lowest yield was observed in the case of the pyridyl substituent (Scheme 22).

Scheme 22



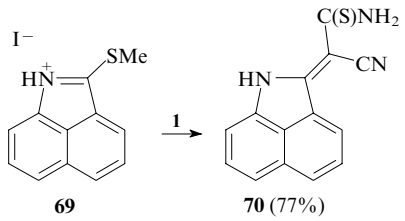
R = 3,4-$Cl_2C_6H_3$, 2-Th, 2-benzo[*b*]furyl, 2-Naph, 2-thenoyl, 3-Py, 2-FC_6H_4, 2-Fu, 2-$MeOC_6H_4$, 3-BrC_6H_4, Ph, 3-$MeOC_6H_4$;
Py is pyridyl, Th is thienyl

Scheme 18



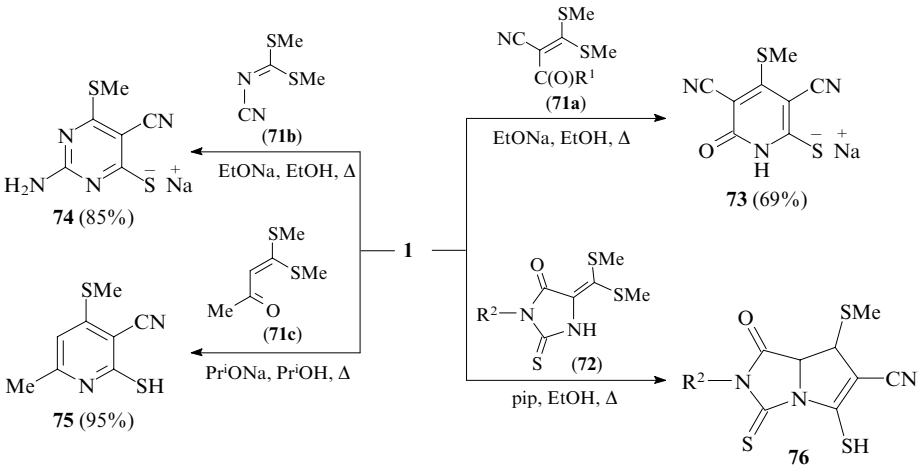
n = 3 (55% yield), 4 (59%)

Scheme 19



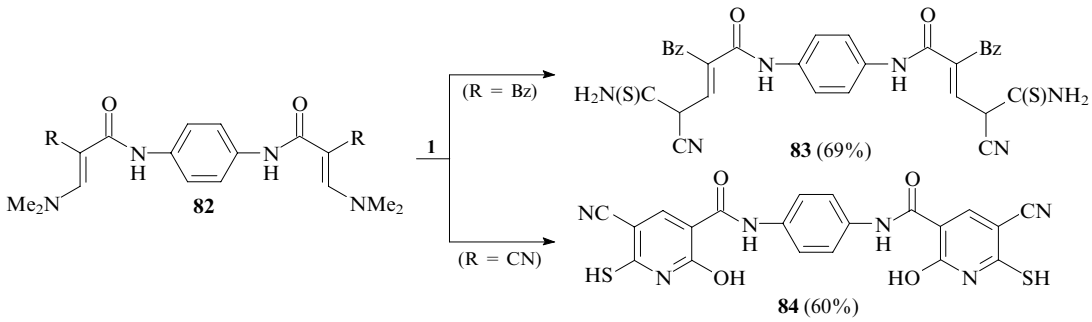
The reaction of α-cyanothioacetamide with bis(β-enaminoketone) **82** containing an anilide group in the α-position provides the isolation of linear products of the S_NVin reaction (**83**). The reaction takes place in refluxing ethanol in the presence of piperidine.[69] The replacement of the benzoyl group in compound **82** by a nitrile group and refluxing of the reaction mixture in DMF in the presence of Et_3N results in the formation of 4-unsubstituted bis-

Scheme 20

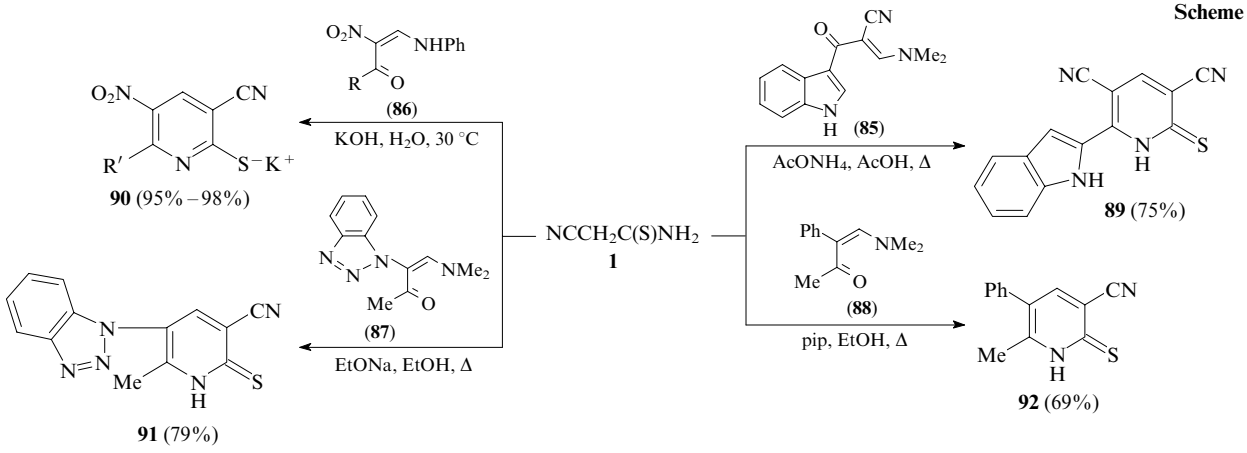


R^1 = EtO (69% yield of **73**), 2-$MeOC_6H_4NH$ (66%); R^2 = H (68% yield of **76**), Ph (71%)

Scheme 23

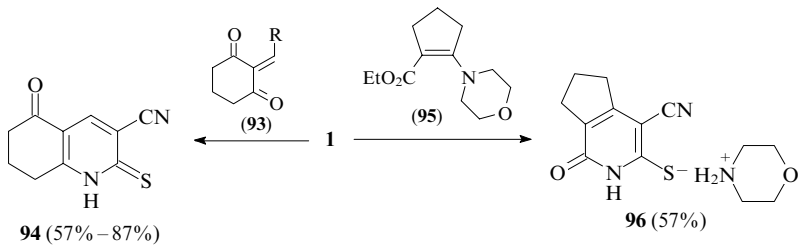


Scheme 24



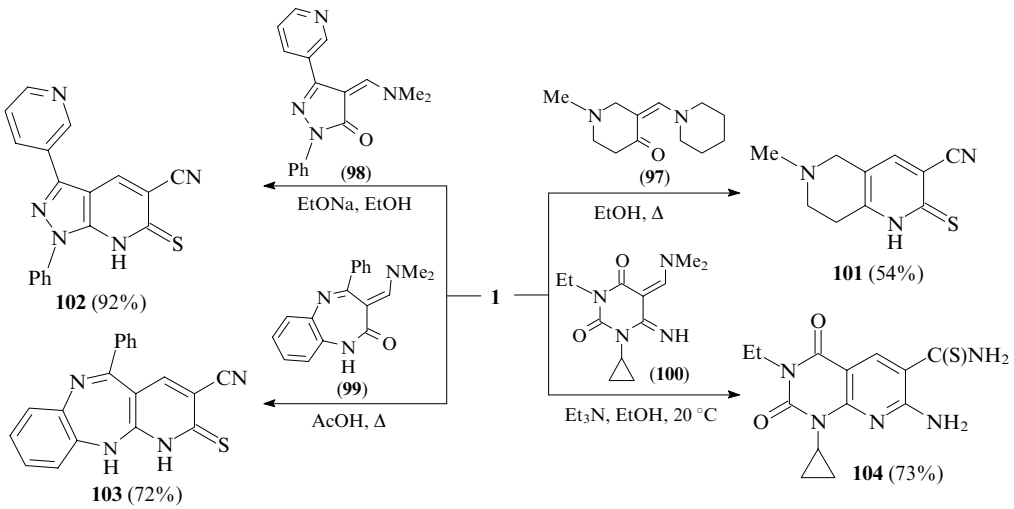
R = OEt, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; R′ = OH, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 25

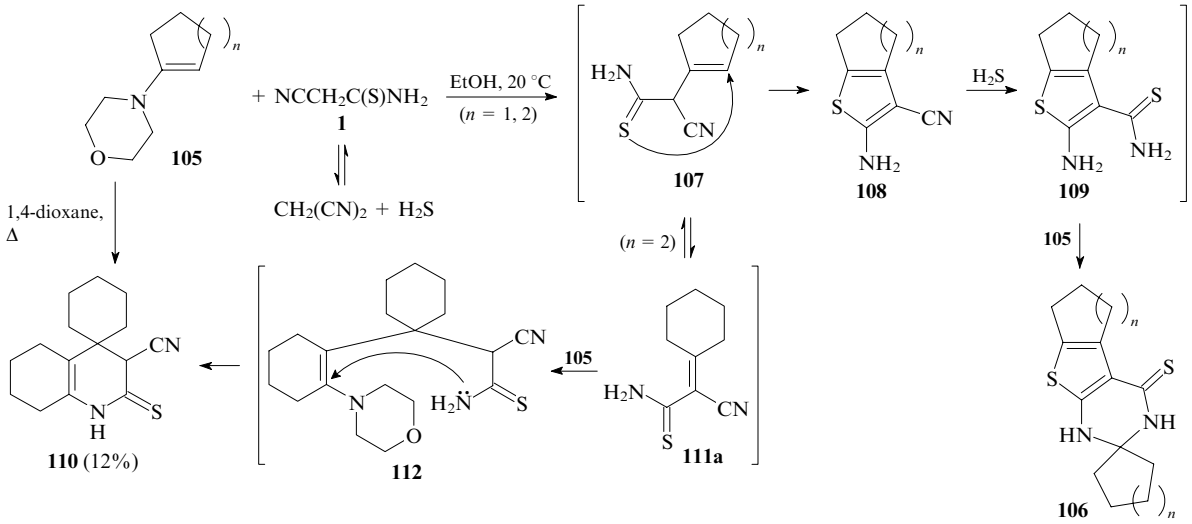


R = NMe_2, NHPh

Scheme 26



Scheme 27



pyridine **84**. The amino group in position 6 of the pyridine ring is hydrolyzed during the reaction (Scheme 23).[70]

β-Enaminoketones **85**–**88** react with α-cyanothioacetamide to give 4-unsubstituted pyridines **89**,[71] **90**,[72] **91**[73] and **92** (Scheme 24).[74]

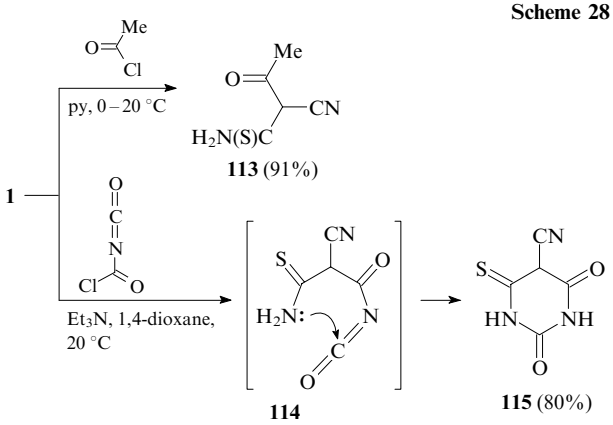
Aminomethylidene cyclohexane-1,3-dione derivatives **93** undergo the S_NVin reactions at 20 °C in the presence of NaH–DMF,[75–77] KOH–EtOH[78] or Et_3N–EtOH[79] to give substituted partly hydrogenated thioxoquinolinone **94**. Enamine **95** is converted by the S_NVin mechanism in ethanol at 20 °C to give morpholinium pyridine-2-thiolate salt **96** (Scheme 25).[80]

Heterocyclic β-enaminoketones **97**–**100** react similarly to compounds **93** to form fused nitrogen heterocycles — 1,6-naphthyridine (**101**),[81] pyrazolopyridine (**102**),[82] benzodiazepine (**103**)[83] and pyridopyrimidine (**104**) (Scheme 26).[84]

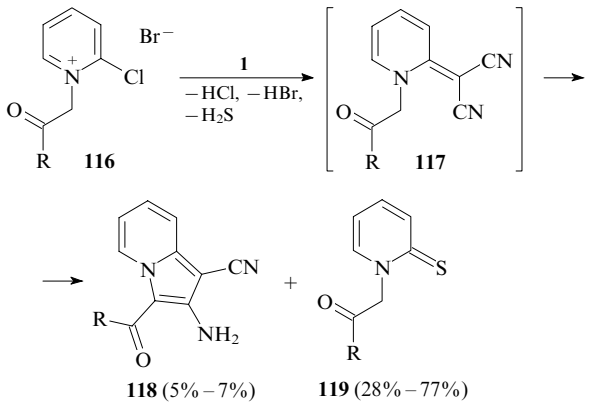
The route of the reaction of morpholinocycloalkenes **105** with CH acid **1** is determined by the reaction conditions, thieno[2,3-*d*]pyrimidines **106** being formed in ethanol at room temperature. The intermediate **107** arising during the S_NVin reaction undergoes intramolecular cyclization to fused thiophene **108**. This is accompanied by H_2S elimination from the starting thioamide **1**; subsequently hydrogen sulfide adds to the nitrile group of molecule **108**. The substituted 2-amino-3-thiocarbamoylthiophene **109** condenses with the starting enamine **105** to give final structure **106** (the yields are 66% for $n = 1$ and 72% for $n = 2$).[85] When this reaction is carried out in 1,4-dioxane with heating of the reaction mixture for 24 h and enamine **105** is taken in a twofold excess, spiro-substituted octahydroquinoline **110** is formed. Apparently, intermediate **111a** adds to enamine **105** to give derivative **112** (Stork alkylation of enamines with alkenes[86]), which then undergoes intramolecular transamination to form final product **110** (Scheme 27).[87]

α-Cyanothioacetamide is readily acylated with acetyl chloride to give 2-acetylcyanothioacetamide (**113**).[88,89] In the first step, chlorocarbonyl isocyanate reacts with the CH acid similarly to acetyl chloride, this gives intermediate **114**, which undergoes intramolecular cyclization to 5-cyanothiobarbituric acid (**115**) (Scheme 28).[90]

Scheme 28



Scheme 29



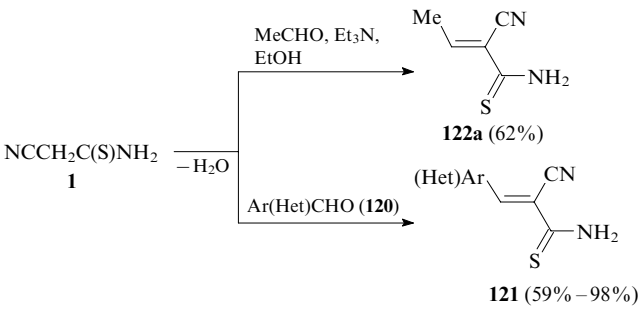
R = OEt, Ph, OMe

N-Benzoyl(alkoxycarbonyl)methyl-2-chloropyridinium bromides **116** react with α-cyanothioacetamide in ethanol at 20 °C in the presence of a twofold excess of Et_3N to give first intermediates **117** and then mixtures of two products — substituted indolizines **118** and pyridinethiones **119** (Scheme 29).[91]

2.4. Knoevenagel condensation

The condensation of α-cyanothioacetamide with carbonyl compounds has been studied in considerable detail, which opens up opportunities for the synthesis of diverse organic compounds with a large practical potential. This is the key reaction for many transformations of α-cyanothioacetamide; when it is carried out with aromatic and heteroaromatic aldehydes **120**, the respective alkenes **121** are formed. Most often, EtOH serves as the solvent, and the employed bases include NaOH,[92] Et_3N,[93–96] piperidine,[97–106] *N*-methylmorpholine[107–110] and *N*-methylpiperazine.[111] The condensation can be carried out without a catalyst on heating in toluene[112] or EtOH.[113,114] In the reaction with aliphatic aldehydes, it is impossible to isolate the alkenes of type **121**, as they undergo further transformations. An example of the synthesis of α-cyanobut-2-enethioamide (**122a**) by the Knoevenagel reaction is known.[115] The highest yields were obtained with 3-nitrobenzaldehyde or 3,4,5-trimethoxybenzaldehyde as the reactant, while the use of 3-furancarbaldehyde resulted in the lowest yield in this reaction, which is attributable to different solubilities of the final alkenes and the possibility of their subsequent transformations (Scheme 30).

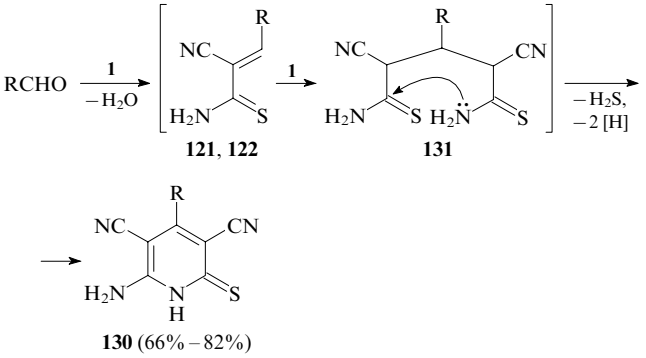
Scheme 30



The use of isovaleric aldehyde as the carbonyl component in this reaction carried out in ethanol at 20 °C in the presence of morpholine resulted in the synthesis of bicyclic product **123**. The mechanism of its formation includes apparently several intermediates (**124**–**129**), which are depicted in Scheme 31.[116]

The condensation of CH acid **1** with other aliphatic aldehydes[117–120] in ethanol at 20 °C and with aromatic aldehydes on refluxing[121–125] in the presence of amines ends in the synthesis of substituted pyridines **130**. The pathway to these products includes the formation of alkenes **121** and **122** in the reaction medium as a result of Knoevenagel condensation followed by the Michael addition of α-cyanothioacetamide to these alkenes. Adduct **131** thus formed is cyclized chemoselectively to pyridines **130**. The highest yield of compounds **130** is attained at the reactant ratio of 2 : 1, which supports the proposed pathway to these products (Scheme 32).

Scheme 32



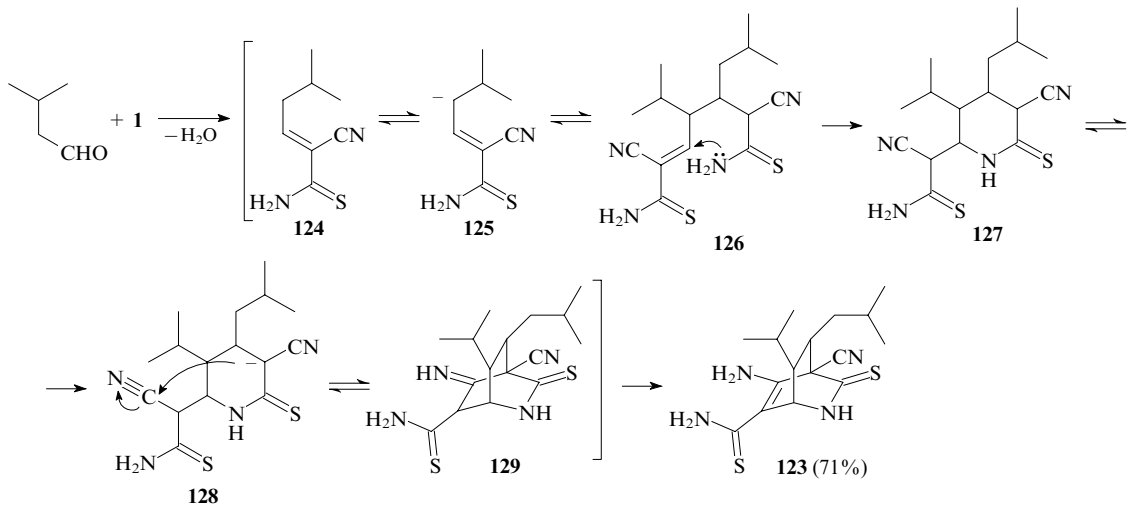
122: R = H, Me, Et, Pr^i, Bu^i, n-C_6H_{13}, n-C_7H_{15}, n-$C_{11}H_{23}$, Me(Ph)CH, Me(Ph)$CHCH_2$, Ph$(CH_2)_2$, Bn; **121**: R = Ar, Het

The aliphatic aldehydes with an active α-hydrogen atom react with α-cyanothioacetamide in ethanol at 20 °C in the presence of morpholine at the 2 : 1 ratio of the reactants to afford 6-unsubstituted morpholinium pyridine-2-thiolates **132** (Scheme 33).[126]

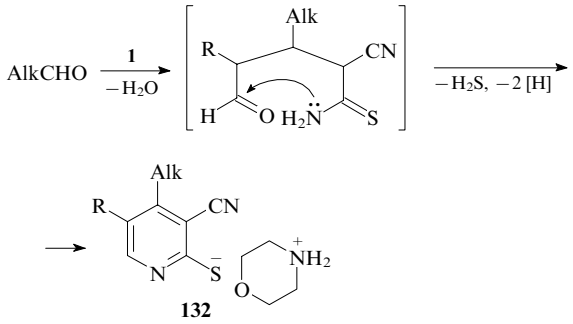
Owing to the geminal positions of other reaction centres with respect to the aldehyde group, the Knoevenagel reaction can be used to prepare products of intramolecular cyclization of the initially formed alkenes — substituted pyridinethiones **133**[127] and **134**[128] and fused pyridinethiones **135**[129] and **136** (Scheme 34).[130]

The Knoevenagel reaction of 3-ethoxysalicylaldehyde (**137**)[131] or pyridoxal analogue **138**[132] with cyanothio-

Scheme 31



Scheme 33



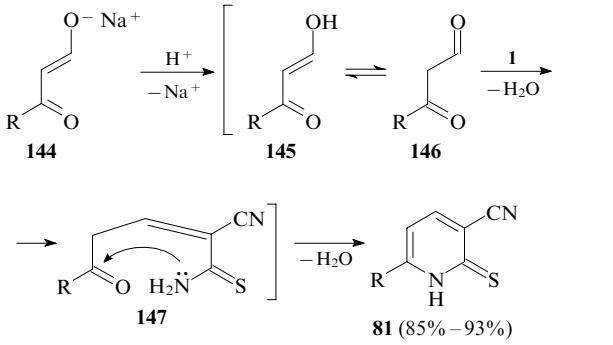
Alk	R	Yield (%)
Et	Me	59
Pr^n	Et	66
Bu^i	Pr^i	71

acetamide results in the formation of fused 2-iminopyrans **139** and **140**, respectively. The reaction occurs in the presence of $AcONH_4$ or piperidine on gentle heating *via* the formation of alkene **141**. The same reaction of 2-piperidinobenzaldehydes **142** affords pyrido[1,2-*a*]quinoline derivatives **143** on heating and microwaving in butanol (Scheme 35).[133]

The sodium salts of β-ketoenols **144** condense with CH acid **1** in ethanol or water on heating in the presence of AcOH and piperidine. The acid medium facilitates the formation of enols **145**, which occur in tautomeric equilibrium with β-ketoaldehydes **146**. In this reaction step, the Knoevenagel condensation takes place to give alkenes **147**, which undergo intramolecular cyclization to 4,5-unsubstituted pyridinethiones **81** (Scheme 36).[134 – 139]

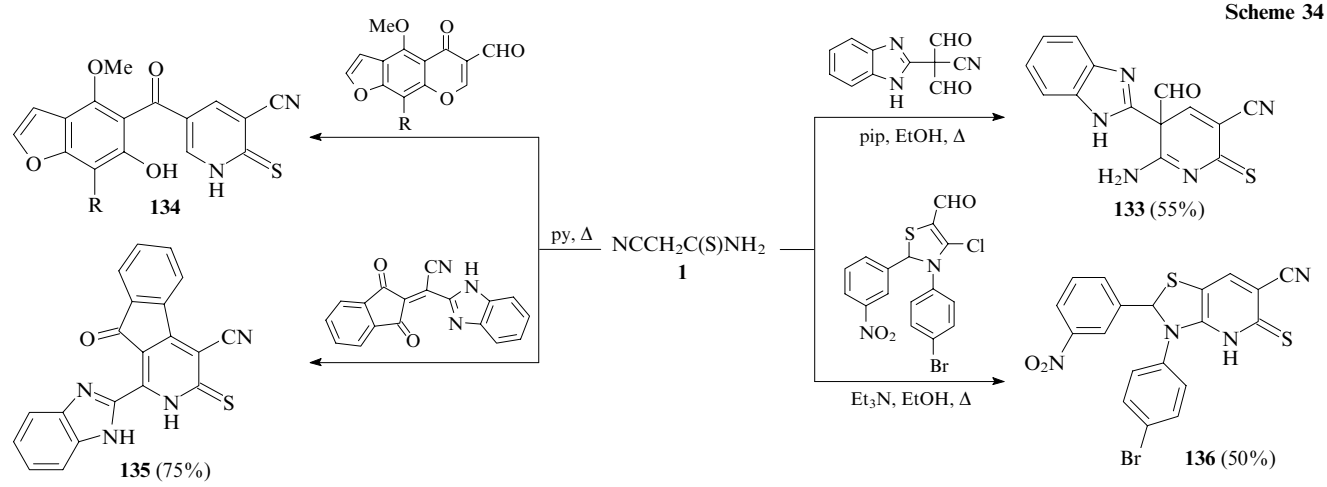
The salts of cyclic ketones **148** and **149** can react with α-cyanothioacetamide as a latent ketoaldehydes. This reaction gives substituted quinolines **150**[140 – 142] and partly

Scheme 36



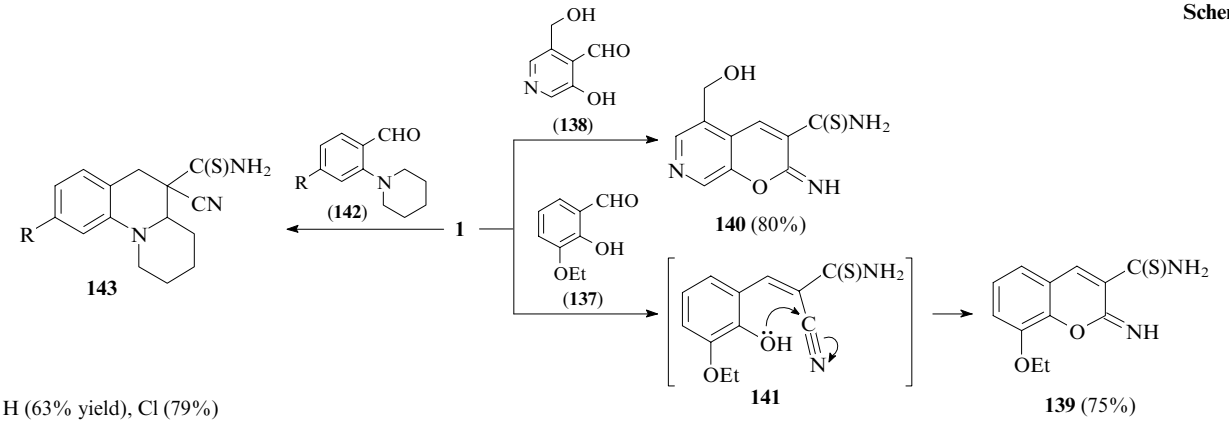
R = Ar, Het

Scheme 34



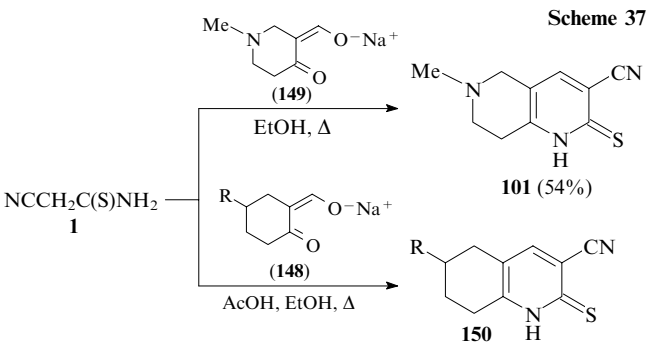
R = H (60% yield), MeO (56%)

Scheme 35



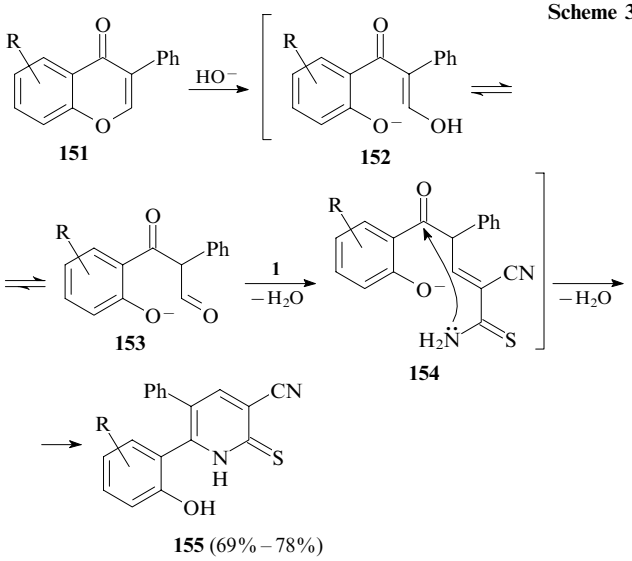
R = H (63% yield), Cl (79%)

Scheme 37



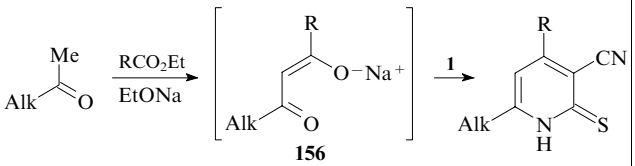
R = H (82% yield), Bu^t (61%)

Scheme 38



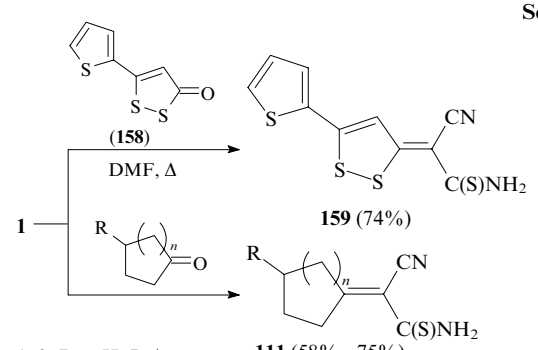
R = H, Alk, OAlk (in different positions)

Scheme 39



Alk = 3,4-(MeO)$_2$C$_6$H$_3$CH$_2$, Bu^i, Bn, cyclo-C$_3$H$_5$, Pr^i; R = CF$_3$, CHF$_2$

Scheme 40

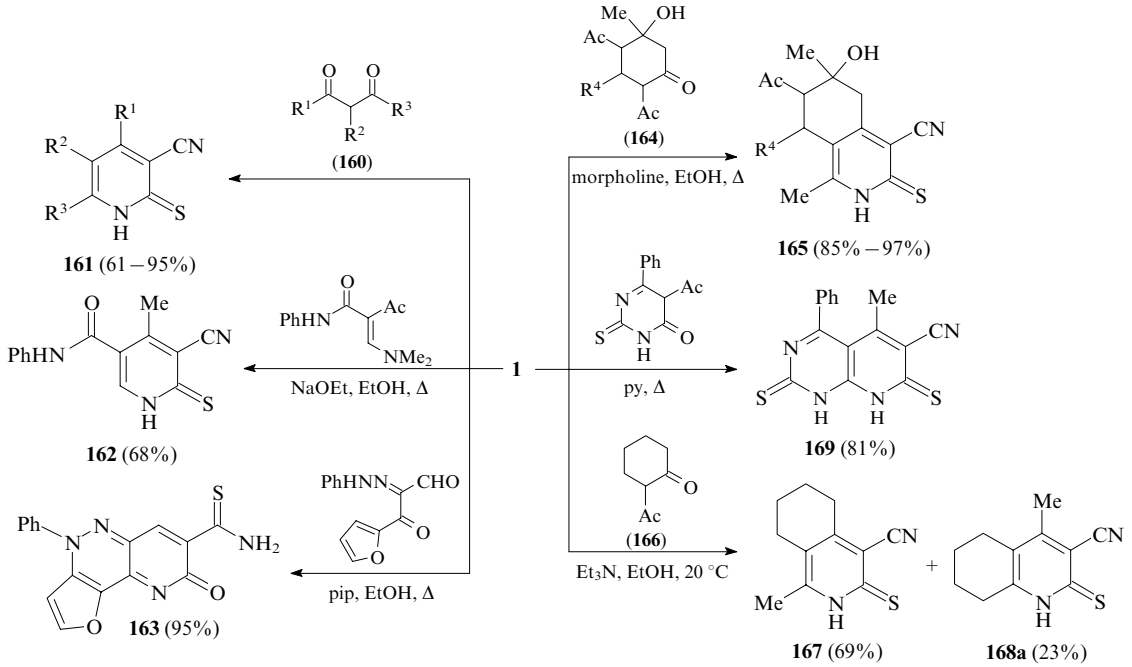


n = 1, 2; R = H, Bu^t

hydrogenated 1,6-naphthyridine **101**, respectively (Scheme 37).[143]

Like salts **144**, substituted isoflavone **151** can also participate in this condensation as a latent ketoaldehyde. In alkaline medium in DMF at 90 °C, the pyran ring is opened to give intermediate **152**, which is converted to ketoaldehyde **153**. The latter participates in the Knoevenagel condensation giving rise to alkene **154**, which undergoes intramolecular cyclization to 4-unsubstituted pyridinethiones **155**, resulting from extensive restructuring (Scheme 38).[144]

Scheme 41



R^1 = Me, CF$_3$, Ar, Het, OEt; R^2 = H, Alk, OAr, CH$_2$Ar; R^3 = Alk, Ar, Het; R^4 = 5-methylfuran-2-yl, 2-Fu, 3-Py; in **160**, instead of R^2 and H, position 2 can be occupied by the =NNHAr moiety; in this case, in **161**, R^2 is N=NAr

The sodium salts **156**, generated *in situ via* the condensation of aliphatic ketones with ethyl di(tri)fluoroacetate in the presence of EtONa, can also react as latent dicarbonyl compounds. They react with CH acid **1** on heating, giving rise to 5-unsubstituted pyridinethiones **157** (Scheme 39).[145]

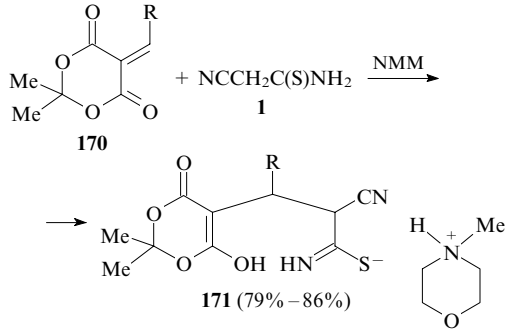
Dehydrodithiolanone **158** and cycloalkanones condense with α-cyanothioacetamide similarly to aromatic aldehydes to give respective alkenes **159**[146] and **111**[147] (Scheme 40).

1,3-Dicarbonyl compounds **160** condense with α-cyanothioacetamide in refluxing ethanol in the presence of aliphatic amines to give 5-unsubstituted pyridinethiones **161** ($R^2 = H$)[148–160] and fully substituted pyridinethiones **161** ($R^2 \neq H$).[161–165] In some cases, after the alkene formation, the α-substituents of compounds **160** are able to react with the amino or cyano group of α-cyanothioacetamide, which affords products **162**[166] and **163**,[167] respectively. The substituted cyclohexanones **164** react under these conditions according to the classic scheme and furnish isoquinolines **165**.[168] Meanwhile, the condensation of 2-acetylcyclohexanone (**166**) with α-cyanothioacetamide leads to a mixture of isoquinoline (**167**) and quinoline (**168a**) derivatives.[169] Substituted thiobarbituric acid is condensed with CH acid **1** in refluxing pyridine being converted to pyridopyrimidine **169** (Scheme 41).[170]

2.5. Michael reaction

Owing to the presence of several functional groups in the molecules of both the Michael donor (α-cyanothioacetamide) and acceptors (functionalized alkenes), the expected adducts can rarely be isolated. The addition of CH acid **1** to Meldrum's acid derivatives **170** in ethanol at 20 °C in the presence of an equimolar amount of *N*-methylmorpholine ends in the formation of salt-like Michael adducts **171** (Scheme 42).[171]

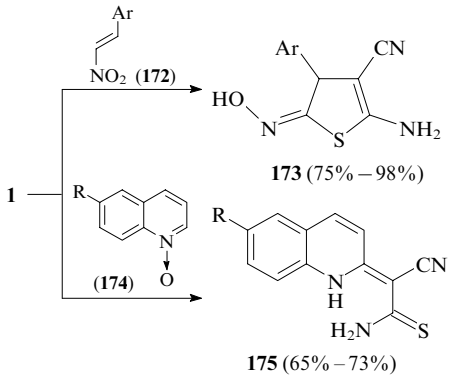
Scheme 42



R = 2-Th, 3-EtO-4-HOC$_6$H$_3$, Ph

Nitrostyrenes **172** react with α-cyanothioacetamide in refluxing ethanol in the presence of morpholine to give substituted dihydrothiophenes **173**.[172] Refluxing of quinoline *N*-oxides **174** with CH acid **1** in acetic anhydride can be used to synthesize quinoline derivatives **175**. In both cases, CH acid **1** adds, in the first step, to the electrohilic site of substituted ethylene **172** or to the α-position of quinoline derivative **174**, respectively. However, in the case of nitroalkenes, intramolecular heterocyclization involving the thiocarbonyl group takes place (Scheme 43).[173]

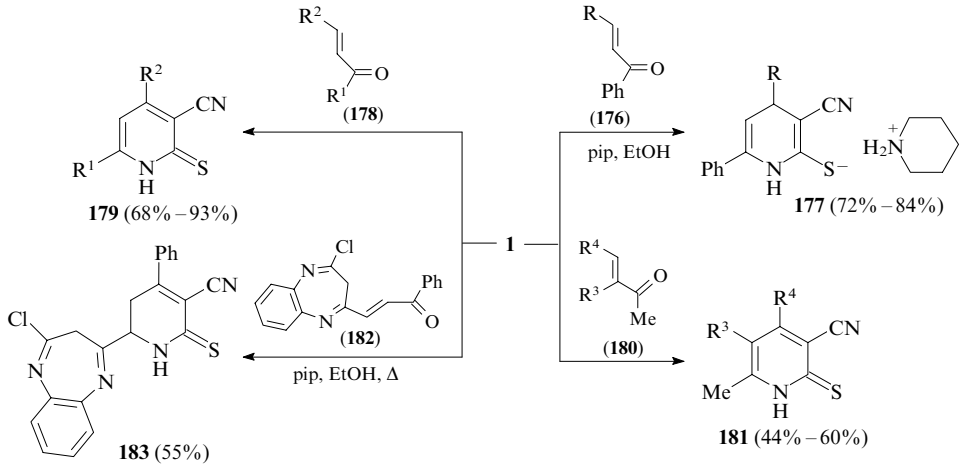
Scheme 43



Ar = Ph, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-Th; R = H, OMe

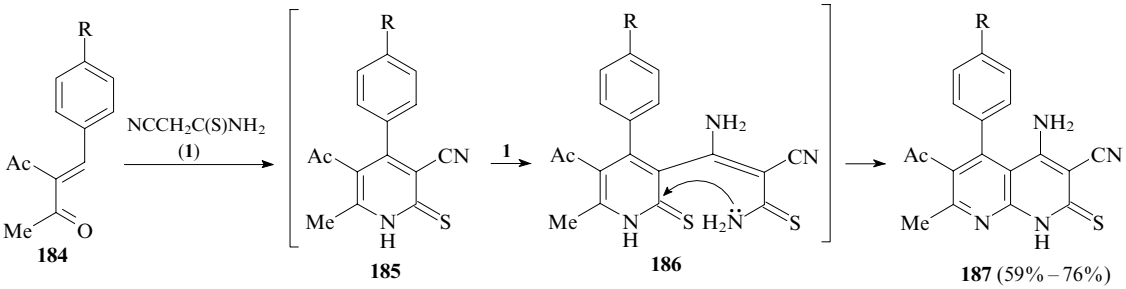
The reaction of chalcones **176** with CH acid **1** at 20 °C gives salts **177**.[174] The reactions of propenones **178** conducted in refluxing EtOH in the presence of AcONH$_4$,[175,176] piperidine,[177–184] NaOH,[185] EtONa[186–188] or 1,4-diazabicyclo[2.2.2]octane,[189] in refluxing methanol in the presence of MeONa[190–192] or in refluxing AcOH[193] can serve for preparing pyridinethiones **179**. α-Substituted propenones **180** are converted to pyridinethiones **181** in this reaction.[194,195] The presence of the benzodiazepine substituent in the β-position of propenone **182** leads to an abnormal reaction pathway under the usual conditions (heating in EtOH in the presence of piperidine): first, the Knoevenagel condensation takes place and then

Scheme 44



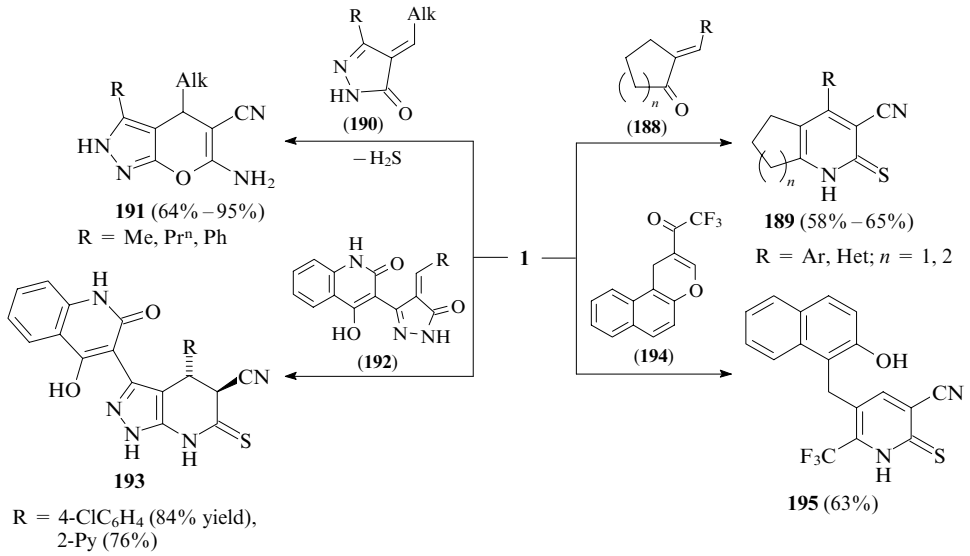
R = Ph, 2-Fu, 2-Th; R^1, R^2 = Me, Ar, Het; R^3 = MeOC(O), Pr^{n}OCH$_2$OC(O), PhS; R^4 = Ph, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4,5-(MeO)$_3$C$_6$H$_2$

Scheme 45



R = H, NO_2, Cl, OMe

Scheme 46



the intramolecular aza-Michael reaction occurs to give 5,6-dihydropyridine-2(1*H*)-thione **183** (Scheme 44).[196]

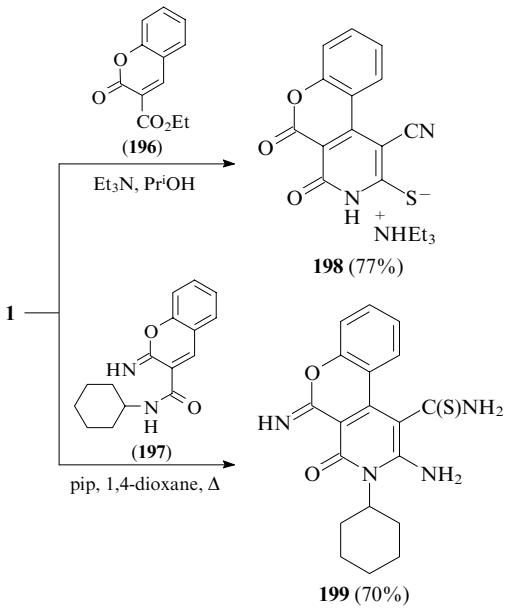
The reaction of alkene **184** with α-cyanothioacetamide conducted in refluxing ethanol in the presence of piperidine does not stop after the formation of expected pyridinethione **185**, as it undergoes the Thorpe reaction with CH acid **1** to form enaminonitrile **186** and then 1,8-naphthyridine system **187** (Scheme 45).[197]

Cycloalkanone derivatives **188** containing an exocyclic double bond in position 2 react with α-cyanothioacetamide on refluxing in lower alcohols in the presence of amines or sodium alkoxides to give fused pyridinethiones **189**.[198 – 202] This reaction for substituted pyrazolones **190** is conducted in ethanol at 20 °C in the presence of morpholine and gives pyrazolopyrans **191**.[203] Refluxing pyrazolones **192** in DMF in the presence of piperidine changes the reaction pathway towards the formation of pyrazolopyridines **193**.[204] The Michael addition of α-cyanothioacetamide **1** to fused pyran **194** in refluxing acetonitrile in the presence of 1,4-diazabicyclo[2.2.2]octane is accompanied by cross-recyclization of compound **194** to give substituted pyridinethione **195** (Scheme 46).[205]

Substituted coumarin **196** and its aza analogue **197** react with CH acid **1** according to the Michael reaction pathway to give heterocyclic systems **198**[206] and **199**,[207] respectively (Scheme 47).

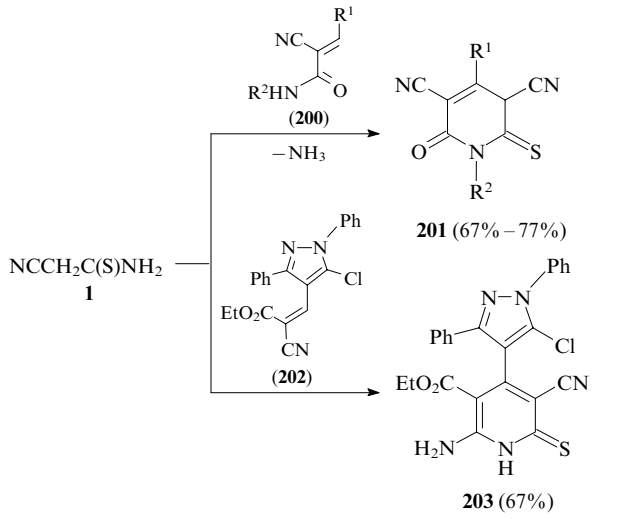
The addition of α-cyanothioacetamide to alkenes **200** takes place in refluxing ethanol in the presence of Et_3N. As the Michael adducts are formed, the anilide moiety intramolecularly transaminates the thioamide moiety with elimination of ammonia to give fully substituted tetrahydropyridinethiones **201**.[208 – 211] The presence of a π-deficient substituent in the β-position of alkene **202** and of the ethoxycarbonyl group instead of the anilide group in its α-position changes the chemoselectivity of conversion of the Michael adduct under similar conditions towards the

Scheme 47



formation of 6-aminopyridinethione derivative **203** (Scheme 48).[212]

Scheme 48

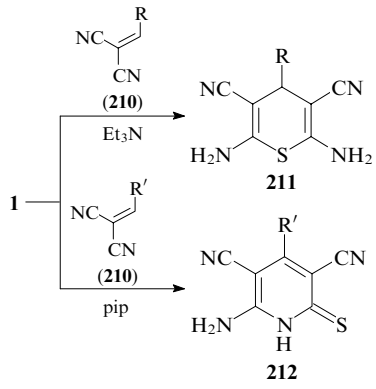


R^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$; R^2 = Ar, Het

Substituted ethyl crotonates **204** add CH acid **1** at 20 °C in ethanol in the presence of *N*-methylmorpholine[213,214] or morpholine[215] to give salts **205**. Similarly to the formation of 4,4-disubstituted pyridines **205**, alkenes **208** and **209** are converted to 4-spiro-substituted pyridines **206**[216] and **207**,[217] respectively. The reaction of acrylothioamide derivative **121a** with α-cyanothioacetamide in refluxing ethanol in the presence of Et_3N is chemoselective: the formation of the Michael adduct is accompanied by intramolecular interaction of the thioamide groups, resulting in the formation of a pyridine ring in compound **130a** (Scheme 49).[218]

The addition of α-cyanothioacetamide to dicyanoalkenes **210** is carried out in ethanol at room temperature in the presence of Et_3N and affords thiopyrans **211**.[219] The use of piperidine as the catalyst for this reaction carried out on refluxing in ethanol directs the reaction along an alternative heterocyclization pathway, resulting in the formation of substituted pyridinethiones **212** (Scheme 50).[220]

Scheme 50



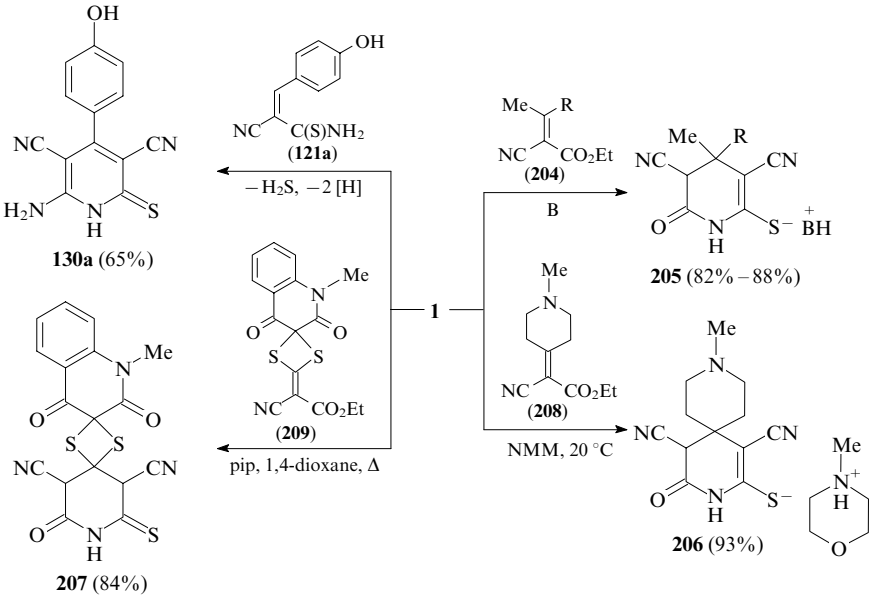
R = 4-MeC_6H_4 (50% yield), 3,4-$(OCH_2O)C_6H_3$ (75%);
R′ = 3-HO-4-$MeOC_6H_3$ (75%), 3-MeO-4-HOC_6H_3 (78%)

Acrylamide and ethyl acrylate derivatives **213** and **214** react with CH acid **1** in ethanol at 20 °C in the presence of *N*-methylmorpholine to afford heterocyclic system **106**[221] and salt **215**,[222] respectively. These compounds could be formed *via* the Michael reaction occurring as the exchange of methylene components (Scheme 51).[223]

2.6. Multicomponent syntheses

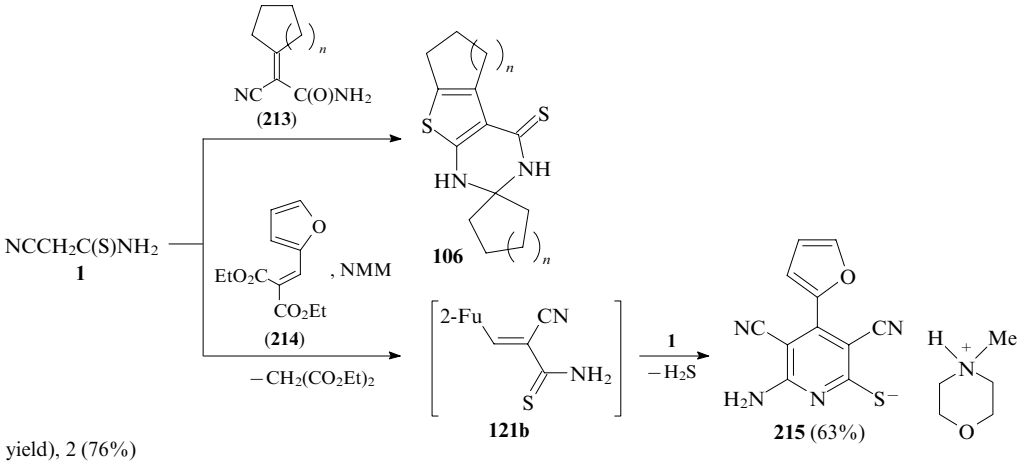
A considerable part of studies devoted to the α-cyanothioacetamide chemistry address multicomponent reactions. This strategy has gained popularity owing to the possibility of one-pot preparation of complex molecules; this reduces the time needed for the synthesis and increases the yields of the desired products. In some cases, the intermediates of these syntheses are unstable and they are not isolated. As a rule, an aldehyde, α-cyanothioacetamide (**1**), CH acid, an alkylating agent and an organic base are introduced into condensations of this type. Ethanol is used, most often, as the solvent. The self-assembly of the molecules often occurs at room temperature.

Scheme 49



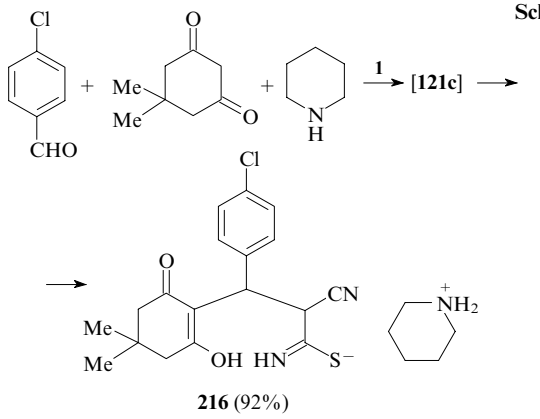
R = Me, Ph, 2-Th; B is *N*-methylmorpholine, morpholine

Scheme 51



n = 1 (68% yield), 2 (76%)

Scheme 52



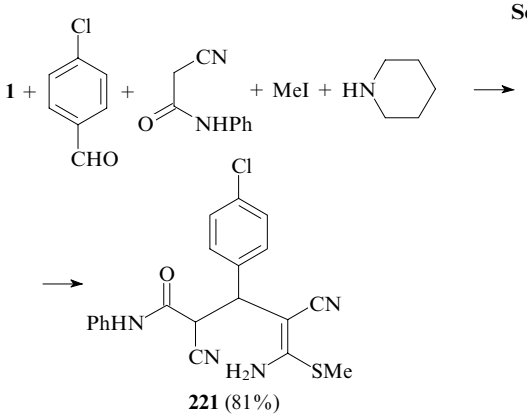
Salt-like Michael adduct **216** is formed in the four-component condensation of α-cyanothioacetamide, 4-chlorobenzaldehyde, dimedone and piperidine in ethanol at 20 °C. The reaction scheme includes the formation of Knoevenagel alkene **121c**, to which dimedone subsequently adds (Scheme 52).[224]

Replacing dimedone by Meldrum's acid (**217**) and replacing piperidine by *N*-methylmorpholine in the above-considered condensation conducted in ethanol at 20 °C leads to the same outcome: salt-like Michael adducts **218** are formed.[225 – 227] On refluxing of the reaction mixture, adducts **218** are converted to tetrahydropyridinethiolate salts **219**,[228 – 230] which were also obtained when Meldrum's acid was replaced by dimethyl malonate.[231]

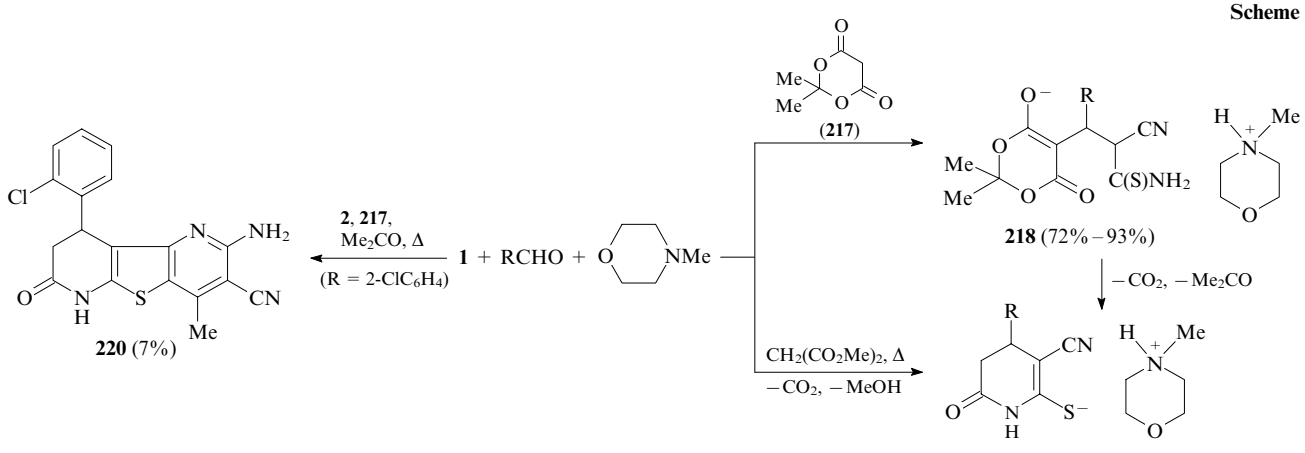
The five-component condensation involving α-cyanothioacetamide, 2-chlorobenzaldehyde, Meldrum's acid, malononitrile (**2**) and acetone occurs on refluxing in EtOH for 10 days in the presence of *N*-methylmorpholine and results in the formation of pyridothienopyridone **220** (Scheme 53).[232]

The multicomponent reaction involving 4-chlorobenzaldehyde, α-cyanothioacetamide, cyanoacetanilide and methyl iodide proceeding in the presence of piperidine at 20 °C ends in the formation of Michael adduct methylthio derivative **221** (Scheme 54).[233]

Scheme 54

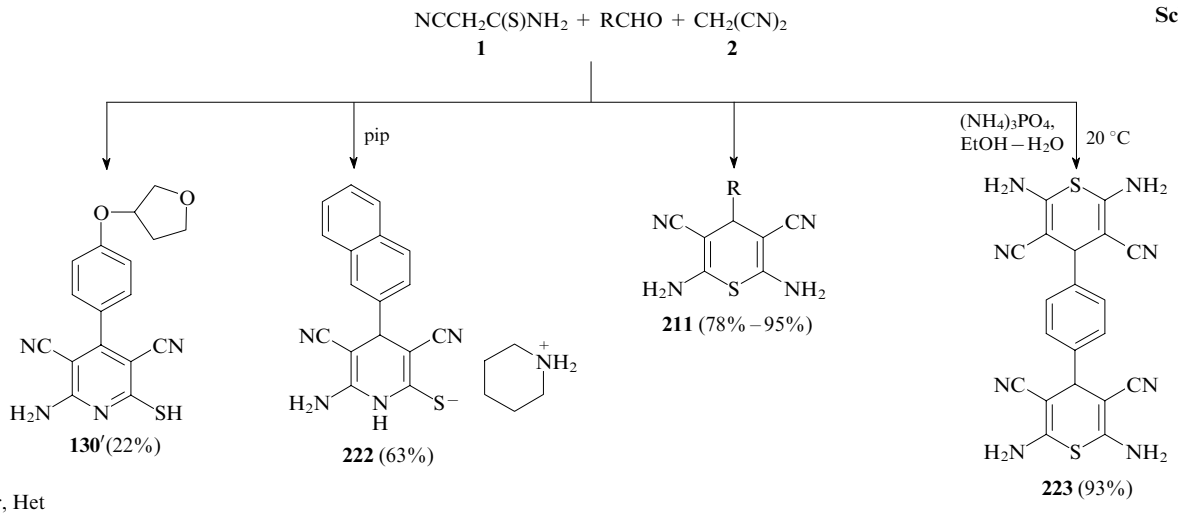


Scheme 53



R = 3-MeO-4-HOC$_6$H$_3$, 2-Fu, 2-EtOC$_6$H$_4$, 2-F-6-ClC$_6$H$_3$, 4-FC$_6$H$_4$, 2-MeOC$_6$H$_4$

Scheme 55

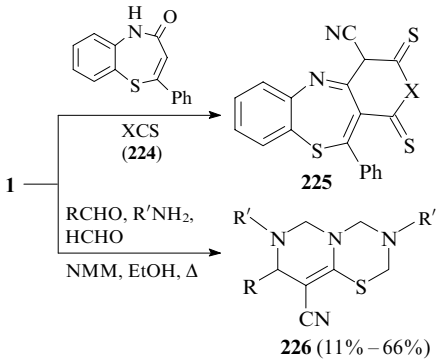


R = Ar, Het

The condensation of α-cyanothioacetamide with aromatic and heteroaromatic aldehydes and malononitrile takes place in ethanol with L-proline as the catalyst at 20 °C (Ref. 234) or in isopropyl alcohol in the presence of Et_3N [235, 236] and gives thiopyrans **211**. The reaction scheme includes the formation of Knoevenagel alkenes and Michael adducts, which are converted to compounds **211** under the reaction conditions. Refluxing of this mixture induces ring transformation of thiopyrans **211** into pyridine **130′** (Ref. 237) or salt **222**.[238] The use of terephthalic aldehyde in this reaction results in the synthesis of 1,4-bis(4-thiopyranyl)benzene **223** (Scheme 55).[239]

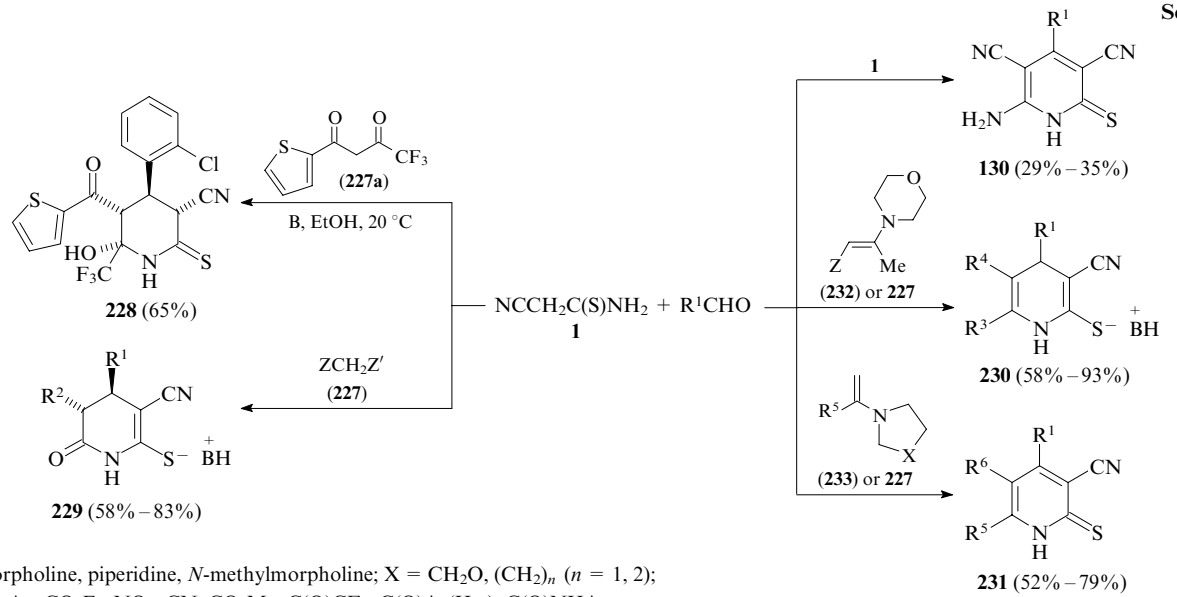
The three-component condensation involving α-cyanothioacetamide, benzothiazepine derivative and cumulenes **224** takes place in a refluxing 1,4-dioxane–DMF mixture in the presence of Et_3N and affords tricyclic fused systems **225**.[240] In the Mannich reaction, α-cyanothioacetamide forms substituted pyrimidothiadiazines **226**. The lowest product yield was observed in the case of acetaldehyde, while the highest yield was attained for 2-chlorobenzaldehyde, which is due to side processes with the participation of aliphatic aldehydes and α-cyanothioacetamide (Scheme 56).[241–243]

Scheme 56



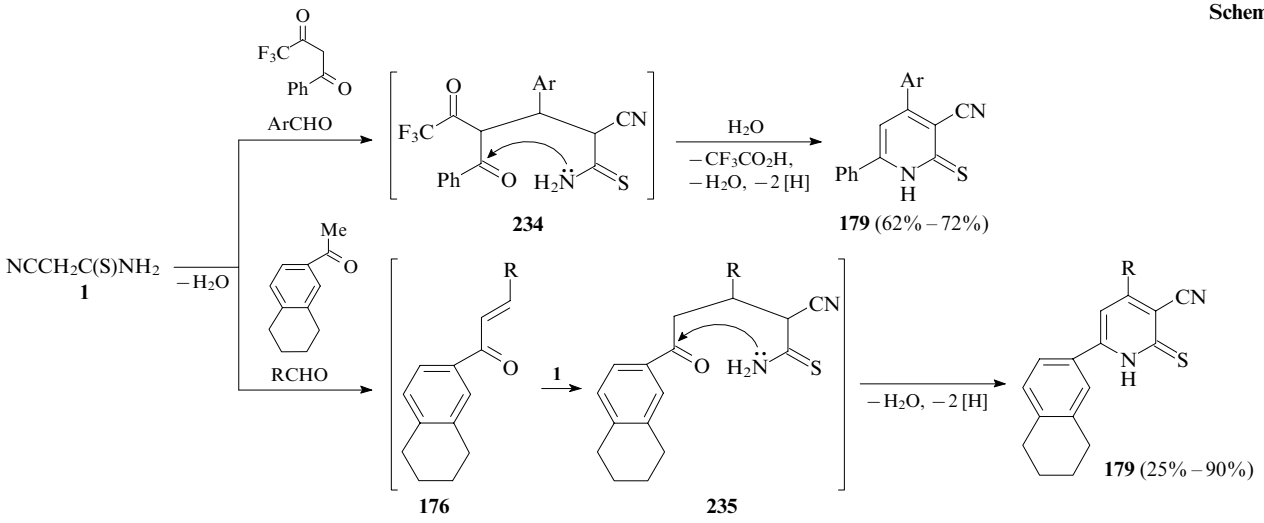
R = Alk, Ar, Het; R′ = Alk, Ph, 3-MeC_6H_4, 4-MeC_6H_4;
X = S (58% yield), PhN (86%)

Scheme 57



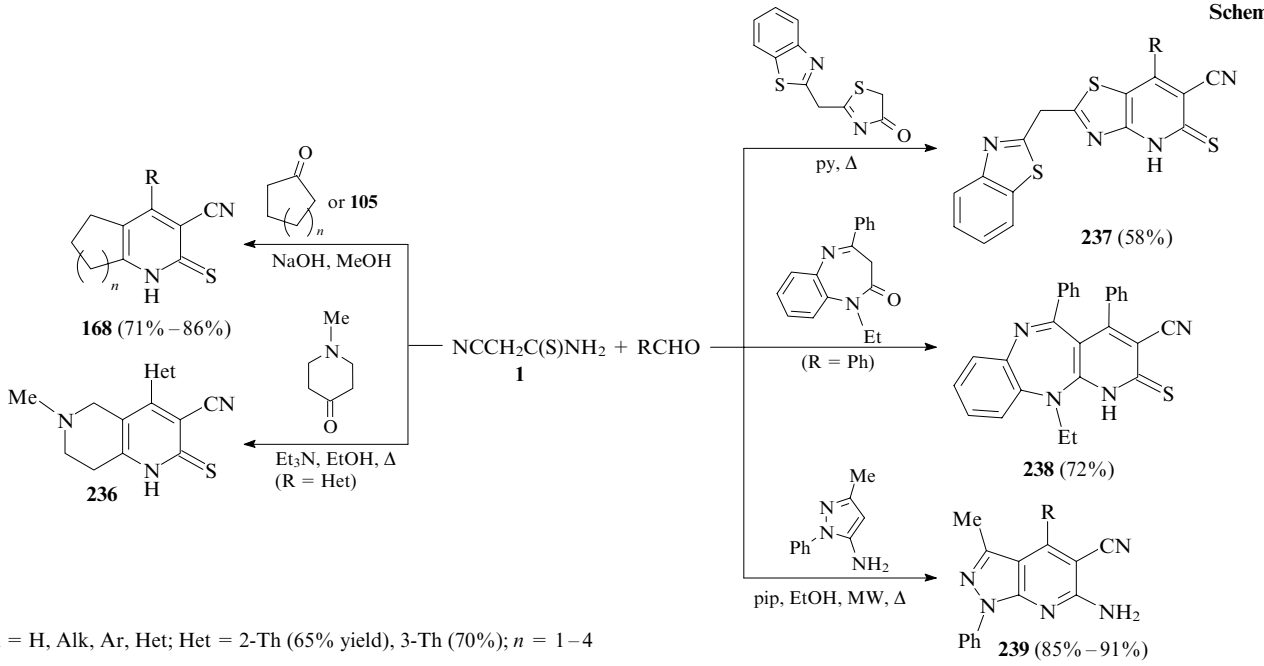
B is morpholine, piperidine, *N*-methylmorpholine; X = CH_2O, $(CH_2)_n$ (n = 1, 2);
Z, Z′ = Ac, CO_2Et, NO_2, CN, CO_2Me, $C(O)CF_3$, C(O)Ar(Het), C(O)NHAr;
R^1 = H, Alk, Ar, Het; R^2 = CO_2Me, CO_2Et, CN, NO_2, Bz, C(O)NHAr;
R^3 = Me, Ar; R^4 = Ac, CO_2Et; R^5 = NH_2, Me, Ph; R^6 = H, CN

Scheme 58



Ar = 2-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$; R = 2,6-F$_2$C$_6$H$_3$, 2,6-Cl$_2$C$_6$H$_3$, 3-EtO-4-HOC$_6$H$_3$, 4-O$_2$NC$_6$H$_4$, 2-Fu

Scheme 59

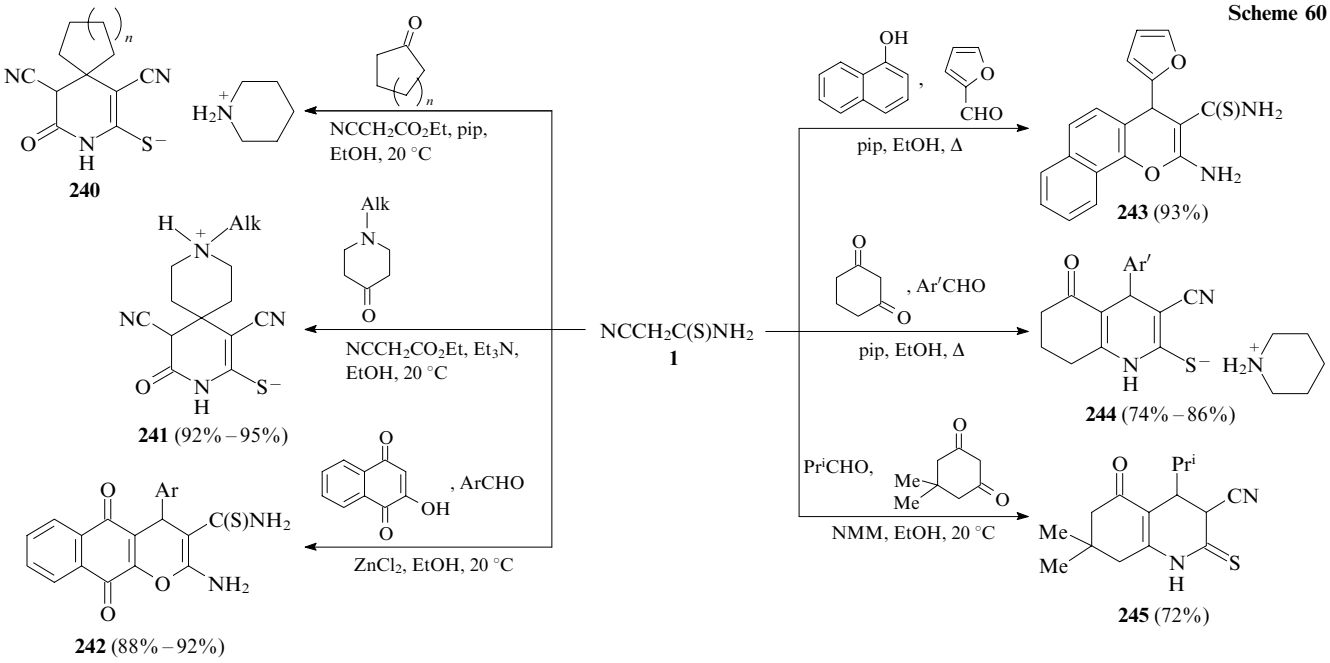


R = H, Alk, Ar, Het; Het = 2-Th (65% yield), 3-Th (70%); n = 1 – 4

The condensation of α-cyanothioacetamide with aliphatic and aromatic aldehydes and CH acids **227** or various enamines is applicable to the synthesis of hexasubstituted piperidine **228**,[244] tetrahydropyridinethiolates **229**[245–258] and dihydropyridinethiolates **230**,[259] and also pyridinethiones **231**.[260–264] The replacement of CH acid **227** by enamines of 1,3-dicarbonyl compounds (**232**)[265,266] or monocarbonyl compounds (**233**)[267–269] does not change the reaction pathway — Knoevenagel alkenes **121** and **122** formed *in situ* alkylate enamines **232** and **233**, which is followed by intramolecular transamination, resulting in the synthesis of salts **230** and 5-unsubstituted pyridinethiones **231**. The lowest yield is observed with increasing solubility of the reactants and products when Z = CO_2 Alk, R′ = Alk. These factors promote the side processes, including the formation of pyridines **130**. CH acid **227** does not have time to undergo the Michael reaction, as this reaction occurs with α-cyanothioacetamide and gives products **130** (Scheme 57).[270–275]

The condensation of α-cyanothioacetamide with aromatic aldehydes, benzoyl-1,1,1-trifluoroacetone and *N*-methylmorpholine in ethanol at 20 °C follows an unusual pathway. Intermediates **234** undergo acyl cleavage to give pyridinethiones **179** (Scheme 58).[276,277] The three-component condensation of CH acid **1** with aromatic aldehydes and 2-acetyltetrahydronaphthalene occurring in refluxing ethanol[278] or butan-1-ol[279] in the presence of $AcONH_4$ starts with the Claisen condensation. Subsequently, α-cyanothioacetamide undergoes the Michael addition to the resulting propenones **176**. Adducts **235** thus formed are intramolecularly cyclized under the reaction conditions to give pyridines **179**. The use of 3-ethoxy-4-hydroxybenzaldehyde provided the highest product yield, while the reaction of 2,6-dichlorobenzaldehyde resulted in the lowest yield,

Scheme 60



Alk = Me, Et, Pr^n, Pr^i; Ar = Ph, 2-HOC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 3,4,5-$Me_3C_6H_2$; Ar′ = 2-ClC_6H_4, 4-ClC_6H_4; n = 1 (76% yield), 2 (67%)

apparently, because of the steric effect (see Scheme 58).[278, 279]

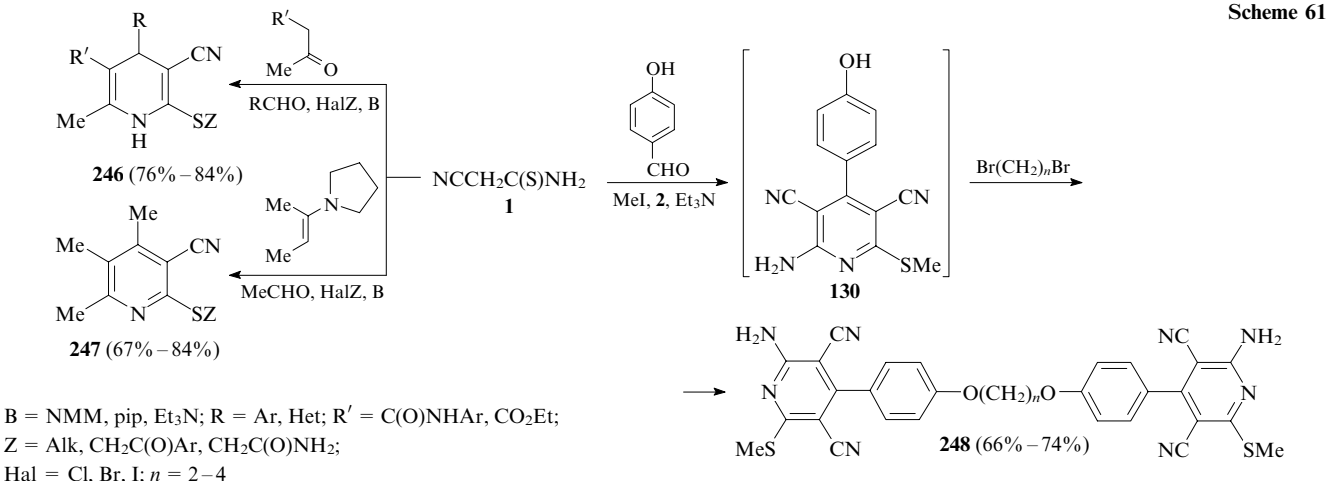
The three-component condensation of α-cyanothioacetamide, aromatic aldehydes and cycloalkanones[280] or their enamines[281 – 287] affords alicyclo[*b*]annulated pyridinethiones **168**. When heterocyclic carbonyl compounds are used as CH acids in this condensation, 1,6-naphthyridines **236**,[288] thiazolopyridine **237**[289] and pyridobenzodiazepine **238**,[290] respectively, are obtained. The replacement of ketones by aminopyrazoles in this scheme gives rise to pyrazolopyridines **239** (Scheme 59).[291]

Under mild conditions, α-cyanothioacetamide condenses with cycloalkanones and ethyl cyanoacetate. As opposed to Scheme 59, in this case, ketones act as the carbonyl components rather than CH acids. Ethyl cyanoacetate adds to the initially formed alkenes **111**; this is followed by intramolecular ammonolysis of the ester group by the amino group of the thioamide moiety to give salts **240**.[292, 293] The reaction of α-cyanothioacetamide with ethyl cyanoacetate and *N*-alkylpiperidones proceeds in a similar way, giving rise to betaines **241**.[294] The three-component condensation, with the Knoevenagel reaction being the key step, was used to prepare fused pyrans **242**,[295] **243**,[296] salts **244**[297] and substituted octahydroquinoline **245** (Scheme 60).[298]

The increase in the number of components in the above-considered condensations by adding alkylating agents can serve for one-pot synthesis of dihydropyridine derivatives as thioethers **246**,[299, 300] pyridines **247**[301] and bis(pyridin-4-ylphenoxy)alkanes **248** (Scheme 61).[302]

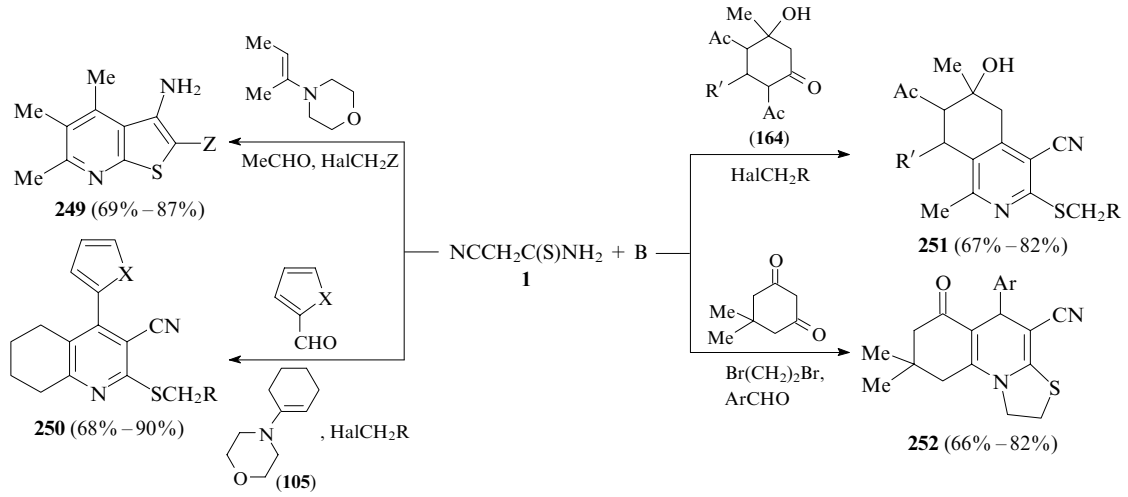
The multicomponent condensations involving α-cyanothioacetamide, carbonyl compounds, CH acids and alkylating agents are convenient for the preparation of thieno[2,3-*b*]pyridines **249**,[303] partly hydrogenated quinolines **250**,[304] isoquinolines **251**[305] and thiazoloquinolines **252**.[306] The self-assembly of the molecules takes place in ethanol at room temperature in the presence of organic base and includes the following reaction sequence: Knoevenagel condensation – Michael reaction – intramolecular heterocyclization – alkylation (Scheme 62).

Scheme 61



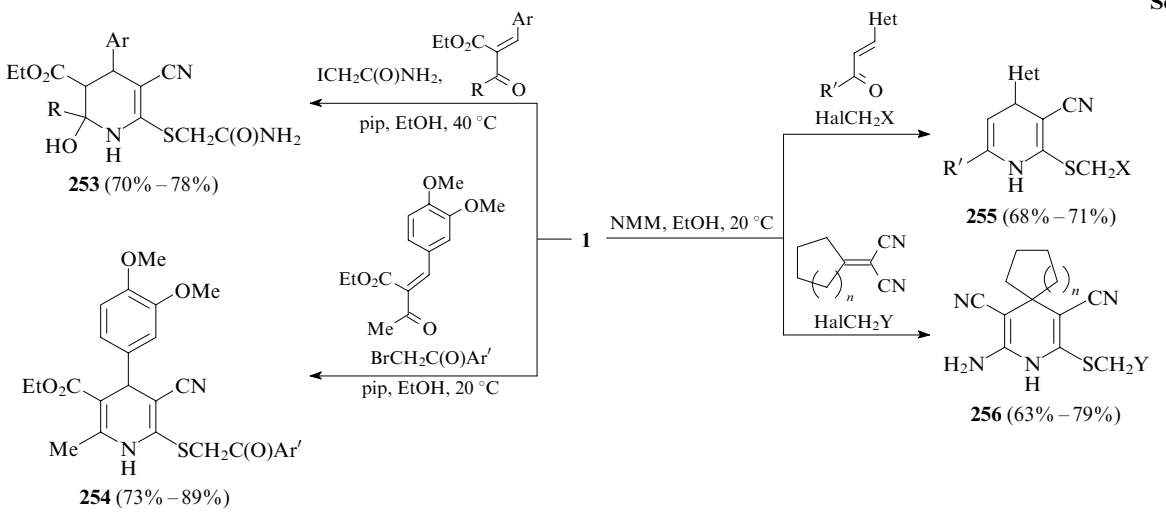
B = NMM, pip, Et_3N; R = Ar, Het; R′ = C(O)NHAr, CO_2Et;
Z = Alk, $CH_2C(O)Ar$, $CH_2C(O)NH_2$;
Hal = Cl. Br. I: n = 2 – 4

Scheme 62



Hal = Cl, Br; Z = C(O)Ar, C(O)NHAr; X = O, S; R = H, CN, CO_2Me, $C(O)NH_2$, CH═CH_2; R′ is 5-methylfuran-2-yl, 2-Fu, 3-Py, Ph, C_6H_4Et-4; B is piperidine, morpholine, *N*-methylmorpholine

Scheme 63



R = Me, Ph, 4-$O_2NC_6H_4$; R′ = 2-Th, Ph, 4-BrC_6H_4; Ar = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$; Ar′ = 2,4-$(MeO)_2C_6H_3$, 4-ClC_6H_4, 4-$MeOC_6H_4$; Het = 2-Th, 2-Fu, 3-Py; Hal = Cl, Br, I; X = H, $H_2NC(O)$, 4-$BrC_6H_4NHC(O)$, $MeCO_2$, NC, $BnCO_2$, $PhNHC(O)$, 4-$MeC_6H_4C(O)$, 2-MeC_6H_4, 3,4-$Cl_2C_6H_3C(O)$; Y = H, 2-MeC_6H_4, Bn, CH_2═CH, 4-$BrC_6H_4NHC(O)$; *n* = 1, 2

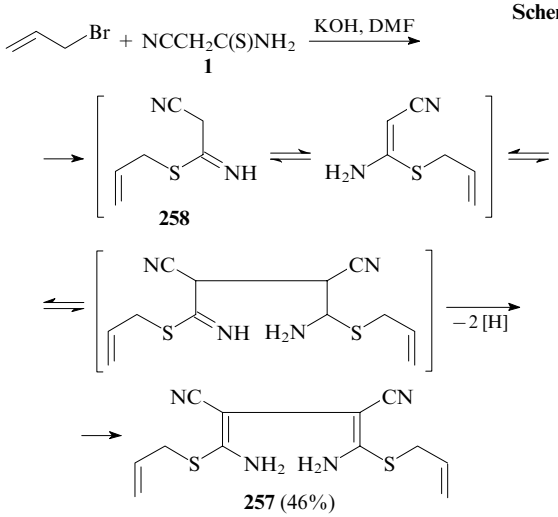
The multicomponent syntheses in which the addition of α-cyanothioacetamide to activated alkenes is the key step are used to prepare functionalized 2-alkylthio-substituted tetrahydropyridines **253**[307] and dihydropyridines **254**,[308] **255** [309] and **256** (Scheme 63).[310]

3. Nucleophilic reactions of the thiocarbonyl group

The reactions of electrophiles at the sulfur atom of molecule **1** is usually not the final step of the process, because of the multifunctional nature of both α-cyanothioacetamide and the electrohile that reacts with it. If allyl bromide is used as the alkylating agent, the reaction carried out in DMF in an alkaline medium at 20 °C affords 2,3-bis[allylthio(amino)-methylene]succinonitrile (**257**) as a result of oxidative dimerization of intermediates **258** (Scheme 64).[311]

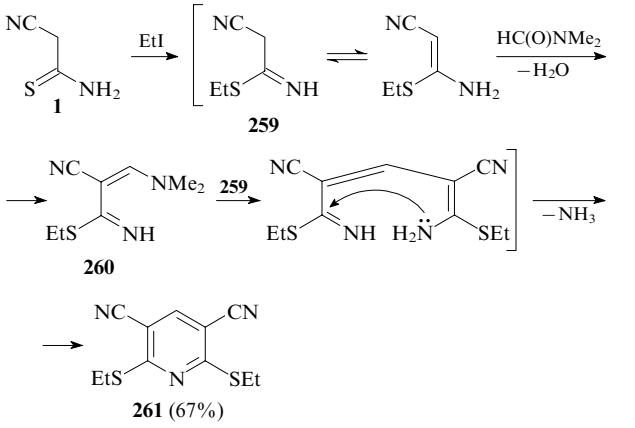
The reaction of CH acid **1** with ethyl iodide in DMF follows a different pathway. As a result of prototropic amine – imine tautomerism, intermediate **259** can condense

Scheme 64



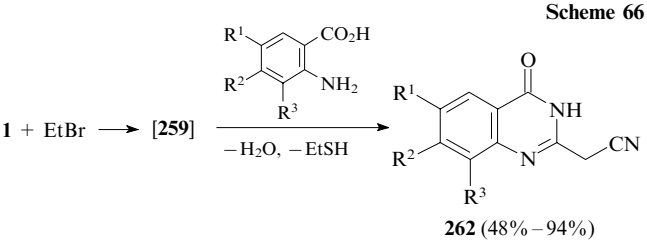
with DMF to give enamine **260**. This is followed by nucleophilic vinylic substitution and then intramolecular transamination to give pyridine **261** (Scheme 65).[312]

Scheme 65



The three-component condensation of α-cyanothioacetamide, ethyl bromide and substituted anthranilic acid on refluxing in ethanol in the presence of EtONa furnishes quinazoline derivatives **262**. Thioimidate **259** undergoes the S_NVin reaction with anthranilic acid followed by intramolecular cyclization. The 2- and 5-substituents of anthranilic acid have considerable influence on the yields of final products, with the yield being low with electron-withdrawing substituents in position 5 because of decreasing basicity of the amino group. An increase in the bulk of the 2-substituent creates steric hindrance (Scheme 66).[313]

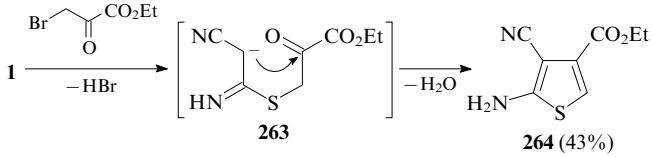
Scheme 66



R^1 = Me, OMe, Cl, Br, I; R^2 = H, OMe, Cl; R^3 = H, Me

The alkylation of α-cyanothioacetamide with ethyl 3-bromopyruvate in an AcOH–pyridine mixture in 4 : 1 volume ratio at 50 °C does not stop after the formation of intermediate **263**, which undergoes the intramolecular Knoevenagel condensation and gives substituted thiophene **264** (Scheme 67).[314, 315]

Scheme 67

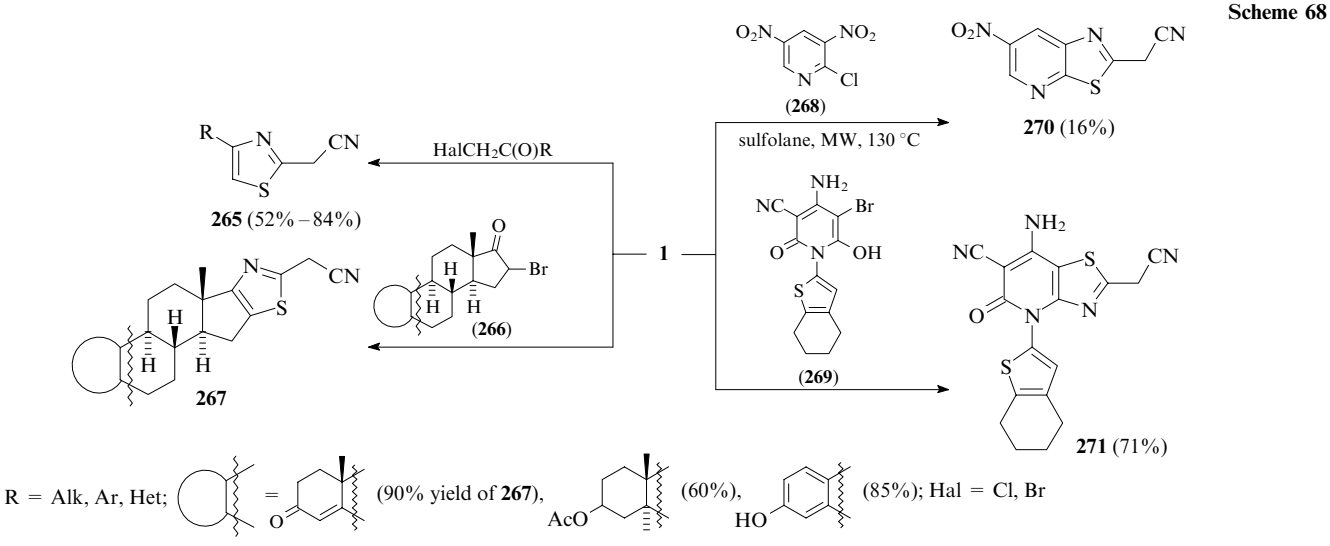


CH acid **1** easily undergoes the Hantzsch reaction on heating in ethanol in the presence of Et_3N,[316–331] in isopropyl alcohol,[332, 333] anhydrous tetrahydrofuran[334, 335] or acetone[336] to give substituted thiazoles **265**. Carbocyclic α-halocarbonyl compounds **266** are converted in this reaction to alicyclo[*d*]fused thiazoles **267**.[337–339] The presence of functional groups in pyridines **268** and **269** in the vicinal position to the halogen atom does not change the reaction pathway — thiazolopyridines **270**[340] and **271**,[341] respectively, are formed. The low yield of compound **270** is apparently attributable to the drastic reaction conditions, which facilitate side processes — elimination of H_2S from α-cyanothioacetamide and its dimerization (Scheme 68).

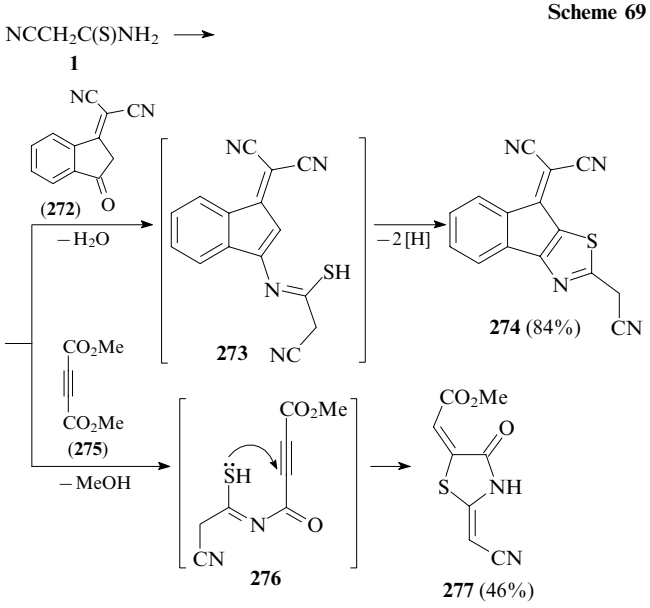
4. Nucleophilic reactions of the amino group

The transformations of α-cyanothioacetamide in which the amino group is involved in the key step are rarely described in the literature. For example, on refluxing of indanone derivative **272** in a DMSO–EtOH mixture, azomethine **273** formed in the reaction undergoes intramolecular cyclization to give fused system **274**.[342] Dimethyl but-2-ynedioate (**275**) reacts with α-cyanothioacetamide in chloroform at room temperature. The product of ammonolysis **276** formed in the first step undergoes intramolecular cyclization, like intermediate **273**, to give substituted thiazolidinone **277** (Scheme 69).[343]

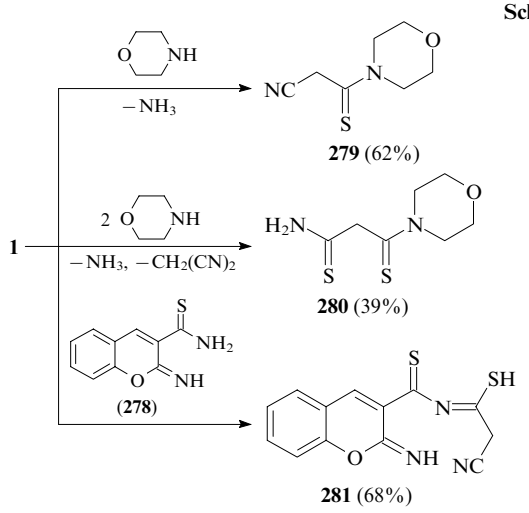
Scheme 68



Scheme 69



Scheme 70



5. Electrohilic reactions of the thiocarbonyl group

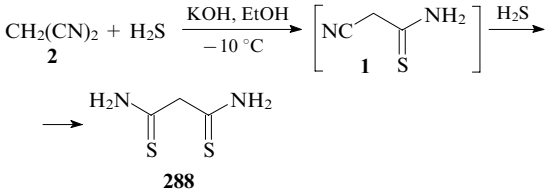
The thioamide group of α-cyanothioacetamide can act as an electrophile; for example, transamination of compound **1** has been studied in considerable detail. The reaction with morpholine [344, 345] proceeds in ethanol at 20 °C and gives different products depending on the reactant ratio. When the ratio is 1 : 1, 3-morpholino-3-thioxopropanenitrile (**279**) is formed, while the 1 : 2 ratio results in the formation of 3-morpholino-3-thioxopropanethioamide (**280**). The reaction of substituted coumarin aza analogue **278** with α-cyanothioacetamide in ethanol in the presence of piperidine affords the corresponding thioacylation, or transamination, product — coumarin aza analogue **281** (Scheme 70).[346]

6. Electrohilic reactions of the nitrile group

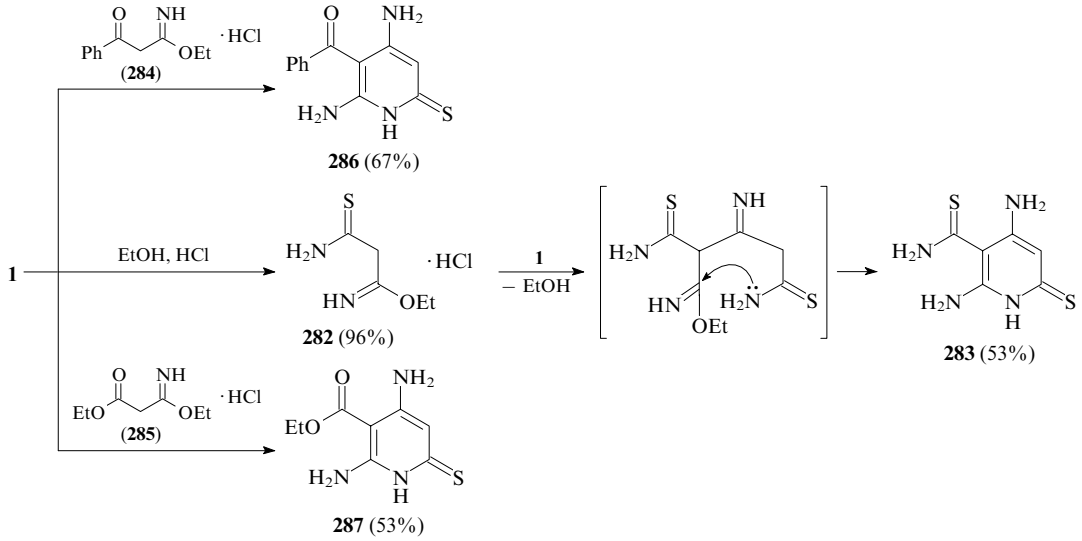
There are several known examples of α-cyanothioacetamide reactions in which the key step is the addition of nucleophiles to the nitrile group. The reaction of compound **1** with ethanol in 1,4-dioxane at 0 °C in the presence of concentrated hydrochloric acid gives salt **282**, which reacts with substrate **1** in refluxing ethanol in the presence of AcONa to finally give substituted pyridine **283**. When salts **284** and **285** are reacted with α-cyanothioacetamide, pyridines **286** and **287**, respectively, are formed (Scheme 71).[347]

The synthesis of propanebis(thioamide) (**288**) comprises stepwise nucleophilic addition of hydrogen sulfide to malonodinitrile (**2**) (Scheme 72).[348] The α-cyanothioacetamide dimerization to substituted pyridine **6** (see Scheme 3) should be reasonably considered as a manifestation of electrohilic properties of the nitrile group.

Scheme 72



Scheme 71



* * *

The popularity of α-cyanothioacetamide among synthetic chemists is rapidly growing. α-Cyanothioacetamide is a commercially available stable reagent, which readily participates in a variety of reactions under mild conditions. The preparative implementation of these syntheses is simple and the yields of target products are, most often, high. The modern trends of using α-cyanothioacetamide in organic synthesis are based on conducting muticomponent condensations of this compound with new and previously used electrohilic reagents that are capable of reacting with the methylene group and participating in intramolecular heterocyclization.[349, 350] This mainly gives nitrogen heterocyclic compounds. The products of these reactions are being extensively studied for the biological activity and as intermediates for the preparation of other fused heterocyclic systems with real or potential biological activities. The small number of publications on the transformations of the nitrile group, which often remains in the final products, attests to the good prospects of further studies of this reagent.

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