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Chemistry of Heterocyclic Compounds **2018**, *54*(11), 989–1019

REVIEW

Heterocyclization reactions using malononitrile dimer (2-aminopropene-1,1,3-tricarbonitrile)

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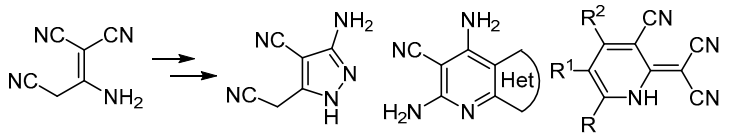


In this work, we provide the first generalized and critical analysis of data on the chemistry of malononitrile dimer (2-aminopropene-1,1,3-tricarbonitrile) – a multifunctional reagent that is widely used for the preparation of diverse heterocyclic systems. The majority of references are from the last 20–25 years.

Keywords: malononitrile dimer, naphthyridines, pyrazoles, pyridines, pyrimidines, cascade reactions, cyclocondensations.

Malononitrile derivatives are known as highly reactive compounds offering rich synthetic possibilities and are actively used for the preparation of various carbo- and heterocyclic products. Of particular significance among malononitrile derivatives is its dimer (2-aminopropene-1,1,3-tricarbonitrile), which was first obtained[1,2] in the middle of 1950s and serves as an important reagent in the synthesis of dyes, biologically active pyridine derivatives, and other compounds. Some chemical properties of malononitrile dimer have been described in a series of review articles,[3–5] mostly in the context of the reactivity of other compounds. A most detailed discussion on the chemistry of malononitrile dimer is available in a dedicated chapter of monograph by Sharanin, Promonenkov, and Litvinov,[6] devoted to the reactions of malononitrile derivatives. A review article on the chemistry of crotononitrile was published in 1998, where some aspects of 2-aminopropene-1,1,3-tricarbonitrile reactivity were briefly discussed.[7] Substantial advances in the chemistry of malononitrile dimer were made over the following two decades, thus we considered it necessary to provide a comprehensive overview of this field in the current work.

The aim of this review is to demonstrate the synthetic potential of malononitrile dimer as a convenient and multifunctional reagent for assembling a wide range of heterocyclic systems. We organize the available references according to the type and size of the target heterocycle.

1. Synthesis, structure, and properties of malononitrile dimer

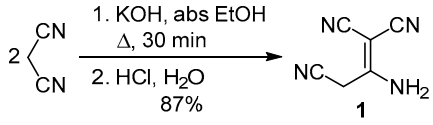
Malononitrile dimer (**1**) is a beige crystalline compound that is soluble in EtOH or water upon heating, stable during storage, safe in handling, and commercially available. The most common approach to the preparation of dimer **1** relies on the dimerization of malononitrile in the presence of various catalysts; some of the early methods for its synthesis are considered in review articles.[4,6] Currently, the preparative procedure proposed by Mittelbach[8] can be considered as the most convenient option providing access to this compound.

Synthesis of 2-aminopropene-1,1,3-tricarbonitrile (1) (Scheme 1).[8] Malononitrile (33 g, 0.5 mol) was added to a cooled solution of KOH (0.25 mol) in anhydrous EtOH (100 ml). The temperature of the stirred reaction mixture was slowly raised to reflux. Potassium salt of dimer **1** precipitated after 5–10 min. After heating for 30 min, the mixture was cooled, the potassium salt was filtered off,

Here and further the corresponding author is marked with *.

washed with cold EtOH, and dried. The salt was dissolved in a small amount of water and acidified with concentrated HCl to pH 4. The precipitated product was filtered off and recrystallized from water, giving dimer **1** in the form of colorless needles, mp 172°C, yield 87%. Replacement of anhydrous EtOH with 96% EtOH decreased the yield to 83%.

Scheme 1

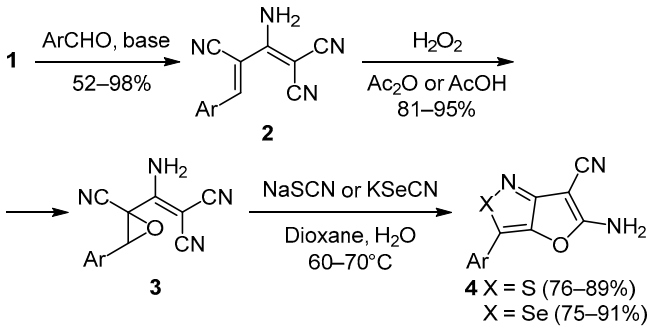


Recently proposed methods for the preparation of dimer **1** rely on the dimerization of malononitrile by the action of sodium powder in THF–ether mixture (61% yield)[9] or sodium ethoxide in anhydrous EtOH (87% yield of compound **1** in the form of sodium salt)[10] and are essentially based on previously published procedures.[2,11] The spectral characteristics of dimer **1** have been described in several original studies,[11–15] as well as discussed in review articles.[4,6] The crystal structure features of compound **1** were studied by X-ray structural analysis.[16] The tautomeric transformations of dimer **1**, the details of the dimerization process, and the structures of the intermediates were studied by quantum-chemical calculations using MNDO method.[17]

2. Synthesis of three–five-membered heterocycles

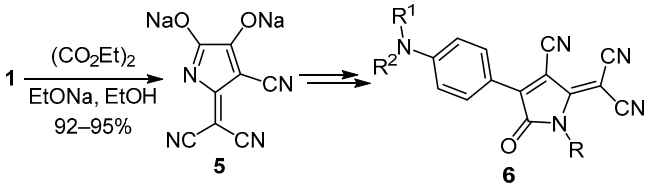
As a compound containing an activated methylene group, dimer **1** readily reacts under the conditions of basic catalysis (piperidine,[18,19] piperidinium acetate[20–22]) with aromatic aldehydes, resulting in the formation of 4-arylbuta-1,3-diene-1,1,3-tricarbonitriles **2** (Scheme 2). The latter were treated with peroxyacetic acid giving 81–95% yields of oxiranes **3**,[23–25] which were easily recyclized in the presence of alkali thio(seleno)cyanates into derivatives of furo[3,2-*c*]isothiazole[26] and -selenazole **4**.[27]

Scheme 2



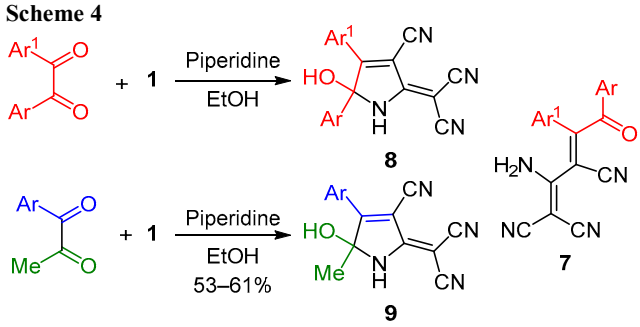
As an active 1,3-C,N-dinucleophile, malononitrile dimer (**1**) reacted in the presence of bases with 1,2-dicarbonyl compounds and analogous dielectrophilic substrates, resulting in the cyclization of five-membered pyrrole ring. The possibilities for the synthesis of substituted pyrroles according to the given scheme were initially demonstrated with the reaction between dimer **1** and diethyl oxalate.[2] Disodium derivative **5** that was thus obtained has found applications in the synthesis of push-pull chromophores **6** of pyrroline series[10,28] (Scheme 3).

Scheme 3



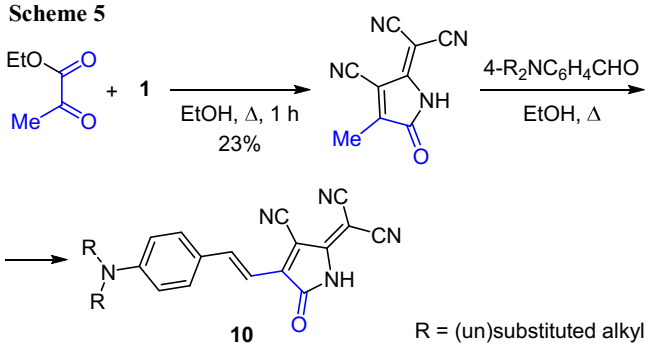
The interaction of dimer **1** with 1,2-diketones has been studied in considerable detail.[29,30] At the same time, it should be noted that the previously published[31,32] acyclic structures of condensation products **7** were incorrect and the products formed in reactions of dimer **1** with diketones actually had the structure of pyrrolines **8**[30,33] (Scheme 4). Recently, it has been demonstrated that the reaction of 1-arylpropane-1,2-diones with dimer **1** proceeded regioselectively and gave pyrroles **9** in 53–61% yields.[34] The selective formation of regioisomers **9** was explained by the deactivation of acetyl group resulting from the enolization in basic medium.

Scheme 4



The preparation of new chromophoric pyrrolines **10** starting by the reaction of ethyl pyruvate with dimer **1** and followed by the condensation of the obtained cyclic product with 4-(dialkylamino)benzaldehydes has been described in the literature (Scheme 5).[9,35,36]

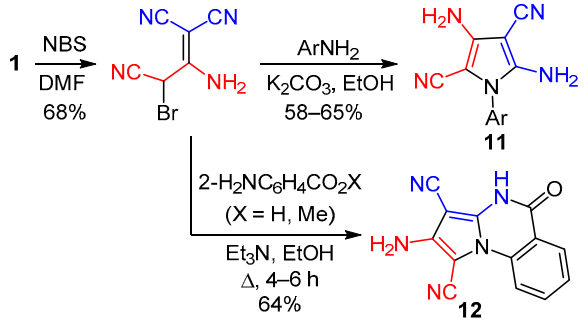
Scheme 5



Functionalized pyrrole derivatives **11** were isolated in moderate yields after the treatment of monobromination product obtained from dimer **1** with anilines (Scheme 6).[37]

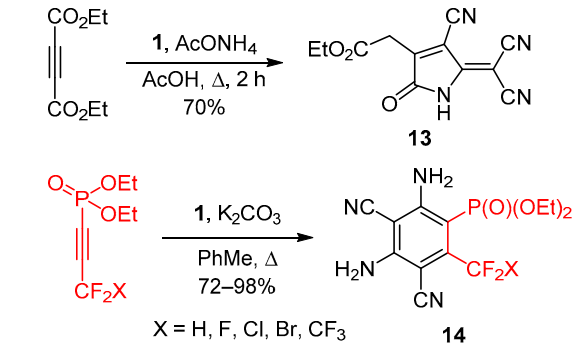
Derivatives of anthranilic acid under the given conditions underwent a cascade reaction, resulting in the formation of pyrrolo[1,2-*a*]quinazolines, for example, compound **12**.

Scheme 6



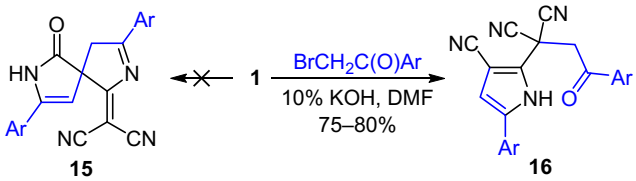
Pyrroline derivative **13** was obtained by reaction of dimer **1** with diethyl acetylenedicarboxylate in the presence of a base (Scheme 7).[38] The reaction apparently was not widely applicable: for example, the reactions of dimer **1** with other highly electrophilic acetylenes gave carbocyclization products **14**.[39]

Scheme 7



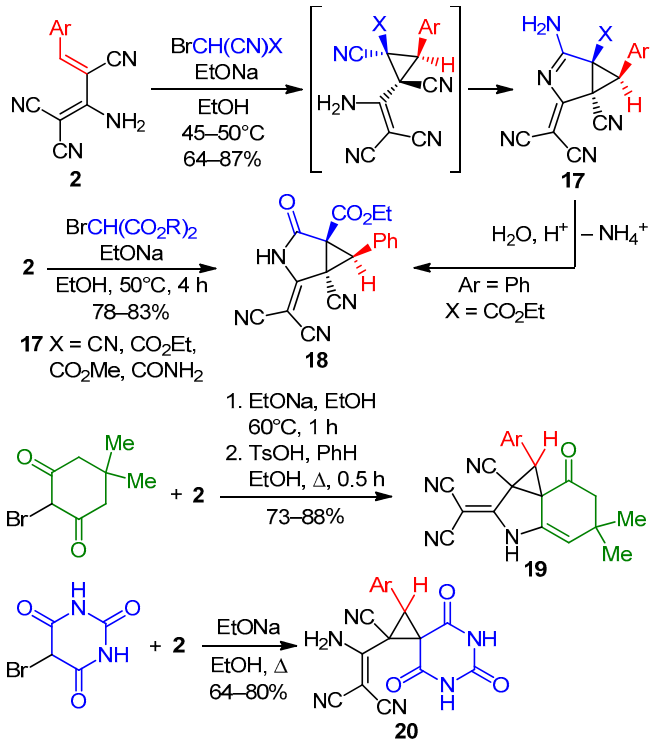
A publication appeared in 2011 where the products obtained by alkylation of malononitrile dimer (**1**) with α-bromo ketones were assigned the structure of spiro-dipyrrolines **15** (Scheme 8).[40] However, subsequent characterization by X-ray structural analysis showed that the reaction products in fact were pyrroles **16**.[41]

Scheme 8



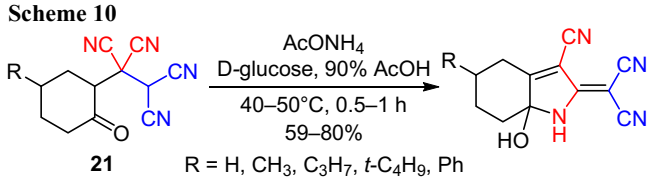
Butadienetricarbonitriles **2** were found to be convenient reagents for the assembly of five-membered heterocyclic systems. Thus, dienes **2** participated in a reaction with α-bromonitriles, resulting in cyclopropane ring closure and further intramolecular 5-*exo-dig* cyclization, leading to bicyclic products **17** (Scheme 9).[22,24,25,42,43] It was noted that the reaction proceeded regio- and stereoselectively with the formation of diastereomers featuring *trans* relationship of the pyrroline moiety and the aryl substituent. As a result of an analogous reaction between dienes **2** and 2-bromo-1,3-dicarbonyl compounds[22,44] pyrrolidine derivatives **18** and **19** were formed. At the same time, it was established that in the case of 5-bromo-barbituric acid the reaction stopped at the stage of spirocyclopropanes **20**.[22]

Scheme 9



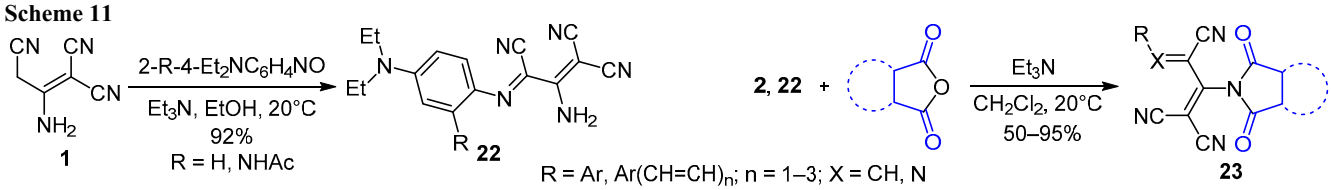
An alternative to the use of malononitrile dimer (**1**) in the synthesis of substituted pyrrolines (for example, from 1,2-diketones[29]) is the rearrangement of compounds **21** – Michael adducts obtained from tetracyanoethylene and cyclohexanones. This rearrangement is catalyzed by D-glucose (Scheme 10),[45] the role of which, according to the proposed mechanism, is to transfer the malononitrile fragment through the formation of addition product at the aldehyde group. In the absence of glucose the product yield decreased to 19–28%.

Scheme 10

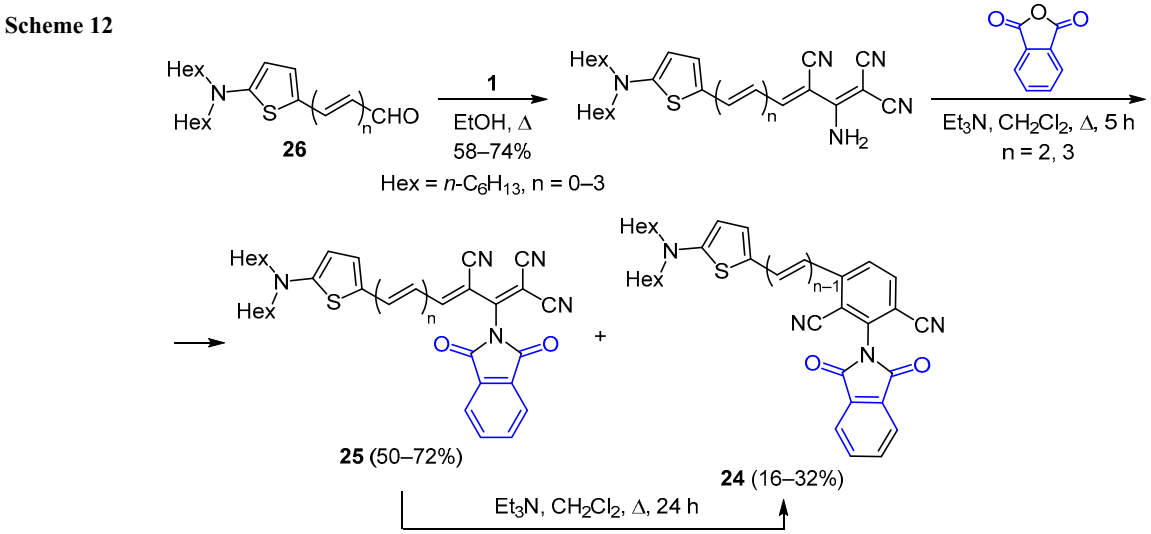


Compounds **2**, as well as 1-azabutadienes **22** obtained by Ehrlich–Sachs condensation reacted quite readily at the amino group with anhydrides of succinic, citraconic, and phthalic acids with the formation of push-pull dyes **23** (Scheme 11).[46–49] It was noted that such modification led to a bathochromic shift of the absorption maximum.

Scheme 11



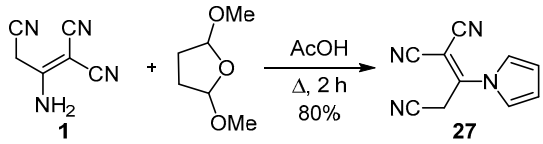
Scheme 12



The purple-colored polymethine dyes **24** were obtained as a result of an unusual carbocyclization reaction, which occurred in parallel with the formation of cyanines **25** through a reaction sequence involving the condensation of malononitrile dimer (**1**) with ω-(2-thienyl)polyenals **26** followed by a reaction with phthalic anhydride (Scheme 12).[50] Longer refluxing of the mixture facilitated complete conversion of compound **25** to compound **24**. It was noted that the cyclization was facilitated by the unusually high dipole moment (>20 D) of molecules **25**, resulting from intramolecular charge transfer. The cyclization was promoted by bases. The reaction occurred with polymethines **25** having n > 1, which could be explained by the increased flexibility of longer polyene chains.

It has been reported in the literature[51] that 2-aminopropene-1,1,3-tricarbonitrile (**1**) underwent Clauson–Kaas reaction, resulting in the formation of pyrrole **27** (Scheme 13), but we consider that these observations need additional experimental verification.

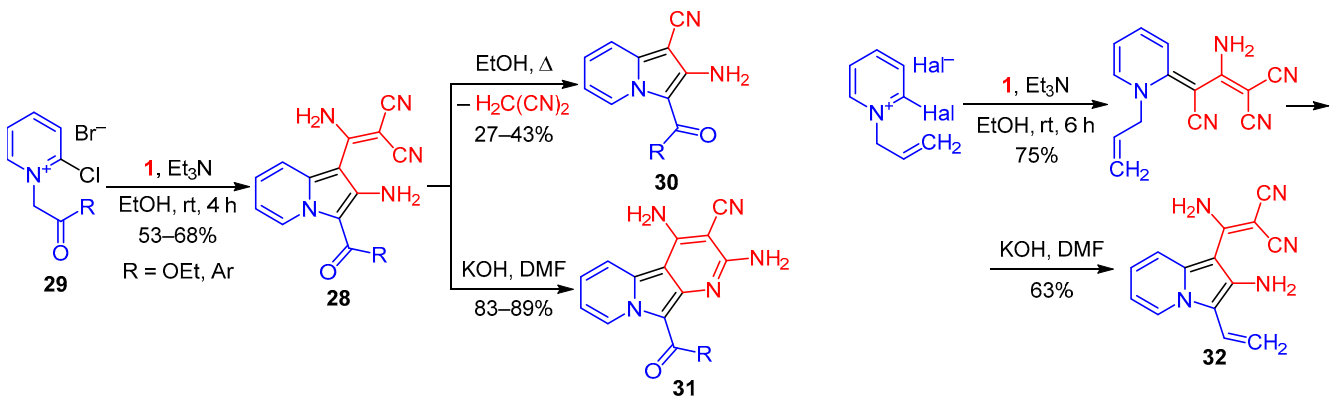
Scheme 13



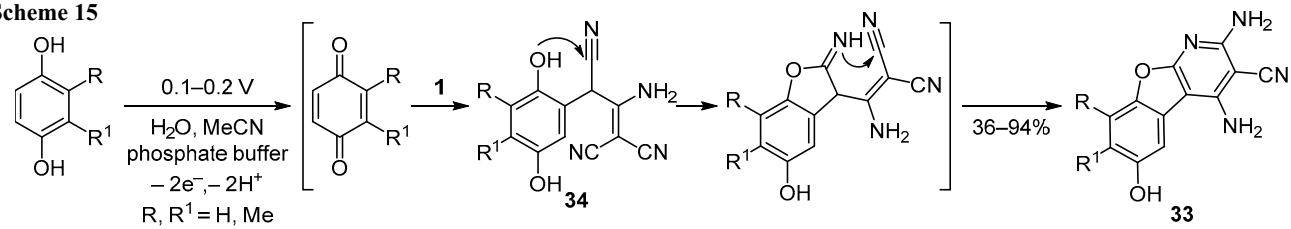
Indolizine derivatives **28** were formed as a result of reaction between Kröhnke–Mukaiyama salts **29** and dimer **1** under mild conditions (Scheme 14).[52] Indolizines **28** showed an interesting dual reactivity: brief heating in alcohols resulted in the loss of a malononitrile molecule and produced indolizines **30**, while treatment with KOH in DMF medium led to tricyclic structures **31**. *N*-Allyl-2-halopyridinium salts under analogous conditions reacted with dimer **1**, providing only the linear product that was cyclized to indolizine **32** upon heating.

A recent publication[53] described an example where furan derivatives were prepared using dimer **1**. Thus, electrochemical oxidation of hydroquinones in the presence

Scheme 14



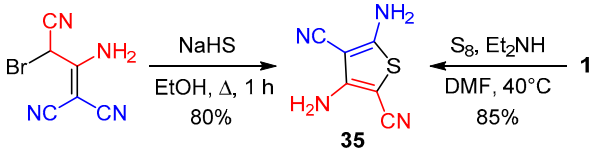
Scheme 15



of malononitrile dimer (**1**) led to the formation of benzofuro[2,3-*b*]pyridines **33**. It was proposed that the reaction proceeded *via* cascade cyclization of Michael adducts **34** involving the formation of non-isolated benzofuran derivatives (Scheme 15).

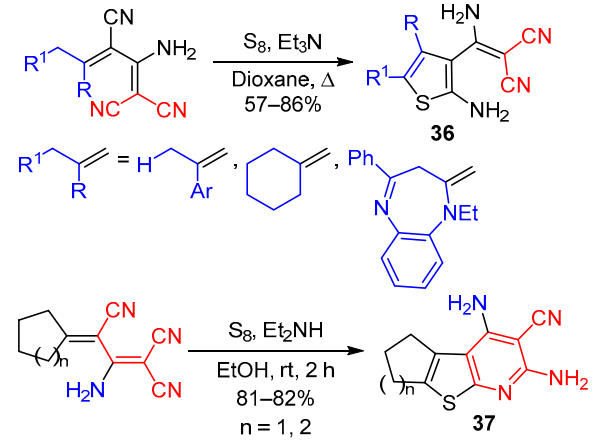
The intermediate product arising from bromination of malononitrile dimer reacted with NaHS with the formation of functionalized thiophene derivative **35**.[54] It should be noted that thiophene **35** was obtained earlier[55] in a better yield by direct thiolation of dimer **1** with elemental sulfur in the presence of diethylamine (Scheme 16).

Scheme 16



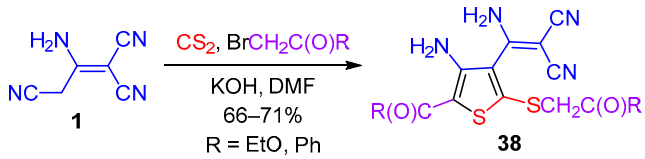
Several publications[56–59] describe the synthesis of thiophene derivatives from malononitrile dimer (**1**) using the Gewald reaction. The product from condensation of dimer **1** with carbonyl compounds reacted with elemental sulfur in the presence of amines upon heating (Scheme 17). The products of this reaction were assigned the structure of 2-aminothiophenes **36**. At the same time, an earlier study by Junek and coworkers used a series of analogous examples[60] to show that the reaction proceeded further even under mild conditions, resulting in the formation of thieno[2,3-*b*]pyridines **37**. Obviously, additional research in this direction is needed.

Scheme 17



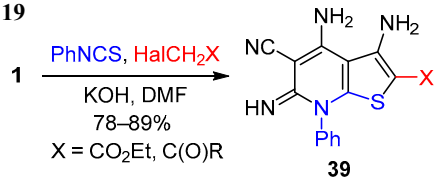
The preparation of functionalized thiophene derivatives **38** in good yields has been also described. The procedure involved treatment of malononitrile dimer **1** with alkylating agents and carbon disulfide in the presence of alkali (Scheme 18).[61]

Scheme 18



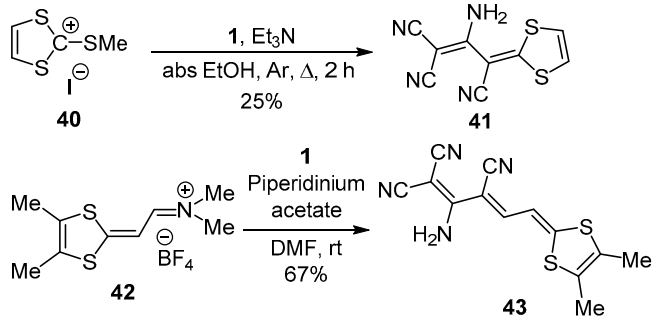
In the case of an analogous reaction using isothiocyanates instead of CS_2, further cyclization of the thiophene intermediates was observed, leading to the formation of thieno[2,3-*b*]pyridines **39** (Scheme 19).[62]

Scheme 19



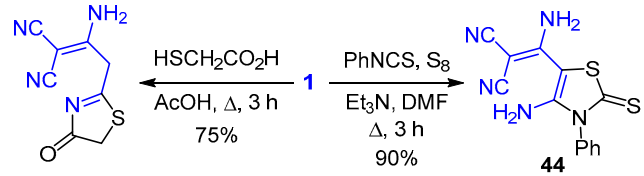
So far only isolated examples have been published where the synthesis of 1,3-dithiol derivatives was accomplished starting from malononitrile dimer (**1**) (Scheme 20). Thus, dithiolium iodide **40** upon treatment with malononitrile dimer (**1**) gave a low yield of 1,4-dithiafulvene derivative **41**.[63] The reaction of polyenals containing a dithiol moiety or the respective iminium salts **42** with dimer **1** enabled the preparation of new merocyanine dyes **43**.[64]

Scheme 20



The reaction of dimer **1** with isothiocyanates in the presence of elemental sulfur provides an accessible route for the preparation of substituted thiazoles **44** (Scheme 21).[65]

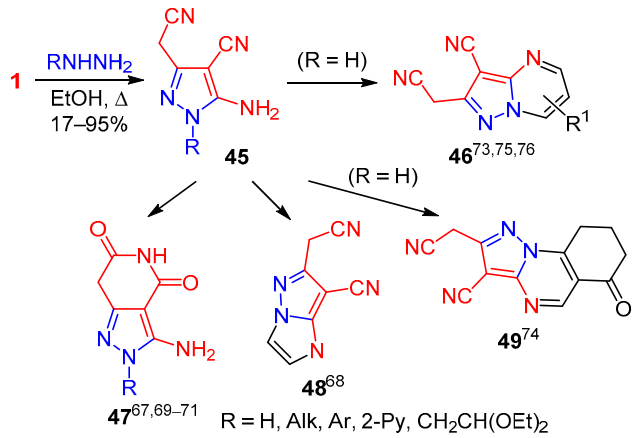
Scheme 21



Another approach to the assembly of thiazole ring on the basis of malononitrile dimer (**1**) involves the interaction with thioglycolic acid at elevated temperature. It was demonstrated that this transformation affects the unconjugated nitrile group (Scheme 21).[66]

The most general method for the preparation of pyrazole derivatives from malononitrile dimer (**1**) is based on the reaction with hydrazines $RNHNH_2$ where dimer **1** acts in the role of β-enaminonitrile substrate. The possibility for obtaining 3-amino-5-(cyanomethyl)-1*H*-pyrazole-4-carbonitriles by this route was first demonstrated in late 1950s.[2,11,67] Since that time, this approach has been used without substantial changes for the preparation of *N*-substituted 3-aminopyrazoles **45**,[68–72] which have found applications in the synthesis of various polyheterocyclic compounds[67–79] – for example, azaheterocycles **46**–**49** (Scheme 22).

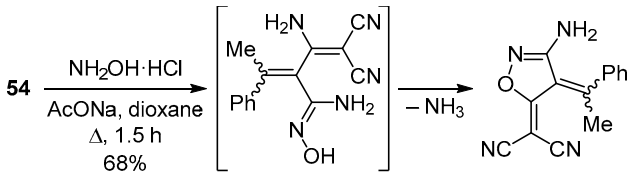
Scheme 22



3-Aminomethylidene derivative of dimer **1** reacted with hydrazines by a different route – with a sequential closure of pyrazole and pyridine rings and the formation of compound **50** (Scheme 23).[80] It was shown that hydrazones **51** in the presence of hydrazines were converted to pyrazoles **52**,[81,82] with further cyclization in the molecule of pyrazolo[3,4-*b*]pyridine **53** occurring upon the treatment with a strong base (EtONa).[81] The products arising from the condensation of malononitrile dimer (**1**) with ketones also reacted with hydrazines with the formation of pyrazole derivatives: thus, the heating of compounds **54** in the presence of $PhNHNH_2$ gave pyrazolines **55**.[57,58] However, it must be noted that insufficient structural characterization of the obtained compounds is available from the literature.[57,58,81,82] The provided spectral data are inconclusive and do not exclude the possibility of alternative structures (for example, tautomers or even regioisomers) for the products of hydrazinolysis. Therefore we consider it necessary to obtain additional experimental data about such products.

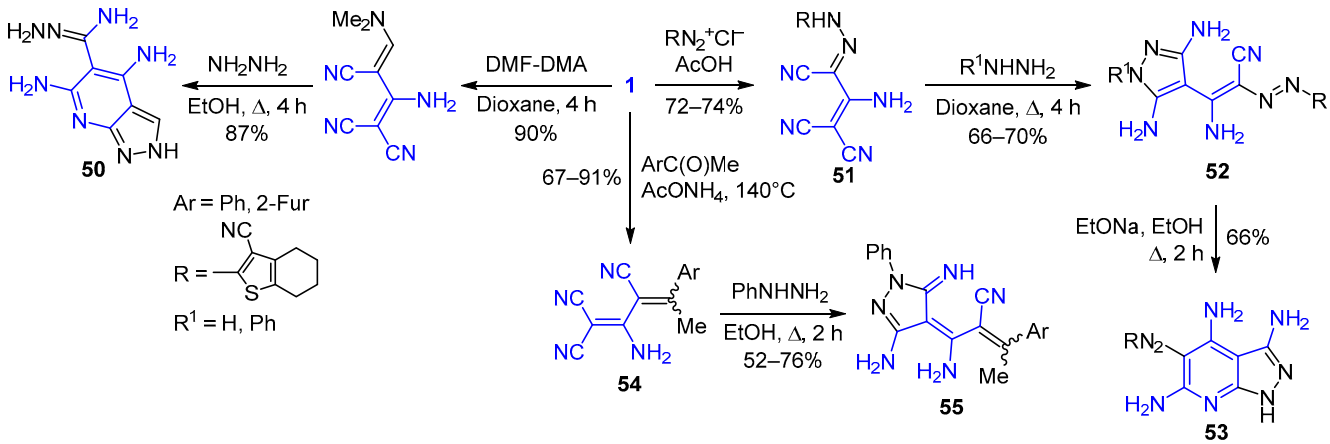
An isoxazole derivative was obtained in a reaction of compound **54** with hydroxylamine (Scheme 24).[58]

Scheme 24

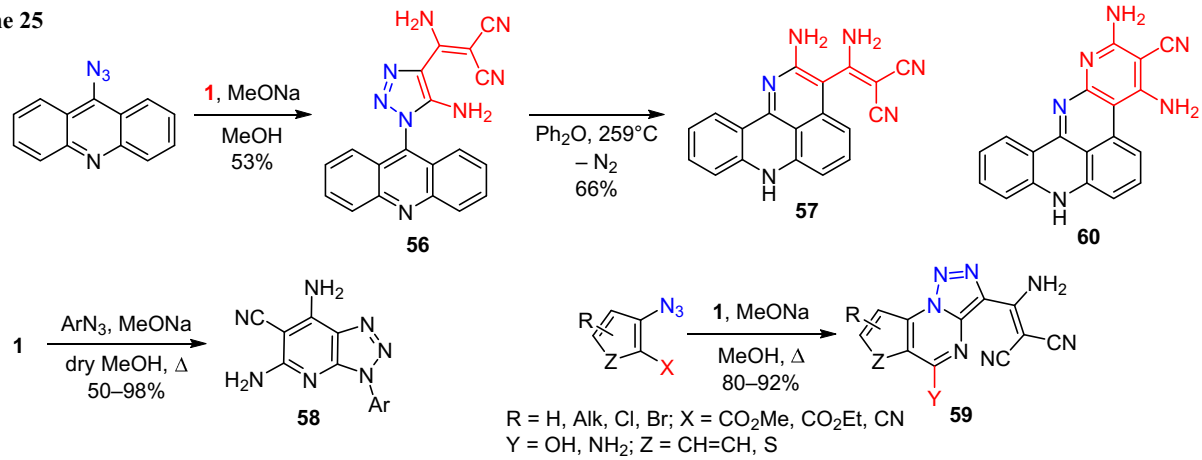


Malononitrile dimer (**1**) readily participated in the Dimroth reaction with azides, resulting in the formation of 1,2,3-triazoles. Thus, 9-azidoacridine reacted with dimer **1** in darkness at room temperature in the presence of MeONa, giving triazole **56** in a moderate yield (Scheme 25). Thermolysis of the latter was performed according to the Graebe–Ullmann method, resulting in substituted pyrido-[4,3,2-*kl*]acridine **57**.[83] It has been recently demonstrated[84a] that the reaction of dimer **1** with aryl azides in refluxing methanol did not stop at the stage of 4-amino-1,2,3-triazole formation and proceeded as a cascade process leading to either triazolo[4,5-*b*]pyridines **58** in up to 98% yields or, in the case of ethers or nitriles derived from *o*-azidoarylcarboxylic acids – to [1,2,3]triazolo[1,5-*a*]pyrimidine derivatives **59**.[84b] Taking into account these results, it must be noted that the spectral dataset for pyridoacridine **57** available in the literature[83] does not in principle exclude the possibility for the formation of isomeric naphthyridino-[4,3,2-*kl*]acridine structure **60** during the thermolysis process.

Scheme 23



Scheme 25

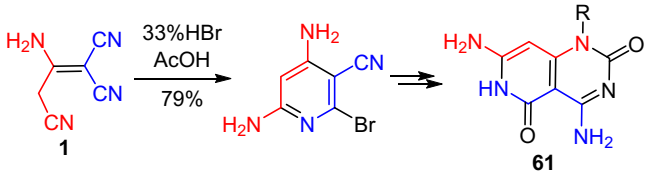


3. Synthesis of pyridine, quinoline, and naphthyridine derivatives

3.1. Malononitrile dimer as C_5–N-synthon in the synthesis of pyridines

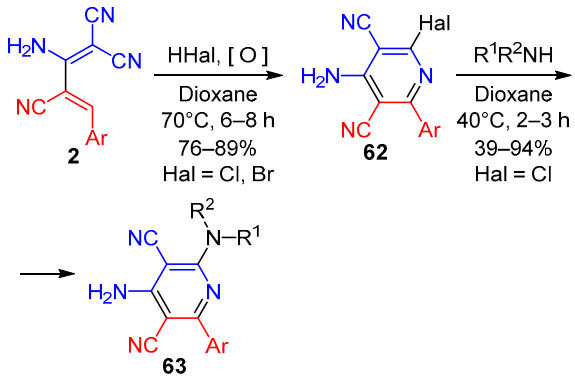
In late 1950s, it was established[2,85] that malononitrile dimer (**1**) readily undergoes intramolecular 6-*exo*-*dig* cyclization in the presence of hydrogen halides in anhydrous THF. Later it was proved that the 2,4-diamino-6-halopyridine-3-carbonitrile structure initially proposed in the aforementioned literature sources[2,85] for the cyclization products was incorrect. In fact, isomeric 4,6-diamino-2-halopyridine-3-carbonitriles were formed.[86] A modified variant of this approach was recently proposed for the synthesis of 4,6-diamino-2-bromopyridine-3-carbonitrile, which has been found to be a convenient precursor for the preparation of hybrid nucleobases **61** (Scheme 26).[87]

Scheme 26



Butadienes **2** reacted with HCl or HBr in the presence of various oxidants (Br_2, SeO_2, O_2, and others) with the formation of 2-halopyridines **62** (Scheme 27).[88]

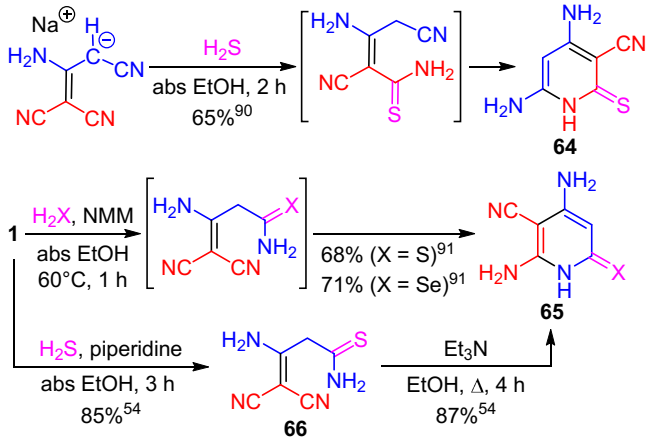
Scheme 27



Ammonolysis products, pyridines **63** showed fluorescence with emission peak at λ 400–460 nm.[89]

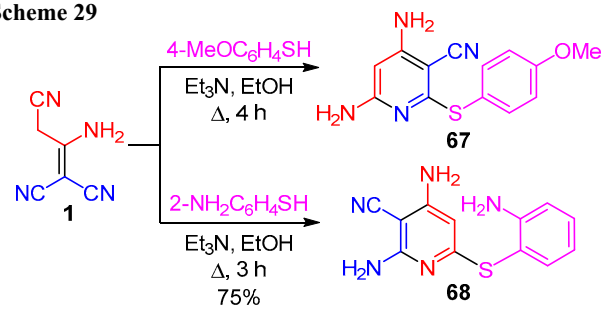
Regarding the cyclization of malononitrile dimer (**1**) in the presence of hydrogen sulfide, there are few literature sources containing contradictory data and additional research is needed in this direction. Thus, according to one publication,[90] bubbling H_2S gas through a solution of sodium salt of dimer **1** in anhydrous EtOH gave a product that was assigned the structure of pyridine-2(1*H*)-thione **64** (Scheme 28). According to other data,[91] the products of reaction between dimer **1** and H_2S or H_2Se in the presence of *N*-methylmorpholine (NMM) were pyridines **65**. The latter interpretation was confirmed by a recent study:[54] an intermediate product was isolated when the reaction was performed under mild conditions and was identified as acyclic thioamide **66**, which was cyclized upon heating to pyridine **65** (X = S).

Scheme 28



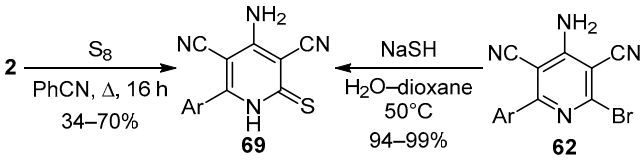
Mercaptans reacted with dimer **1** in a less predictable manner. For example, the formation of pyridine **67** from 4-methoxythiophenol has been described, although no spectral data or experimental procedures were revealed (Scheme 29).[92] On the other hand, according to the data of another work,[93] 2-aminothiophenol reacted with dimer **1** at the non-conjugated cyano group with the formation of compound **68**. It should be added that thioglycolic acid derivatives in reactions with dimer **1** gave thiazole derivatives[66] instead of pyridine derivatives (Scheme 21).

Scheme 29



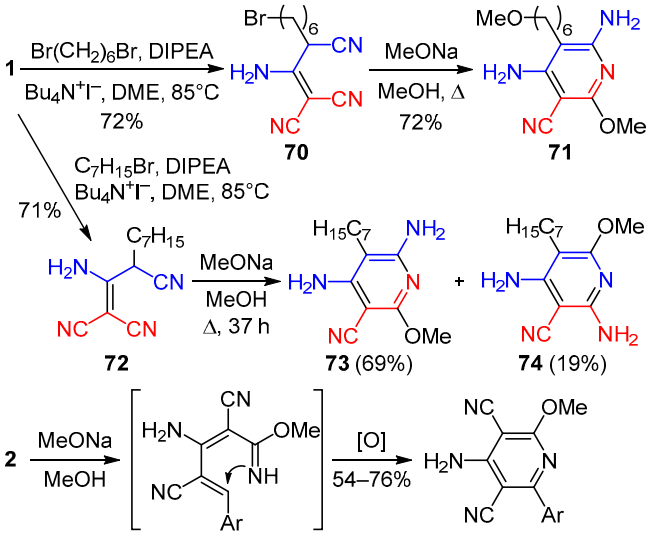
A recently described reaction of butadienetricarbonitriles **2** with elemental sulfur in benzonitrile led to the formation of pyridine-2(1*H*)-thiones **69** with a wide range of yields (34–70%).[94] An alternative route to thiones **69** was based on nucleophilic substitution of bromine atom in 2-bromopyridines **62** (Scheme 30).[94]

Scheme 30



C-Alkyl derivative of malononitrile dimer **70** reacted with methoxide ion at the conjugated nitrile group with the formation of 2-methoxypyridine **71** (Scheme 31).[95] It should be noted that, according to the data from the same research group,[96,97] analogous reactions with 2-heptyl derivative **72** proceeded nonselectively and produced a mixture of the regioisomeric pyridines **73** and **74** as a result of competing attacks at the conjugated and non-conjugated CN groups, which is in agreement with the results obtained by Junek and coworkers.[98] 4-Arylbuta-1,3-diene-1,1,3-tricarbonitriles **2** containing electron-donating substituents in the ring underwent attack by methoxide ion at the C-1 atom, followed by cyclization and oxidation of the intermediate, forming the respective 2-methoxypyridines.[21,22]

Scheme 31

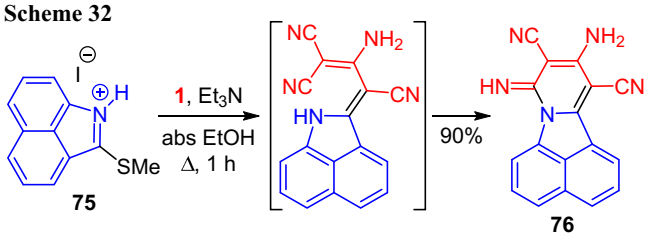


3.2. Malononitrile dimer as C_4-synthon in the synthesis of pyridines

As a compound containing an activated methylene group, dimer **1** can react with various C=N- or C≡N-electrophiles followed by cyclization into pyridine derivatives. The examples of reactions between dimer **1** and amidines, cyanates, iminoesters, and other types of compounds described in older literature sources (before 1990) have been considered in detail in a review article.[6]

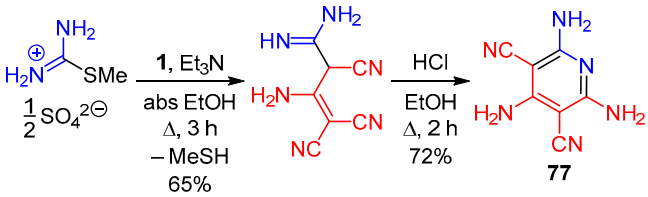
Nucleophilic substitution of methylsulfanyl group in compound **75** by anion of dimer **1** was accompanied by spontaneous cyclization forming a derivative of a new heterocyclic system – benzo[*cd*]pyrido[1,2-*a*]indole **76** (Scheme 32).[99]

Scheme 32



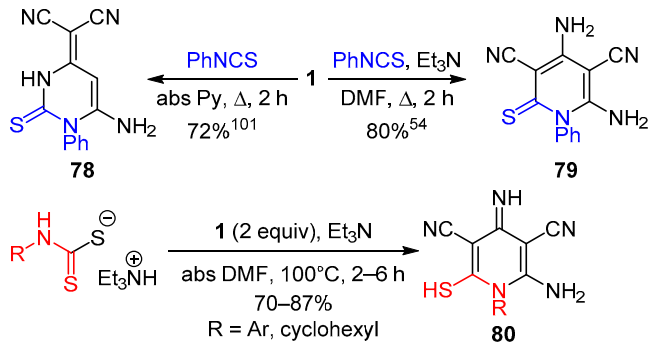
The reaction of dimer **1** with isothiuronium salt allowed to isolate an intermediate with linear structure that was cyclized in acidic medium with the formation of triaminopyridine-3,5-dicarbonitrile **77** (Scheme 33).[100]

Scheme 33



The literature sources from recent years contain contradictory data about the reactions of malononitrile dimer (**1**) with isothiocyanates. According to one study,[101] the reaction with PhNCS in refluxing pyridine resulted in the formation of substituted pyrimidine **78** (Scheme 34). At the same time, the results of other studies[54,62a,102] supported conclusions that cyclization leads to the formation of pyridine ring. Thus, the preparation of thioxopyridine **79** was accomplished in a high yield as a result of a reaction

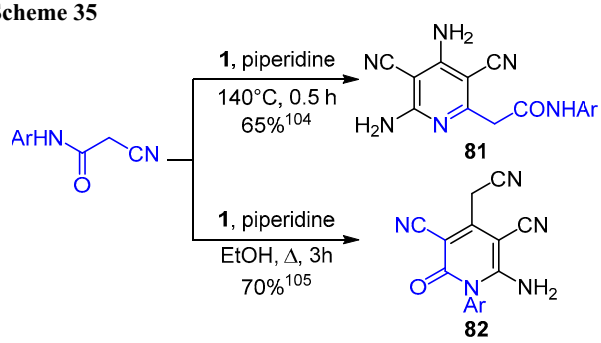
Scheme 34



between dimer **1** and PhNCS in refluxing DMF in the presence of a base.[54] It is interesting to note that triethylammonium dithiocarbamates reacted[103] with malononitrile dimer not as S-nucleophiles, but rather in similar fashion to isothiocyanates; the reaction products analogous to compounds **79** were found to exist as 4-imino-2-mercapto tautomers **80**.

It is known from the literature that malononitrile dimer (**1**) readily participates in Thorpe reaction with activated nitriles in the presence of bases, followed by cyclization of the linear intermediates and formation of substituted pyridines.[6] Another example of a similar transformation can be found in a recent publication[104] describing the synthesis of α-(2-pyridyl)acetamides **81** (Scheme 35). However, according to other sources,[105] dimer **1** reacted with cyanoacetamides in the presence of a base as enamino-dinitrile with the formation of pyridylacetonitriles **82**.

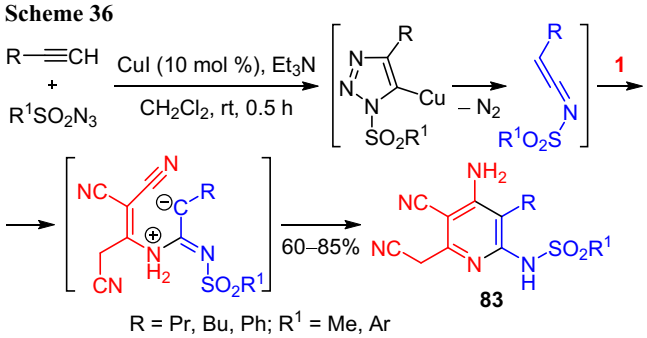
Scheme 35



3.3. Malononitrile dimer as C_3–N-synthon in the synthesis of pyridines

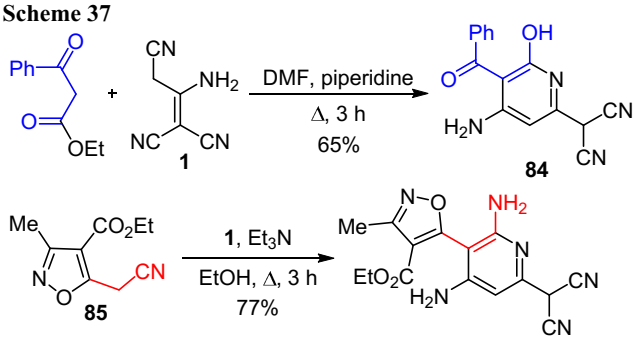
Very few examples are known where pyridine ring was constructed using dimer **1** as a source of C_3–N fragment. It was shown[106] that dimer **1** reacted with *N*-sulfonyl-ketenimines (generated *in situ* from terminal acetylenes and sulfonyl azides) with the formation of substituted pyridines **83** in good yields (Scheme 36). Contrary to expectations, ethyl benzoylacetate reacted with dimer **1** not as a 1,3-di-electrophile, but rather as a reagent containing activated methylene group, with the formation of pyridine **84** (Scheme 37).[107] Analogous reactivity was also observed in the case of (isoxazol-5-yl)acetonitrile **85**.[108] However, taking into account other data about the reactivity of β-dicarbonyl compounds and nitriles containing activated methylene groups in reactions with dimer **1** (chapters 3.2., 3.4.1.), the obtained results must be further refined.

Scheme 36



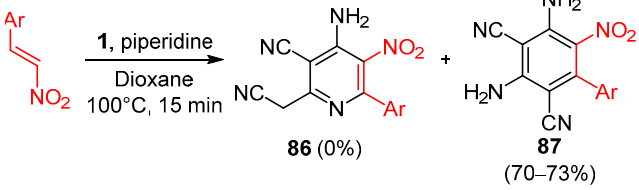
R = Pr, Bu, Ph; R^1 = Me, Ar

Scheme 37



When attempting to obtain pyridines **86** by a reaction of dimer **1** with β-nitrostyrenes, only carbocyclization products **87** were isolated (Scheme 38).[109]

Scheme 38

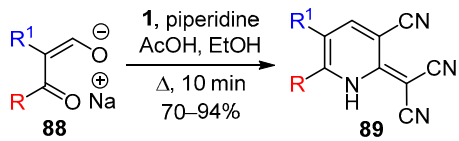


3.4. Malononitrile dimer as C–C–N-synthon in the synthesis of pyridines

Malononitrile dimer (**1**) participates in reactions with various 1,3-dielectrophilic reagents – β-diketones, keto esters, and activated alkenes – with the formation of functionalized pyridine derivatives. The material presented below has been arranged according to the types of reagents used.

3.4.1. The reactions of malononitrile dimer with 1,3-dicarbonyl compounds. α-Formyl ketone enolate sodium salts **88** easily reacted with malononitrile dimer (**1**), forming after acidification (3-cyanopyridin-2(1*H*)-ylidene)-malononitriles **89** in high yields (Scheme 39).[110] As shown by the results of X-ray structural analysis,[111] the reaction occurred selectively, with the formation of a single regioisomer – the product arising from initial condensation at the more active aldehyde group.

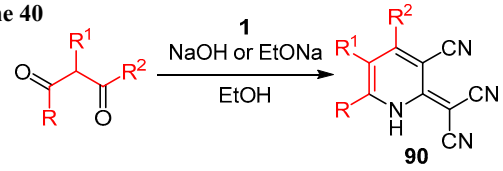
Scheme 39



R = Me, Ar; R^1 = H, Me

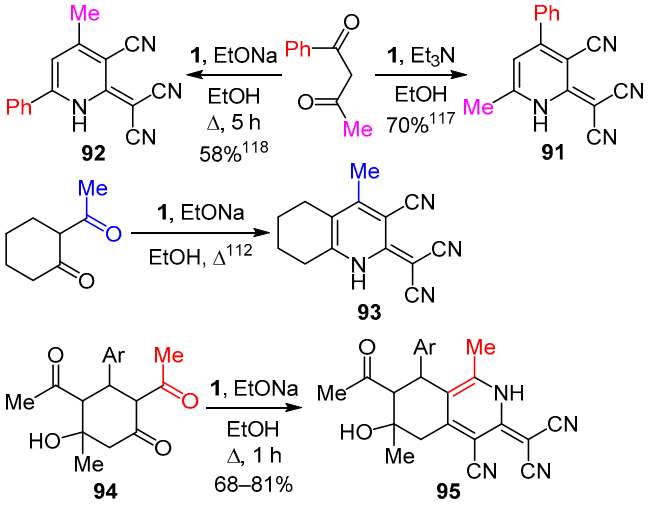
The reaction of 1,3-diketones with dimer **1** was first reported in 1964 by Junek[112] and has been explored by several other researchers since then.[113–118] This variant of Guareschi–Thorpe synthesis has been performed with different catalysts – aqueous 10% NaOH solution,[112,116] piperidine,[112,114,115] Et_3N,[117] EtONa.[112,118] The best yields of pyridines **90** (Scheme 40) – up to quantitative conversion – were obtained by performing the reaction in aqueous alkali solutions.

Scheme 40



It should be pointed out that in the majority of studies concerning the reaction of dimer **1** with unsymmetrical β-diketones it was assumed that a single regioisomer was formed with the least sterically hindered substituent at position 4 of the pyridine ring. Nevertheless, there are contradictory assertions in the literature about this issue. Thus, it has been claimed[117] that the condensation product obtained in reaction of dimer **1** with benzoylacetone was pyridine derivative **91**, while other authors reported[118] the isomeric product **92** (Scheme 41). It is known[112] that the reaction of dimer **1** with 2-acetylcyclohexanone leads to quinoline derivative **93**, but a recent publication[119] showed that β-cycloketoles **94** initially reacted at the endocyclic C=O group and were further cyclized into isoquinolines **95**. A series of analogous Guareschi–Thorpe cyclization reactions have been used[120] to show that the reaction in the case of 2-acetylcycloalkanones can proceed nonselectively and lead to the formation of mixtures containing regioisomeric products with very similar spectral characteristics. Taking into account the insufficiently strong proof (in our opinion) for the selectivity of the described processes,[112,117–119] the obtained results must be viewed with caution.

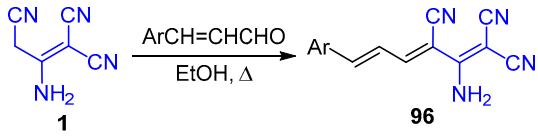
Scheme 41



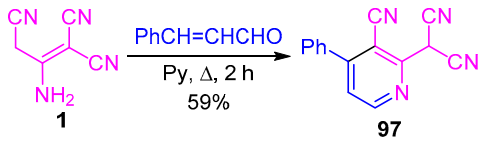
3.4.2. Reactions of malononitrile dimer with α,β-unsaturated carbonyl compounds. According to several studies,[49,50,121] malononitrile dimer (**1**) undergoes Knoevenagel condensation with α,β-unsaturated aldehydes in refluxing EtOH with the formation of hexatriene-1,1,3-tricarbonitriles **96** (Scheme 42).

However, there are data indicating that the reaction of dimer **1** with cinnamic aldehyde in pyridine gives the cyclization product for which the structure of 4-phenylpyridine **97** was proposed on the basis of ^{1}H NMR spectroscopy (Scheme 43).[122]

Scheme 42

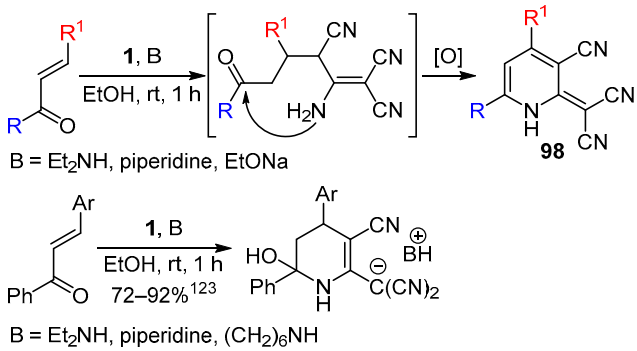


Scheme 43



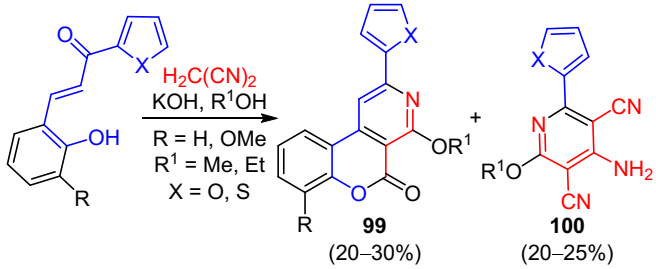
In contrast to aldehydes, the reaction of α,β-unsaturated ketones with malononitrile dimer (**1**) in the majority of cases proceeded as Michael addition followed by cyclization into (pyridin-2(1*H*)-ylidene)malononitriles **98** (Scheme 44).[116,118,123] There are also isolated reports on the preparation of stable Michael adducts[124] and partially hydrogenated pyridine analogs **98** in this reaction.[116,123,125]

Scheme 44



Malononitrile reacts with 1-(hetaryl)-3-(2-hydroxyphenyl)-2-propen-1-ones in the presence of alcoholic alkali solutions, forming a mixture of benzopyrano[3,4-*c*]-pyridines **99** and pyridines **100** (Scheme 45).[126] The formation of products **100** was explained by the authors of the cited publication by alcoholysis of the starting chalcones and dimerization of malononitrile under the conditions of the synthesis.

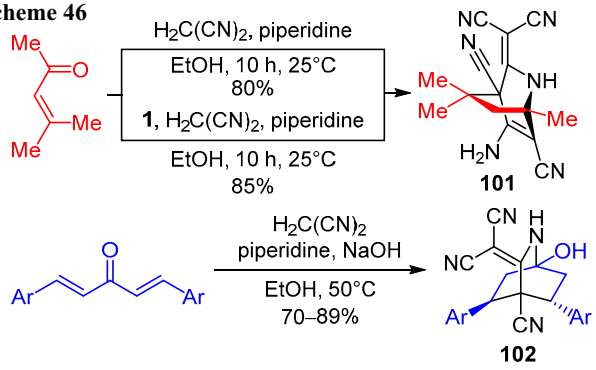
Scheme 45



Mesityl oxide participated in a reaction with malononitrile in the presence of piperidine[127] or In(OTf$_3$)–Et$_3$N[128] with the formation of azabicyclo[2.2.2]octene **101**. According to the proposed mechanism,[127] $H_2C(CN)_2$ was

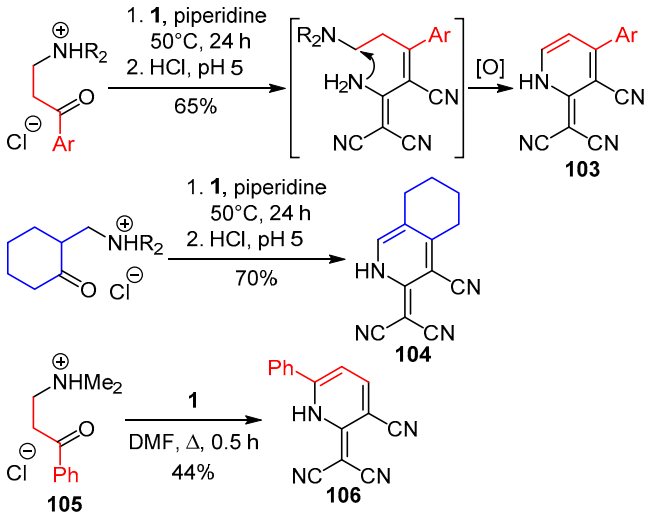
dimerized at the initial step, which was confirmed by the synthesis of product **101** in a higher yield from dimer **1** (Scheme 46). Isoquinuclidines **102** were obtained in a reaction of dibenzalacetones with sodium salt of dimer **1** (formed *in situ* from $H_2C(CN)_2$ and NaOH).[129]

Scheme 46



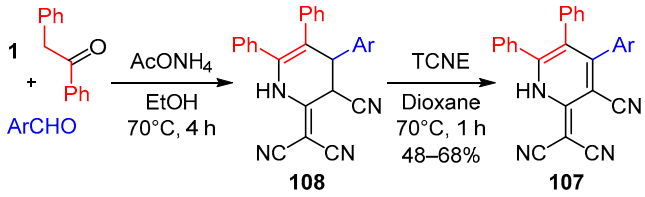
Mannich bases obtained by aminomethylation of ketones can serve as precursors of unsaturated ketones in reactions with malononitrile dimer (**1**). However, there are contradictory data in the literature on the regioselectivity of such reactions and the structures of the products. Thus, it has been reported[130] that the reaction of β-amino ketone hydrochlorides with dimer **1** proceeds as a tandem process involving Knoevenagel condensation and cyclization, leading to pyridines **103** or isoquinolines **104** (Scheme 47). The opposite regioselectivity was described in an earlier study[122] where the product arising from reaction of Mannich base salt **105** with dimer **1** was assigned the structure of pyridine derivative **106**.

Scheme 47



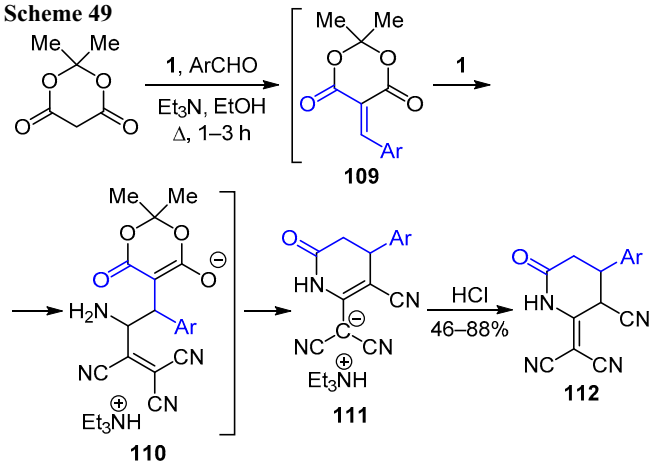
An alternative method for the synthesis of (pyridin-2(1*H*)-ylidene)malononitriles was based on the reaction of dimer **1** with a compound containing activated methylene group and aldehyde. The α,β-unsaturated ketone in this case was generated during the reaction; the components containing activated methylene groups can be selected from α-cyano ketones,[131] *N*-(phenacyl)pyridinium salts,[123,132] and others. In a recent example[133] demonstrating the feasibility of such approach dimer **1** was used in a reaction with ArCHO and deoxybenzoin. The target pyridines **107** were obtained after treating the crude product with tetracyanoethylene (TCNE) as oxidant. Tetrahydropyridines **108** could be isolated in the absence of an oxidant (Scheme 48).

Scheme 48



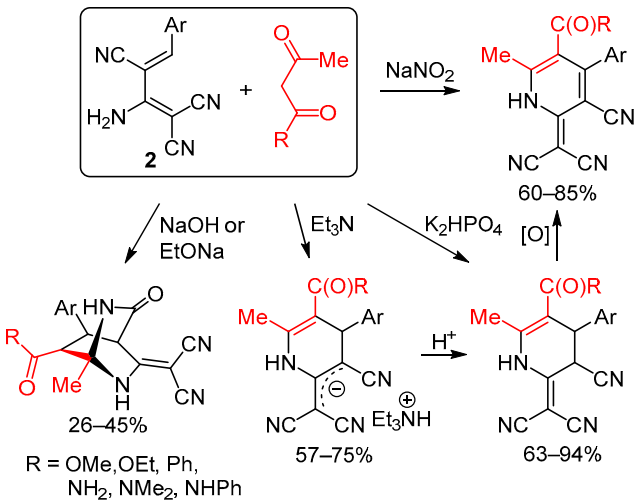
The condensation of malononitrile dimer (**1**) with aldehydes and Meldrum's acid in the presence of Et_3N proceeded *via* the formation of arylidene derivatives **109** and Michael adducts **110**; the products of this process were salts **111;** lactams **112** were isolated after acidification (Scheme 49).[134]

Scheme 49



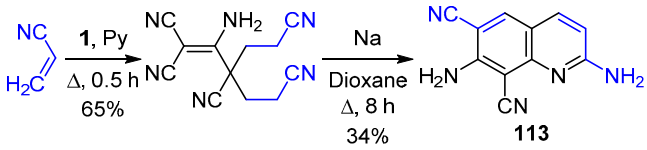
The opposite approach was also successful, starting from the condensation of dimer **1** with aldehydes and using the obtained butadienes **2** in reactions with various carbonyl compounds (Scheme 50).[135] By varying the starting reagents and reaction conditions, it was possible to perform the syntheses of a series of pyridine derivatives.

Scheme 50



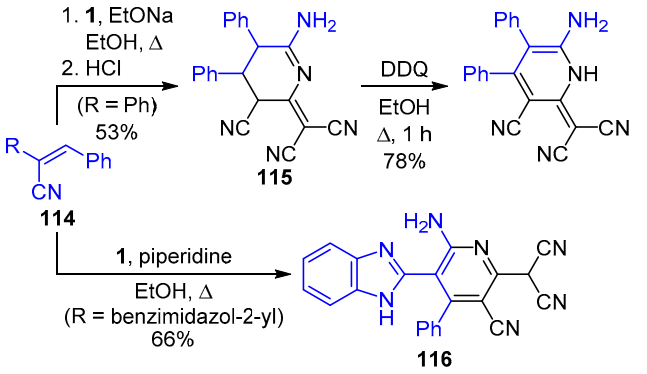
3.4.3. Reactions of malononitrile dimer with α,β-unsaturated nitriles. Acrylonitrile reacted with dimer **1**, producing the C,C-dicyanoethylation product, which was cyclized in the presence of metallic sodium, producing a low yield of quinoline derivative **113** (Scheme 51).[122]

Scheme 51



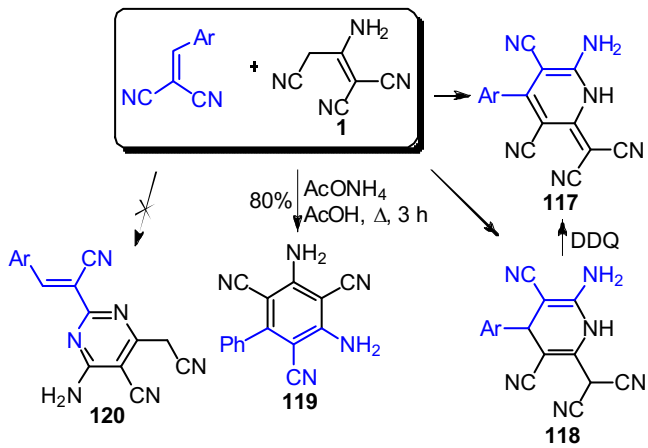
Unsaturated nitrile **114** (R = Ph) reacted with dimer **1**, forming tetrahydropyridine **115** that could be oxidized with dichlorodicyanoquinone (DDQ) (Scheme 52).[136] At the same time, hetero analog **114** (R = benzimidazol-2-yl) gave directly aromatic product **116**.[137]

Scheme 52



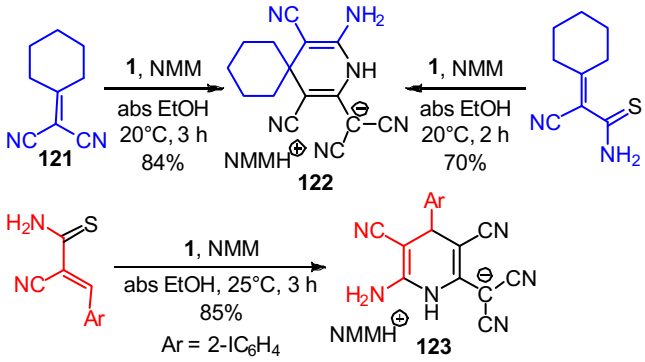
The base-catalyzed reactions of dimer **1** with arylmethylidenemalononitriles have been studied in considerable detail. Generally, the reaction products are 2-(dicyanomethylene)pyridines **117**, 1,4-dihydropyridines **118**, or their mixtures (Scheme 53).[80,138,139] The direction of the reaction substantially depends on the type of the aromatic substituent Ar, as well as on the reaction conditions. Products with partially saturated ring structures were favored in the cases of heterocyclic substituents Ar, as well as phenyl substituents bearing *ortho*-substituents (even under relatively harsh reaction conditions), while aromatization occurred quite readily in the case of Ar = Ph, 4-RC_6H_4. Performing the process under mild conditions (0°C) also favored the preservation of the 1,4-dihydropyridine system.[138a,b] 1,4-Dihydropyridines **118** can be easily oxidized to pyridines **117** with DDQ.[138b] The formation of carbocyclic product **119** in a high yield has been described[80] when the reaction was performed in AcOH in the presence of $AcONH_4$. The earlier reports[140] on the isolation of pyrimidines **120** from reactions of dimer **1** with arylmethylenemalononitriles have not been confirmed and are apparently erroneous.

Scheme 53



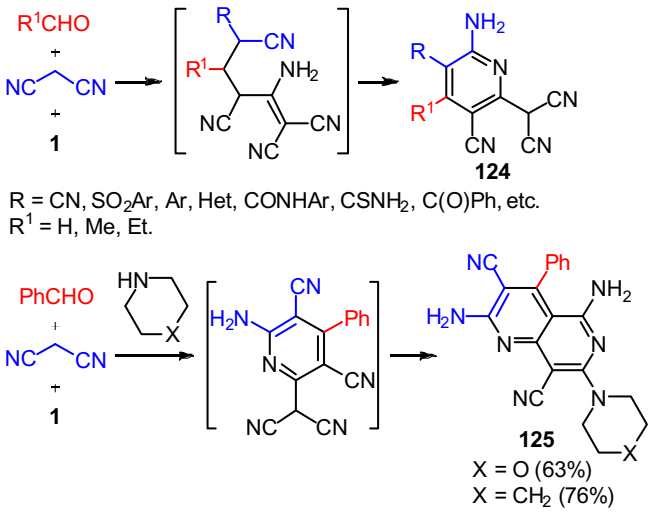
Unsaturated dinitrile **121** reacted with malononitrile dimer (**1**) with the formation of the expected product **122** (Scheme 54).[141] It was established that 2-cyanothioacrylamides under analogous conditions were cyclized with the participation of thioamide group instead of the nitrile group, giving pyridines **122** or **123** as a result.[141,142]

Scheme 54



A convenient modification of the approaches described above is the three-component cyclocondensation of aldehydes with nitriles containing an activated methylene group and malononitrile dimer (**1**). In this case, the unsaturated nitrile was generated *in situ*, giving pyridine derivatives **124** as products (Scheme 55). Aldehydes suitable for this reaction include formaldehyde[143,144] and aliphatic[131,145] aldehydes. It is interesting to note that an analogous reaction between benzaldehyde, malononitrile, and its dimer in the presence of cyclic secondary amines[146]

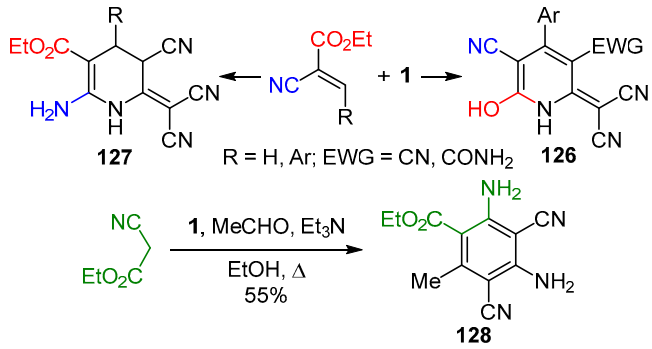
Scheme 55



resulted in the formation of naphthyridines **125**, apparently as a result of cascade transformation of the $=C(CN)_2$ group in the presence of amines.

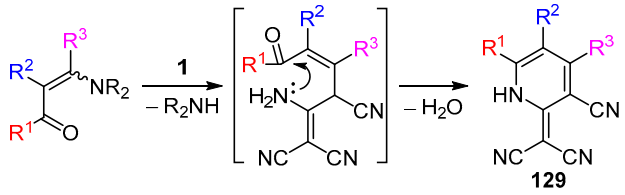
Contradictory data are found in the literature about the reactions of 2-cyanoacrylates with malononitrile dimer (**1**). Thus, it has been reported[147] that cyanoacrylates react with dimer **1** with the formation of products **126** that are structurally related to Guareschi imides. However, earlier studies indicated that 2-aminonicotinates **127** were formed in the reactions of dimer **1** with 2-cyanoacrylates (or cyanoacetic ester and formaldehyde) under analogous conditions (base catalysis, heating) (Scheme 56).[138b,148] Besides that, the preparation of ester **128** in a reaction of acetaldehyde with dimer **1** and cyanoacetic ester has been described.[131] It can be concluded that additional detailed studies will be needed for complete understanding of the regioselectivity in the reactions of dimer **1** with 2-cyanoacrylates.

Scheme 56



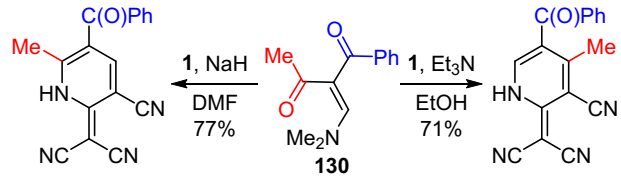
3.4.4. Reactions of malononitrile dimer with push-pull alkenes. The reaction of malononitrile dimer (**1**) with β-enaminoketones can be illustrated with the following overall scheme (Scheme 57).

Scheme 57



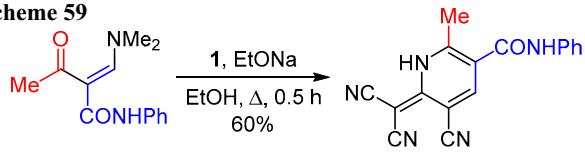
The reaction proceeds as a vinyl substitution at the activated multiple bond and selectively leads to pyridines **129**, as confirmed by a large number of syntheses.[38,149–157] Nevertheless, the work by Junek[157] and later publications[158] describe examples using the opposite sequence of steps (condensation at C=O group → S_NVin) leading to isomeric products. Thus, depending on the reaction conditions, regioisomeric condensation products were formed from enaminodiketone **130** and dimer **1** (Scheme 58).[158]

Scheme 58



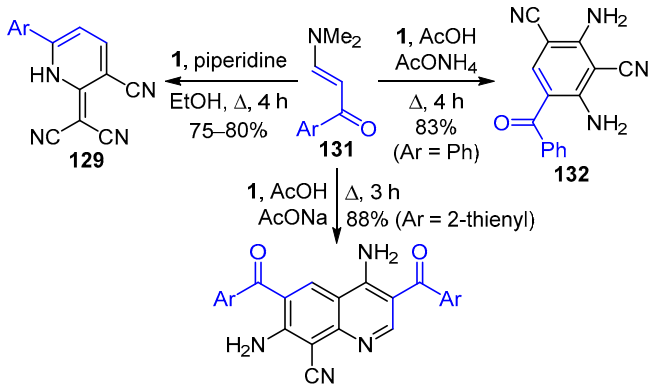
When 2-aminomethylidene derivatives of unsymmetrical 1,3-dicarbonyl compounds or their analogs are used, the cyclization reaction, as a rule, proceeds at the more reactive group (Scheme 59).[159]

Scheme 59



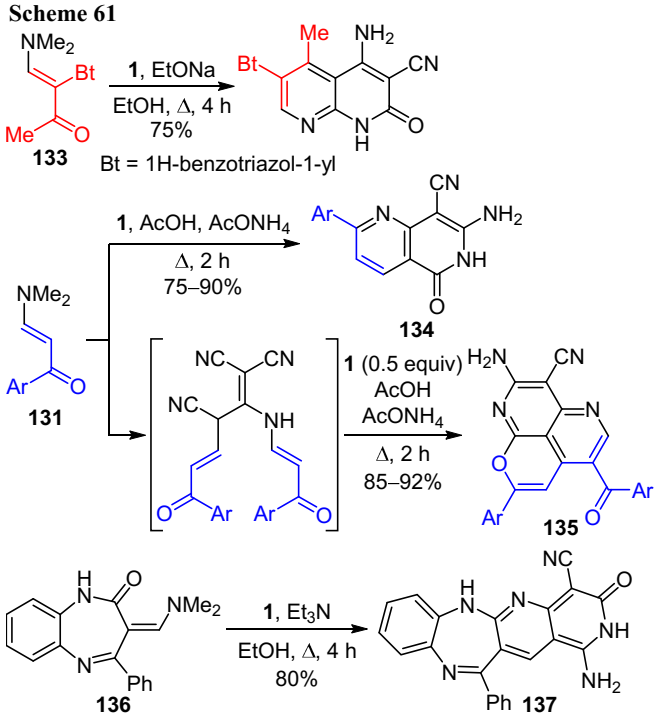
In the case of the simplest enaminoketones **131** products **129** were often obtained in mediocre yields. This was explained by the possibility of a competing process leading to the formation of substituted ketones **132** in parallel with the closure of the pyridine ring.[80,160,161] Optimization of the reaction conditions allowed to direct the process toward either hetero- or carbocyclization route (Scheme 60).[80]

Scheme 60



In several cases it was noted that the reaction proceeded further. For example, the reaction of enaminoketone **133** with malononitrile dimer (**1**) unexpectedly resulted in the formation of 1,8-naphthyridine derivative (Scheme 61).[162]

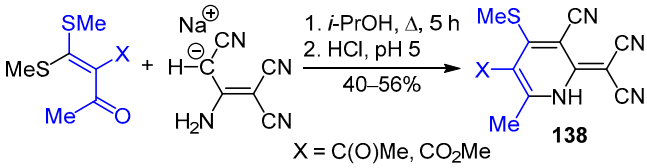
Scheme 61



According to the data from another study,[38] enaminoketones **131** under conditions similar to those proposed for the synthesis of benzophenones **132** were converted to 1,6-naphthyridines **134**, while 2:1 reagent ratio resulted in pyrano[4,3,2-*de*][1,6]naphthyridines **135**.[38] The reaction of benzodiazepinone aminomethylidene derivative **136** with dimer **1** produced polycyclic product **137** (Scheme 61).[163]

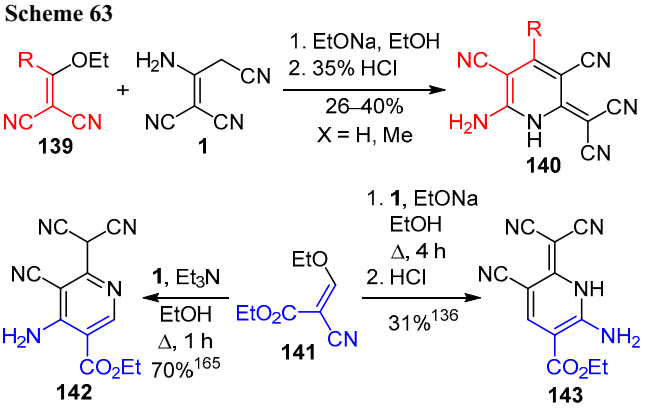
Dithioacetals of α-oxoketenes reacted with the sodium salt of malononitrile dimer according to the S_NVin → cyclization scheme, forming 4-(alkylsulfanyl)pyridines **138** (Scheme 62).[164]

Scheme 62



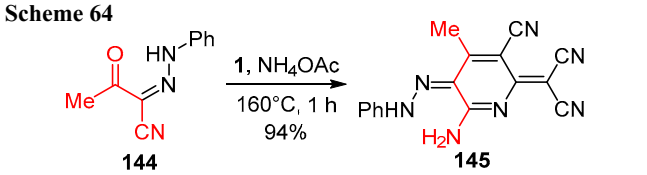
The reaction of malononitrile dimer (**1**) with push-pull alkenes **139** produced the expected pyridine derivatives **140** (Scheme 63).[136] At the same time, the product from the reaction of dimer **1** with ester **141** was assigned the structure of 4-aminopyridine **142**,[165] which was later revised on the basis of X-ray structural analysis results to the isomeric structure **143**.[136]

Scheme 63



3.4.5. Synthesis of pyridines from malononitrile dimer and other 1,3-dielectrophilic reagents. It was shown that solvent-free fusion of malononitrile dimer (**1**) with α-ketohydrazone **144** in the presence of a base led to the formation of dihydropyridine **145** in a practically quantitative yield (Scheme 64).[166]

Scheme 64

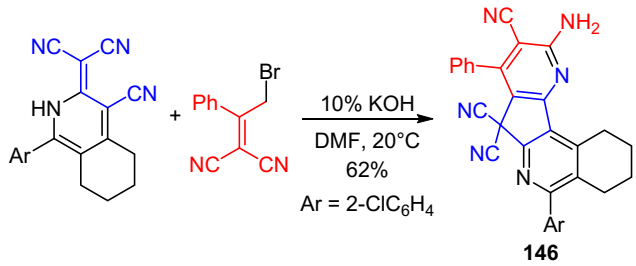


3.5. Some reactions of (3-cyanopyridin-2(1*H*)-ylidene)malononitriles

(3-Cyanopyridin-2(1*H*)-ylidene)malononitriles are readily prepared in a reaction of dimer **1** with 1,3-dielectrophilic reagents or by other methods suitable for the construction of 2-amino-1,1,3-tricyanopropene motif in the molecule (see the review articles[6,167]). Due to the presence of closely arranged cyano groups, these compounds present rich possibilities for performing various heterocyclization reactions. The most important approaches to the transformation of these derivatives of malononitrile dimer (**1**) are described below.

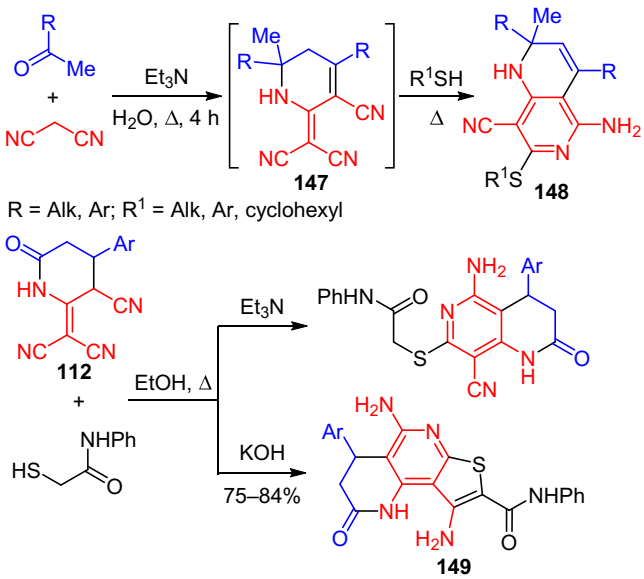
It has been demonstrated[149,150] that (3-cyanopyridin-2(1*H*)-ylidene)malononitriles in alkaline media are selectively alkylated at the middle carbon atom of the malononitrile moiety. Furthermore, depending on the structure of the alkylating agent and the reaction conditions, the isolated products may arise exclusively from *C*-alkylation or polycyclic structures **146** may be obtained by spontaneous further cyclization (Scheme 65).

Scheme 65



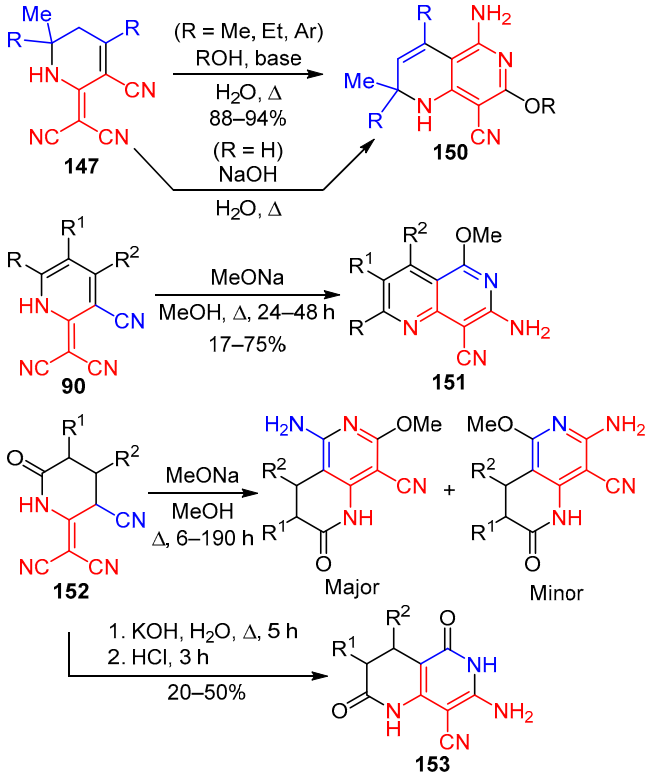
The thiolysis of tetrahydropyridines **147** by reaction with mercaptans occurred selectively at one of the cyano groups of the dicyanomethylidene moiety. The resulting spontaneous cyclization produced 1,6-naphthyridines **148** in 38–95% yields.[168,169] It was noted that the reaction was equally successful with both aliphatic mercaptans and thiophenols. In the case of reaction between 2-(dicyanomethylidene)piperidines **112** and α-mercaptoacetanilide, depending on the reaction conditions either [1,6]naphthyridines or products of further Thorpe–Ziegler cyclization – thieno[2,3-*h*][1,6]naphthyridines **149** were obtained[134] (Scheme 66).

Scheme 66



There are contradictory data in the literature regarding the interaction of (3-cyanopyridin-2(1*H*)-ylidene)malononitriles with O-nucleophiles. For example, pyridines **147** in the presence of bases reacted selectively with phenols[168] or alcohols[169] with the formation of 7-(alk/aryloxy)-1,6-naphthyridines **150**. When the reaction was performed in the presence of a strong base (NaOH), 7-hydroxy-substituted analogs were also isolated.[168] At the same time, the reactions of compounds **90** with sodium methoxide in methanol showed different regioselectivity of the initial attack by methoxide ion, which eventually led to the formation of 5-methoxynaphthyridines **151** (Scheme 67).[116] However, in the case of compounds **152**, the treatment with sodium methoxide produced a mixture of regioisomeric solvolysis products.[170] On the other hand, hydrolysis with aqueous alkali solution[170] or in acidic medium[38] led to 6-oxonaphthyridines (for example, forming the structure of compounds **153**).

Scheme 67

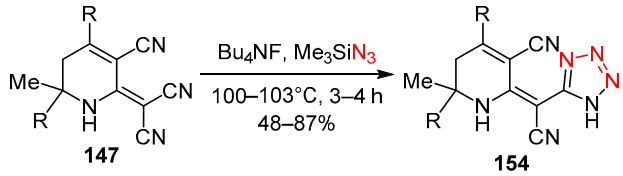


Thus, the regioselective direction of reactions between (3-cyanopyridin-2(1*H*)-ylidene)malononitriles and O-nucleophiles substantially depended both on the structure of the substrate and the activity of the reagent.

The reaction of (3-cyanopyridin-2(1*H*)-ylidene)malononitriles with N-nucleophiles has been studied in considerable details. The reaction of pyridines **147** with trimethylsilyl azide led to the formation of tetrazoles **154** in moderate to good yields (Scheme 68).[171]

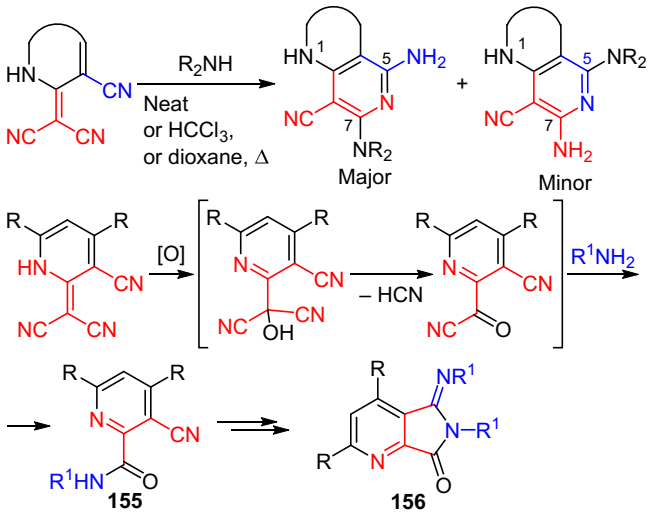
The reactions of (3-cyanopyridin-2(1*H*)-ylidene)-malononitriles with primary and secondary amines occurred mostly regioselectively as nucleophilic addition at one of the nitrile groups in the $=C(CN)_2$ moiety and was

Scheme 68



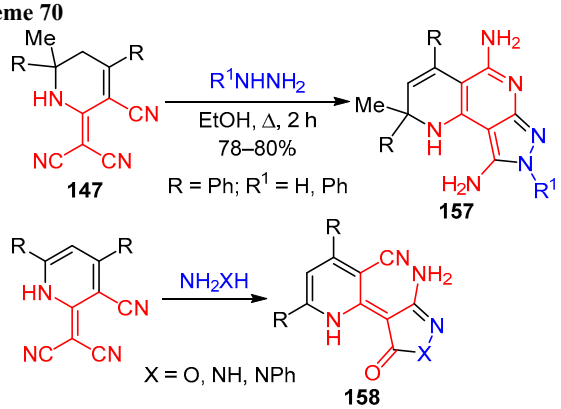
followed by spontaneous cyclization leading to 7-amino-1,6-naphthyridines (Scheme 69).[172–174] Detailed investigation of the reaction mechanism[174] showed that the solvent polarity, type of amine, and steric hindrance in the pyridine substrate had a crucial effect on the selectivity of the reaction and the content of the minor 5-amino-1,6-naphthyridine isomer (less polar reaction medium promoted the exclusive formation of 7-amino isomer). Another side reaction during this process was oxidative decyanation[174] that produced noticeable yields (up to 35%) of picolinamides **155** or pyrrolo[3,4-*b*]pyridines **156**. This direction of the reaction can be completely suppressed by performing the reaction under argon atmosphere.

Scheme 69



It has been demonstrated[158,175,176] that the hydrazinolysis of (3-cyanopyridin-2(1*H*)-ylidene)malononitriles reliably produces pyrazolo[3,4-*h*][1,6]naphthyridine derivatives. For example, refluxing compounds **147** with hydrazines in alcohol solution produced products **157** in good yields[176] (Scheme 70). The results of earlier studies[114,115] pointed to

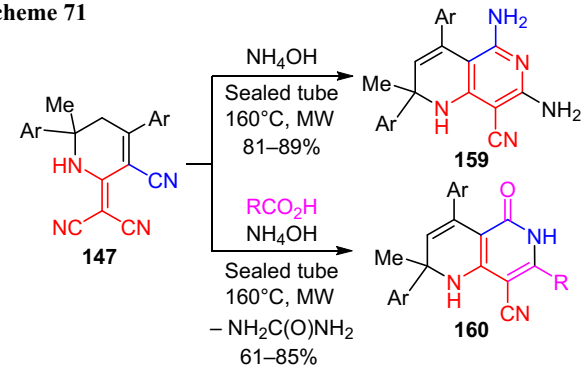
Scheme 70



the formation of azoles **158** as a result of reactions between (3-cyanopyridin-2(1*H*)-ylidene)malononitriles and hydrazines or hydroxylamine under similar conditions, but it appears that these experimental observations need additional verification.

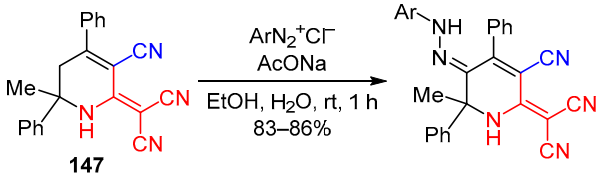
The reaction of (3-cyanopyridin-2(1*H*)-ylidene)malononitriles with ammonia leads to various products depending on the reaction conditions and the molecular structure of the substrate. Thus, compounds **147** gave good yields of 5,7-diamino-1,6-naphthyridines **159** when irradiated with microwaves in aqueous ammonia solution, but naphthyridines **160** were obtained under analogous conditions in the presence of carboxylic acids (Scheme 71).[177] It should be also noted that earlier studies involving the treatment of related substrates with aqueous ammonia[114] or NH_4OAc in AcOH[38] led only to hydrolysis or gave products of further transformations.

Scheme 71



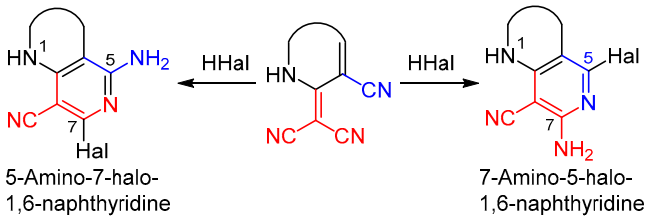
As vinylogs of malononitrile dimer, pyridines **147** participate in azo coupling reactions with diazonium salts (Scheme 72).[176]

Scheme 72



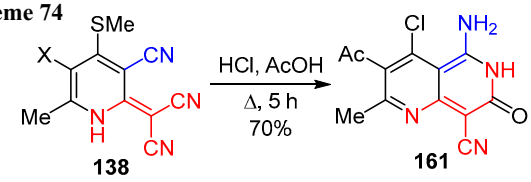
According to publications by various authors, the cyclization of (3-cyanopyridin-2(1*H*)-ylidene)malononitriles by the action of HBr or HCl can give 7-amino-5-halo-1,6-naphthyridines[113,170,178] or their isomers – 5-amino-7-halo-naphthyridines[116] (Scheme 73). This topic was studied in detail. It was established that the regioselectivity of the reaction was substantially affected by several factors, namely, solvent polarity affecting the tautomeric equilibrium between the dicyanomethylene and dicyanomethyl forms of the substrate, planar configuration of the reactive site, reaction temperature, the relative basicity of the cyano groups, and the presence of a substituent at position 4 of the pyridine ring.[118] Careful attention to the reaction conditions and the selection of suitable substrates in the majority of the cases allowed to achieve high regioselectivity or even regiospecificity in the given reaction.

Scheme 73



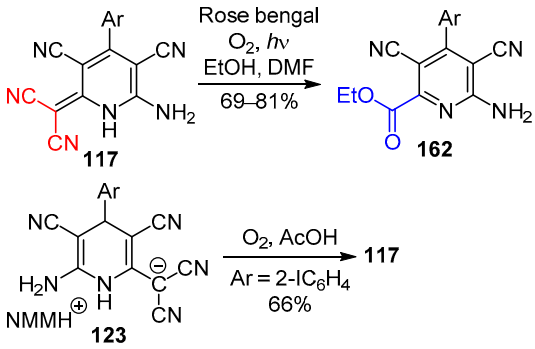
It has been reported[164] that refluxing of 4-(methylsulfanyl)pyridine **138** (X = Ac) in an HCl solution in AcOH resulted in nucleophilic substitution of the methylthio group with chlorine atom and cyclization to naphthyridine **161** (Scheme 74).

Scheme 74



The oxidation of dicyanomethylene moiety can be considered to be a promising but so far insufficiently explored area in the chemistry of (3-cyanopyridin-2(1*H*)-ylidene)malononitriles. Thus, the photooxidation of dicyanomethylenepyridines **117** with air oxygen in the presence of rose bengal as sensitizer produced good yields of picolinates **162** (Scheme 75).[179] However, it should be noted that for partially hydrogenated analogs of compounds **117** the main direction of oxidation was merely aromatization of the di- or tetrahydropyridine ring.[136,138b,142] For example, the treatment of dicyanomethylide **123** with acetic acid under air atmosphere led to the formation of oxidation product **117** in 66% yield.[142]

Scheme 75

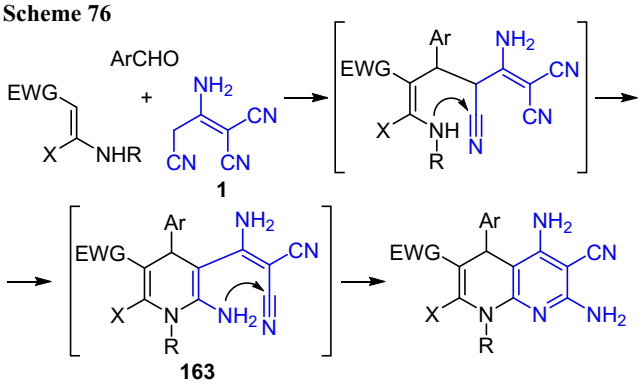


3.6. Synthesis of 1,8-naphthyridine derivatives from malononitrile dimer

Besides the methods considered in chapter 3.5. for the preparation of 1,6-naphthyridine derivatives by cyclization of 1,5-dinitriles belonging to pyridine series, several examples are known for the construction of 1,8-naphthyridine system starting from malononitrile dimer (**1**). This approach is generally applicable and involves a cascade reaction of enaminocarbonyl compound (or related push-pull alkene) with a carbonyl compound and dimer **1** (or

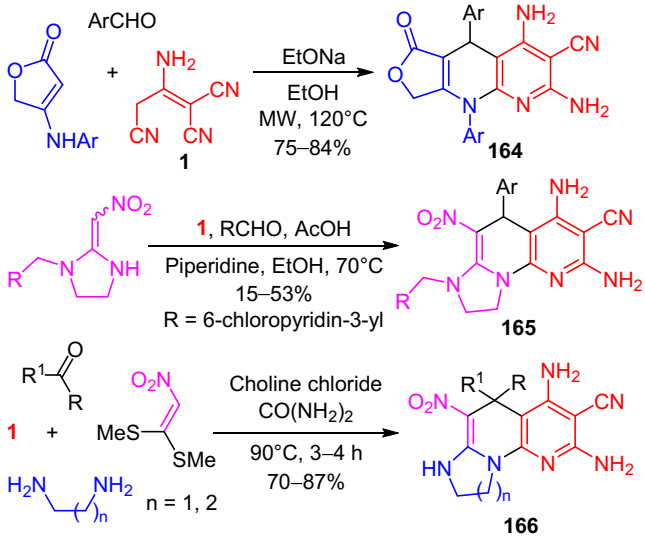
product of their condensation). The initial 1,4-dihydropyridine intermediate **163** formed by a Hantzsch-type condensation contained a δ-aminopentadienonitrile moiety, which was transformed by spontaneous cyclization into the second pyridine ring (Scheme 76). The reaction occurred upon heating in basic medium and, as a rule, gave high yields of 1,8-naphthyridines.

Scheme 76



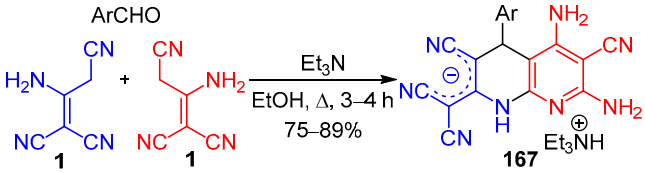
The given approach allowed to obtain a large number of fused 1,8-naphthyridine derivatives by starting from various enaminoketones, enaminoesters[180–184] or ketenaminals.[185–187] Among examples illustrating the possibilities offered by this method, we should mention the synthesis of furo[3,4-*b*]naphthyridines **164**[181] or the preparation of compounds with insecticidal activity against the *Aphis craccivora Koch* aphid – imidazo[1,2-*a*][1,8]-naphthyridines **165**[187] (Scheme 77). It should be noted that the synthesis of fused 1,8-naphthyridines **166** can be achieved within the framework of a four-component domino process by generating ketenaminals *in situ*.[186]

Scheme 77



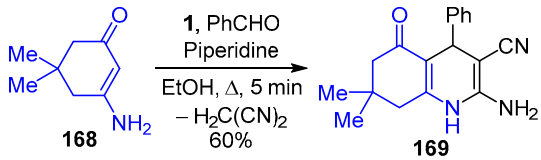
The reaction of aldehydes with 2 equiv of malononitrile dimer (**1**) in the presence of a base followed a similar route.[188] The intermediates were apparently 4-arylbuta-1,3-diene-1,1,3-tricarbonitriles **2**, which underwent a Michael addition of a second equivalent of dimer **1** and after a chain of cascade transformations formed dicyanomethylides **167** in good yields (Scheme 78).

Scheme 78



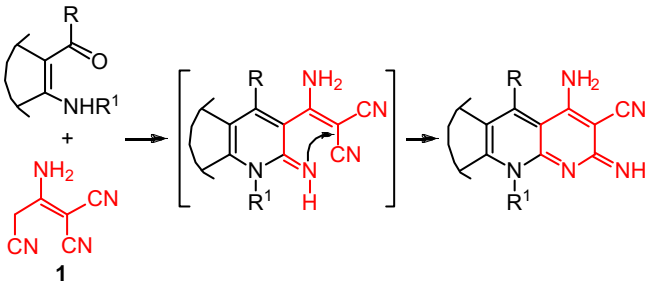
Among the few limitations of the strategy outlined above we should note the unsuccessful attempt to obtain naphthyridines from *N*-unsubstituted enamine dimedone **168**: in that case the competing process predominated with the elimination of malononitrile and formation of quinoline **169** (Scheme 79).[182]

Scheme 79



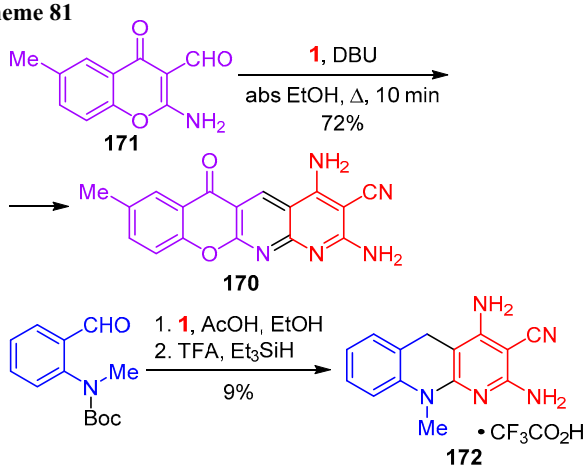
Another strategically important approach to the assembly of 1,8-naphthyridine system is based on the interaction of 1,4-aminocarbonyl compounds with dimer **1** according to the Friedländer reaction mechanism followed by 6-*exo*-*dig* cyclization of the δ-iminonitrile moiety (Scheme 80).

Scheme 80



The first example of such transformations was described by Junek already in 1963.[18] A one-pot method was recently reported for the preparation of chromeno[2,3-*b*][1,8]-naphthyridine **170** from 2-amino-4-oxochromene-3-carbaldehyde **171** (Scheme 81).[189] Another example of a

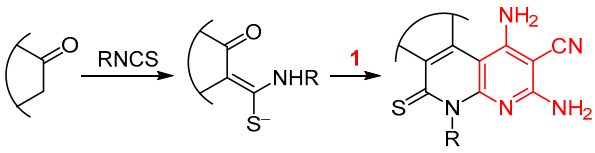
Scheme 81



tandem process on the basis of the Friedländer reaction and subsequent cyclization was used in the synthesis of benzonaphthyridine **172**.[190]

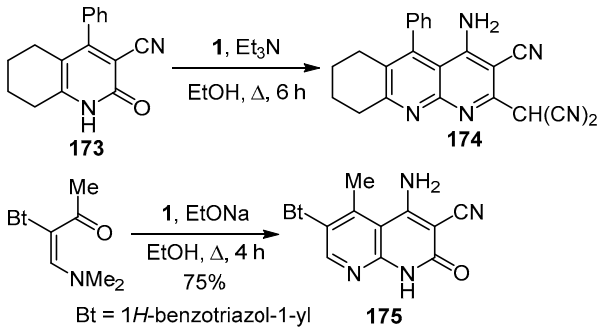
A method is known for the preparation of 1,8-naphthyridines using the reaction of dimer **1** with β-oxothioanilide anions generated *in situ* from compounds with activated methylene groups and isothiocyanate (Scheme 82).[191,192]

Scheme 82



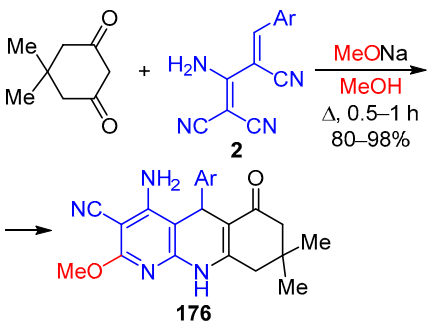
An unusual condensation of 3-cyanoquinolin-2-one **173** and dimer **1** has been described that occurred under relatively mild conditions and led to the formation of naphthyridine **174** (Scheme 83).[193] However, taking into account the reaction conditions and the absence of essential analytical data on product **174** and the known types of reactivity of the starting compounds, we strongly believe that the aforementioned interpretations should be in doubt. The reported synthesis of naphthyridine **175**, described in an earlier work, also seems to be in question.[194]

Scheme 83



An original method was proposed for the preparation of functionalized naphthyridines **176** on the basis of a reaction between 4-arylbuta-1,3-diene-1,1,3-tricarbonitriles **2** with dimedone in the presence of sodium methoxide (Scheme 84).[21]

Scheme 84

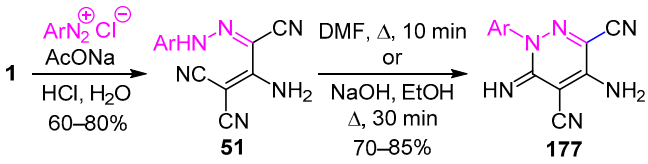


4. Synthesis of diazine derivatives

4.1. Synthesis of pyridazine derivatives

It was observed in the early 1980s that the azo coupling reaction in the case of malononitrile dimer (**1**) led to hydrazones **51**, which were readily cyclized upon heating

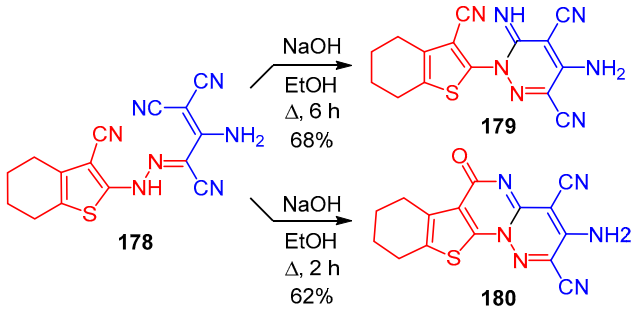
Scheme 85



or treatment with alcoholic alkali solutions, leading to the formation of pyridazines **177** (Scheme 85).[138e,194]

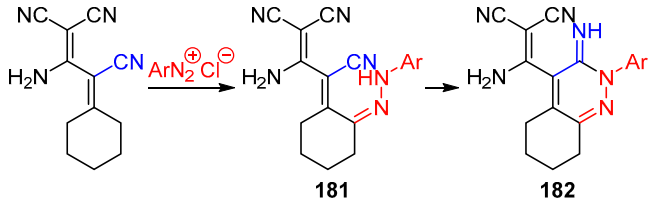
This approach has been successfully used in recent years for the preparation of functionalized pyridazines.[195–198] In the cases when the diazo component contains functional groups, further processes of cascade heterocyclization become possible. Thus, hydrazone **178** was converted to pyridazine **179** by refluxing in an alcoholic alkali solution,[82] however, according to other sources[81] the reaction under the same conditions proceeded further with the formation of tetracyclic product **180** (Scheme 86).

Scheme 86



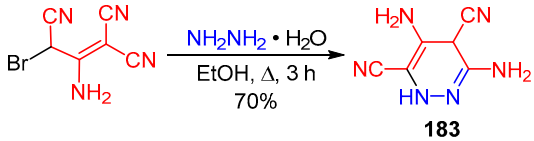
The products arising from malononitrile dimer condensation with ketones reacted with diazonium salts at the activated methylene group.[58,199] The azo coupling product that was thus obtained underwent cyclization in the presence of a strong base. Thus, refluxing of compound **181** in alcohol solution of EtONa gave cinnoline **182** (Scheme 87). It was noted that the attempts to achieve further cyclization led only to hydrolysis at the imino group.[199]

Scheme 87



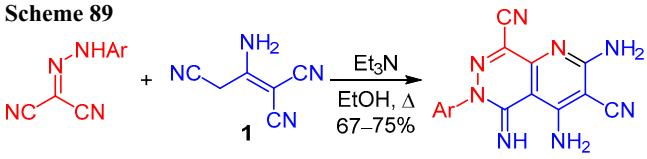
The bromination product obtained from malononitrile dimer reacted with hydrazine with the formation of a compound that was identified as pyridazine **183** (Scheme 88).[37]

Scheme 88



Another important approach to the preparation of pyridazine derivatives is based on the interaction of dimer **1** with azo coupling products obtained from compounds containing activated methylene groups. The possibilities from using such an approach were first demonstrated already in 1986, with the example of reaction between dimer **1** and arylazomalononitriles (Scheme 89).[200]

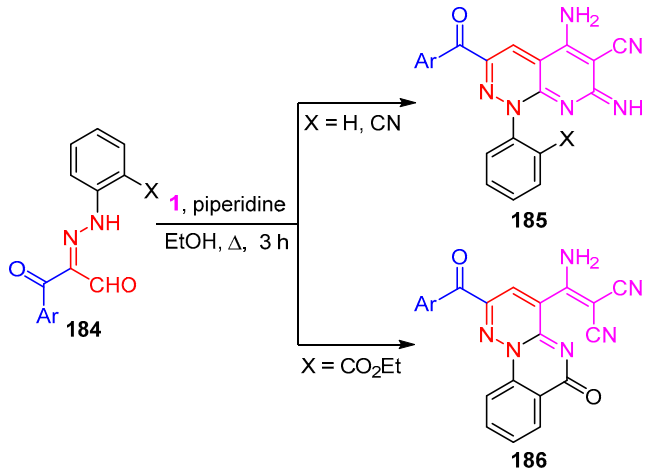
Scheme 89



As a rule, the reaction did not stop at the stage of pyridazine ring formation and subsequent cascade processes led to fused ring structures. In the case of unsymmetrically substituted arylhydrazones ArNHN=C(X)Y, the nucleophilic attack by anion of dimer **1** in the majority of cases proceeded selectively and was directed at only one of the substituents X or Y. On the basis of dataset obtained from reactions of malononitrile dimer (**1**) with arylazo derivatives of acetylacetone and acetoacetic ester,[166,201] α-formyl ketones,[202–204] cyanoacetic ester,[205] α-cyano ketones,[166,205,206] and cyanothioacetamide,[207,208] substituents can be arranged in the following order according to decreasing susceptibility toward nucleophilic attack: CHO > RC(O) > C≡N > CO_2Et / $C(S)NH_2$.

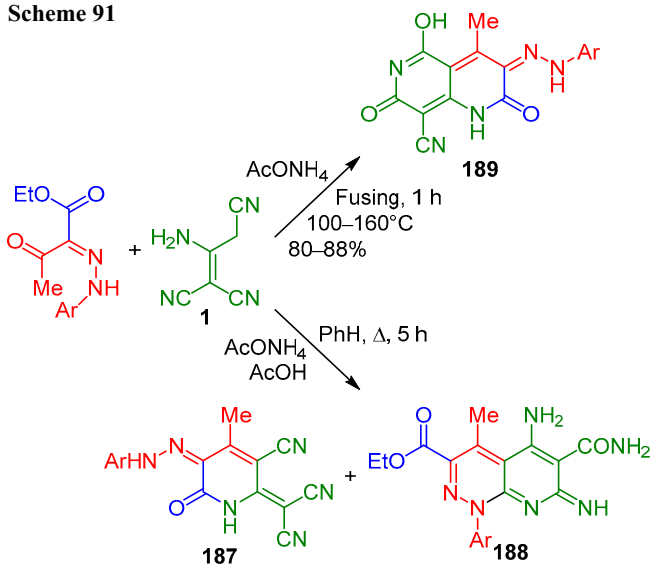
Thus, the reactions of hydrazones **184** with dimer **1** led to the formation of pyrido[2,3-*c*]pyridazines **185**, while the presence of an ester group at the *ortho* position of the aryl substituent allowed to change the direction of the reaction toward the formation of tricyclic products **186** (Scheme 90).[202–204]

Scheme 90



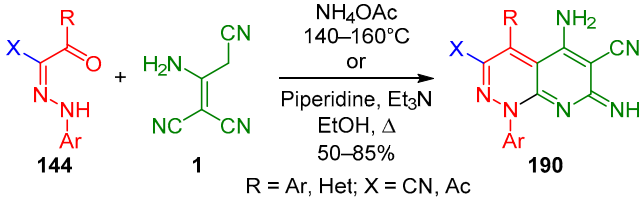
In some cases the reaction gave peculiar results. For example, the reaction of dimer **1** with arylazoacetoacetic ester gave mixtures of pyridines **187** with the expected pyridopyridazines **188** in approximately equal amounts (Scheme 91).[201] Changing the conditions of cyclocondensation reactions led to a major change in the regioselective direction of the process and formation of 1,6-naphthyridine **189**.[166]

Scheme 91



2-Arylhydrazonylidene-3-oxobutyronitriles **144** also react in unusual manner, resulting in the formation of 2-(dicyanomethylidene)pyridines **145** (Scheme 64),[166] although other α-ketohydrazones under the same conditions formed the expected pyridopyridazines **190** (Scheme 92).[166,201,205,206]

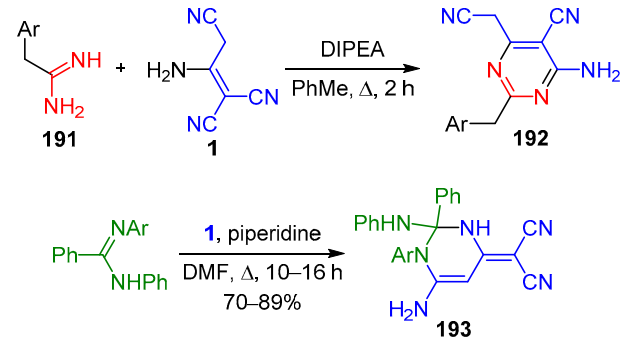
Scheme 92



4.2. Synthesis of pyrimidine derivatives

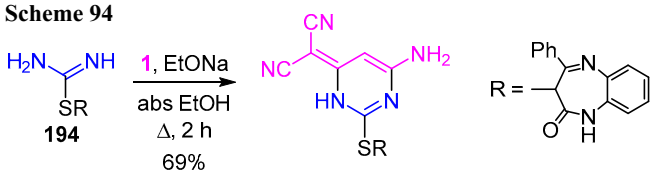
Malononitrile dimer (**1**) can act as enaminonitrile in reactions with amidines **191**, leading to vinyl substitution of amino group followed by cyclization step producing pyrimidines **192**.[209] It should be noted that the reaction is not universally applicable. Thus, it has been demonstrated earlier by Junek and coworkers that the reactions of dimer **1** with formamidine and acetamidine produce pyridine derivatives.[210] In the case of *N*,*N*'-disubstituted amidines, as demonstrated in a recent work,[211] pyrimidine derivatives **193** were formed (Scheme 93).

Scheme 93



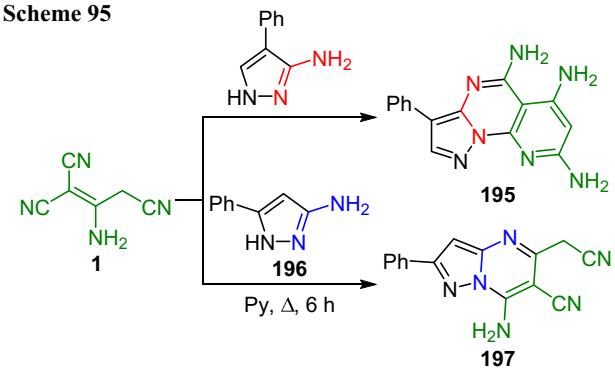
It has been reported[212] that *S*-substituted thioamidine **194** under the conditions of basic catalysis participates in a reaction with dimer **1**, producing dihydropyrimidine in 69% yield (Scheme 94). However, it should be pointed out that dimer **1** reacted differently with isothiuronium salts in the presence of bases[100] (Scheme 33).

Scheme 94



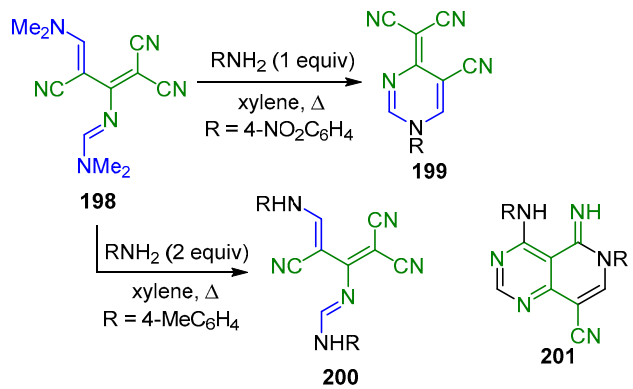
Synthesis of tricyclic product **195** *via* cascade reaction of 3-amino-4-phenyl-1*H*-pyrazole with dimer **1** has been reported (Scheme 95).[213] At the same time, according to literature data, isomeric 5-phenylpyrazole **196** reacted differently – with the formation of pyrazolo[1,5-*a*]-pyrimidine **197**.[214] Obviously, the details of aminoazole reactions with malononitrile dimer (**1**) should be studied in greater detail.

Scheme 95



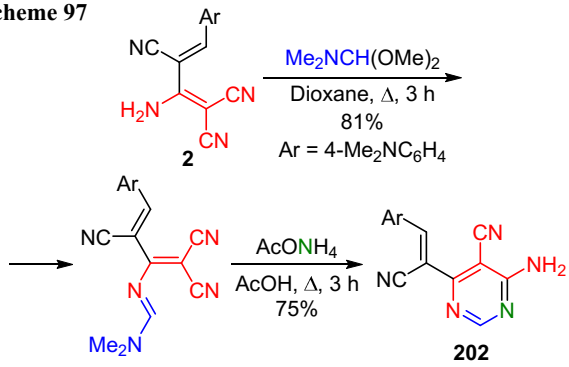
It has been reported that the product obtained by treatment of malononitrile dimer (**1**) with 2 equiv of dimethylformamide dimethyl acetal, compound **198**, participated in reactions with primary amines, and depending on the ratio of the starting reagents the products were either pyrimidine **199** or the condensation product **200** (Scheme 96).[195] It should be noted here that the given reaction has been previously studied in detail by Mittelbach and Junek,[215] who showed that the reaction of compound **198** with amines actually led to the formation of pyridopyrimidines **201**.

Scheme 96



2-Aminobutadiene-1,1,3-tricarbonitrile (**2**) reacted with dimethylformamide dimethyl acetal at the amino group[78] and the condensation product was further treated with ammonium acetate in refluxing acetic acid, producing a good yield of pyrimidine **202** (Scheme 97).

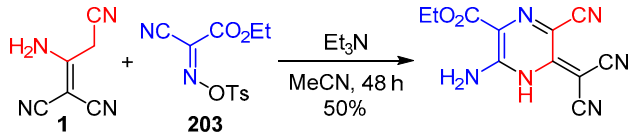
Scheme 97



4.3. Synthesis of pyrazine derivatives

The only found example for the preparation of pyrazine derivatives was based on the treatment of dimer **1** with tosylate **203** in the presence of a base (Scheme 98).[216]

Scheme 98

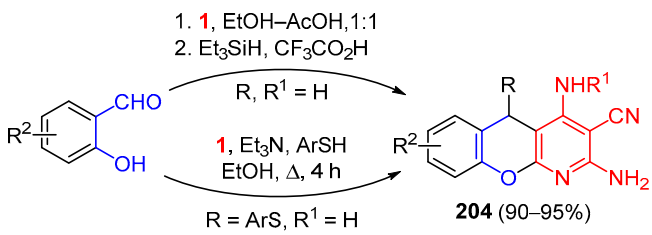


5. Synthesis of oxygen- and sulfur-containing heterocycles

5.1. Synthesis of chromenopyridine derivatives

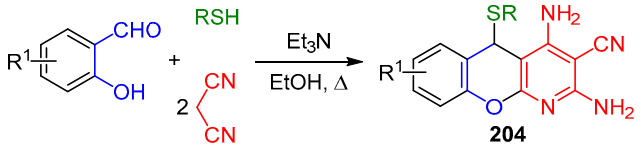
A significant number of studies in recent years have been devoted to the chemistry of chromeno[2,3-*b*]pyridine. The interest toward this heterocyclic system is motivated by recent discoveries of its broad spectrum of biological activity, allowing to consider these structures as examples of the so-called privileged scaffolds. Thus, compounds **204** (R = ArS, R^1 = H) have shown good activity against hepatitis C virus and liver fibrosis,[217,218] as well as moderate anticancer activity.[92] Chromeno[2,3-*b*]pyridines **204** (R = H, $HC(CN)_2$, R^1 = H, alkyl) act as inhibitors of mitogen-activated protein kinases MK-2.[190,219] The standard synthetic approach for the construction of tricyclic system **204** is the reaction of salicylic aldehydes with dimer **1** in the presence of a reducing agent (Et_3SiH)[190,219] or mercaptans[92] (Scheme 99).

Scheme 99



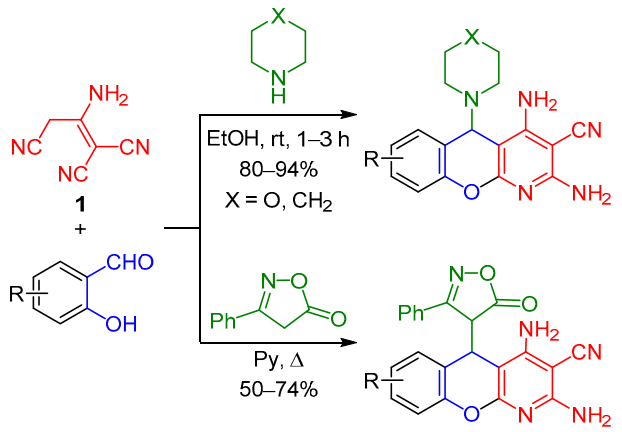
A successful modification of this synthesis was discovered by using 2 equiv of malononitrile instead of dimer **1** (Scheme 100).[220] The reaction between 2-hydroxybenzaldehydes, malononitrile, and mercaptans proceeded in the presence of Et_3N, therefore it was logical to assume that malononitrile dimer (**1**) in this case was generated *in situ*, although alternative mechanisms for this synthesis cannot be completely excluded. Despite the high yields of products **204** in the proposed variant, which in some cases reached 85–90%,[92,220,221] some additional improved procedures have been recently published, providing practically quantitative yields and relying on the application of such exotic catalysts as Fe_3O_4@SiO_2–NH_2 nanocomposite,[222] ZrP_2O_7 nanoparticles,[223] chitosan functionalized with citric acid,[224] SnO nanoparicles,[225] and others. In our opinion, the justification of such modifications for solving real synthetic challenges is doubtful. It was also established[92] that using microwave irradiation allowed to obtain the target products **204** with yields not exceeding 45%.

Scheme 100



Mercaptans in the reaction with dimer **1** and 2-hydroxybenzaldehydes could be successfully replaced with other nucleophiles (Scheme 101), such as secondary amines[226] and 3-phenylisoxazol-5(4*H*)-one.[227]

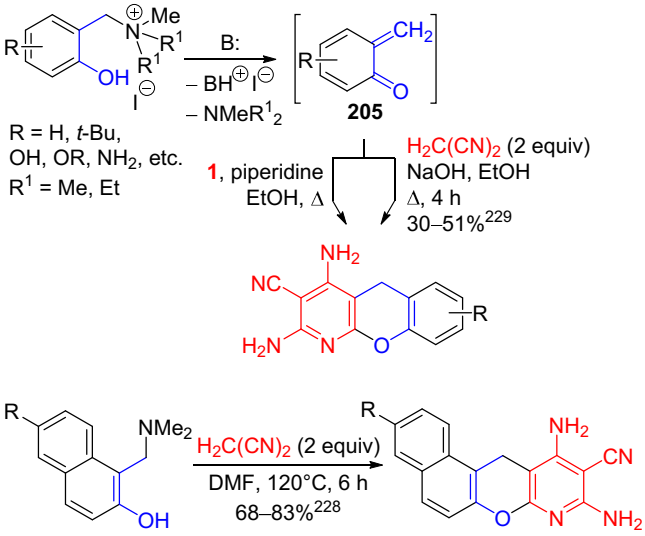
Scheme 101



An alternative approach to the synthesis of structures **204** was based on the interaction of *o*-quinone methides **205** with dimer **1**[190a] or 2 equiv of malononitrile[228,229] (Scheme 102). In the latter case, malononitrile dimer (**1**) was likely formed during the reaction in the presence of base.

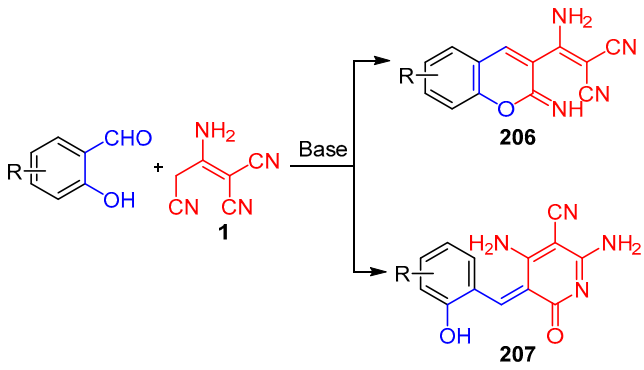
The structure of products arising from the reactions of malononitrile dimer (**1**) with salicylic aldehyde and its

Scheme 102



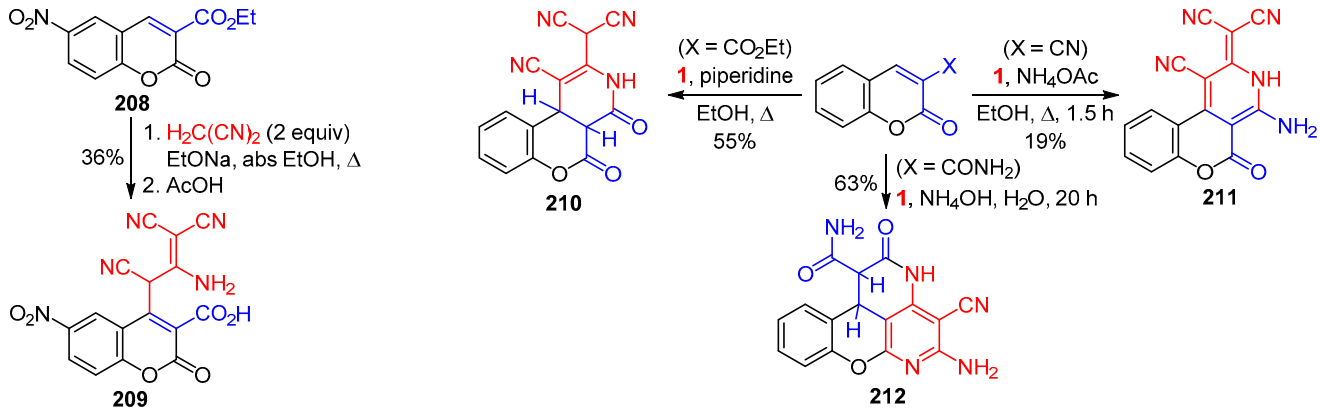
analogs in the absence of nucleophilic agents (mercaptans, amines etc.) has been the matter of discussions for a long time. A publication by Junek[230] and several later studies[231] have shown that the condensation process generally stopped at the stage of 2-iminochromenes **206** (Scheme 103) and, contrary to expectations, did not lead to the formation of chromenopyridine derivatives. At the same time, some data point to the formation of dihydropyridine **207** under the conditions of this reaction.[115,232]

Scheme 103



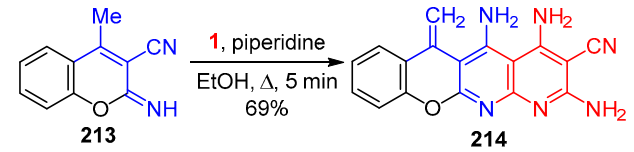
Malononitrile dimer (**1**) is capable of addition to coumarins at the C-4 atom, with the formation of either Michael adducts or chromenopyridine derivatives. Thus, a reaction of nitro-substituted 3-ethoxycarbonylcoumarin **208** with *in situ* generated dimer **1** led to the formation of compound **209** (Scheme 104).[233] At the same time, a method is known from the literature for the preparation of chromenopyridine **210** from dimer **1** and an unsubstituted coumarin analog **208** (Scheme 104).[234] 3-Cyanocoumarin reacted with dimer **1** in the expected way,[235] *via* Michael addition followed by cyclization to chromenopyridine **211**. However, 3-carbamoylcoumarin reacted by a different mechanism – with recyclization step leading to the formation of chromeno[4,3,2-*de*][1,6]naphthyridine **212**.[236]

Scheme 104



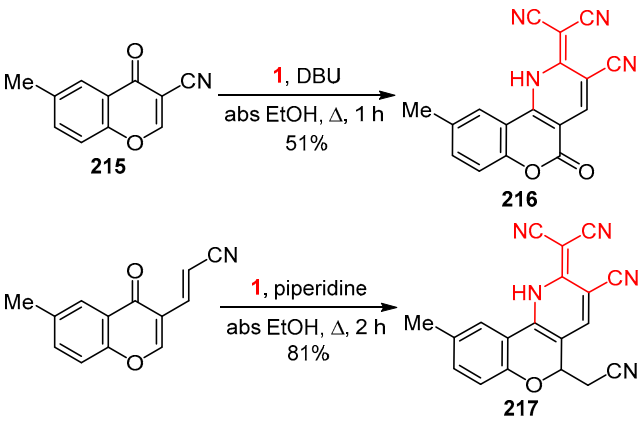
Treatment of iminochromene **213** with malononitrile dimer (**1**) produced chromenonaphthyridine **214** (Scheme 105).[237] In this case, the nucleophilic attack by anion of dimer **1** was directed at the cyano group of chromene, instead of the C-4 position, which probably can be explained by steric hindrance.

Scheme 105



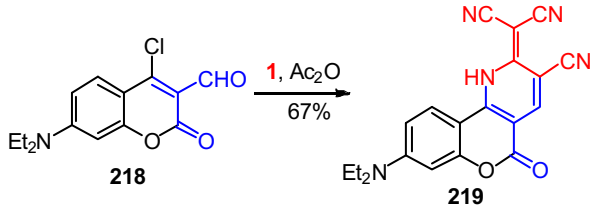
3-Cyanochromone **215** reacted with malononitrile dimer (**1**) in the presence of diazabicycloundecene (DBU), leading to recyclization and the formation of chromeno-[4,3-*b*]pyridine **216** in a moderate yield (Scheme 106).[189] Another example of a similar recyclization can be found in the recently described synthesis of chromenopyridine **217** from vinylogous nitrile **215**.[238]

Scheme 106



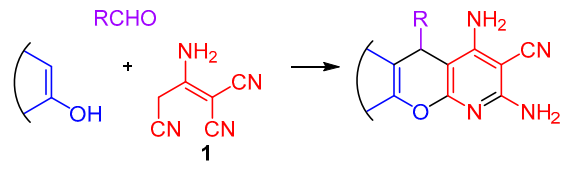
The reaction of 4-chloro-3-formylcoumarin **218** with dimer **1** proceeded as a tandem Knoevenagel condensation – nucleophilic substitution process and led to the formation of chromenopyridine **219** that was characterized as a fluorescent dye (Scheme 107).[239]

Scheme 107



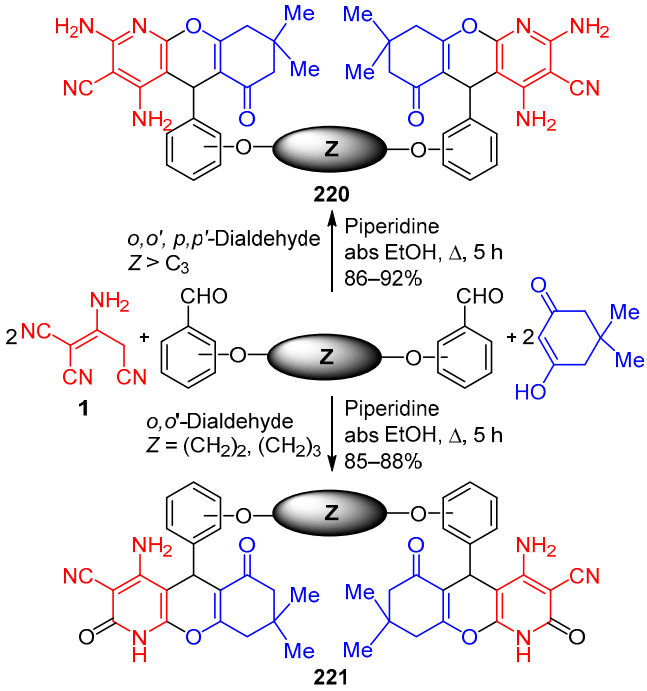
An important method for the preparation of chromeno-[2,3-*b*]pyridines is the reaction of aldehydes, malononitrile dimer (**1**) (or products of their condensation) with reagents serving as sources of C–C–O fragment: activated phenols, enols of carbonyl compounds, and others. The reaction was catalyzed by bases: alkali metal alkoxides or amines (Scheme 108). Suitable sources of the C–C–O fragment include dimedone,[21,240–243] activated phenols[92,244–246] and α-naphthol,[247] 1,3-cyclohexanedione,[240] 4-hydroxyquinolin-2(1*H*)-one,[240] kojic acid,[240] and 3-methyl-1*H*-pyrazol-5(4*H*)-one.[248]

Scheme 108



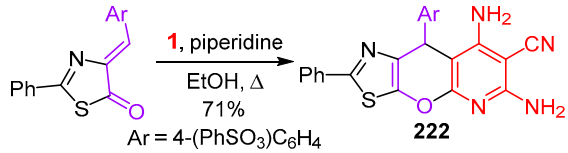
As a rule, the synthesis of chromeno[2,3-*b*]pyridines according to the given scheme proceeded without complications and gave high yields. One of the relevant publications reported an unusual change in the direction of the reaction between malononitrile dimer (**1**), dimedone, and aromatic dialdehydes depending on the length and position of the linker Z in the starting dialdehydes, leading to selective formation of either compounds **220** or the partial hydrolysis products **221** (Scheme 109).[241] The formation of the latter compounds occurred in the case if the linker was quite short (no longer than 2-3 methylene groups) and connected the *ortho* positions of aromatic rings in the dialdehydes.

Scheme 109



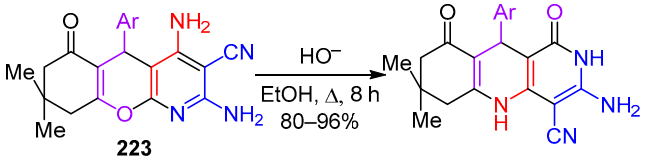
Compound **222** showing strong fungicidal activity against the pathogens *Helminthosporium oryzae* and *Pyricularia oryzae* was synthesized in 71% yield from dimer **1** and 4-arylidene-2-phenylthiazolin-5-one (Scheme 110).[249]

Scheme 110



Among the most interesting transformations of chromeno[2,3-*b*]pyridines we should note the recently discovered recyclization of compounds **223** to 1,6-naphthyridine derivatives by the action of alkali in alcohol solutions (Scheme 111).[250] The reaction presumably occurred by an ANRORC mechanism, giving high yields of the products.

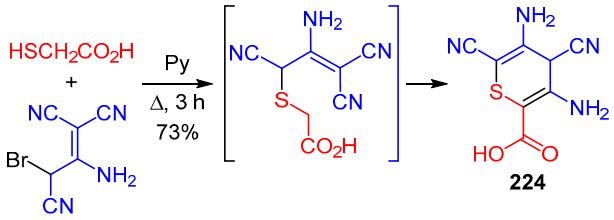
Scheme 111



5.2. Synthesis of thiopyran and thiochromene derivatives

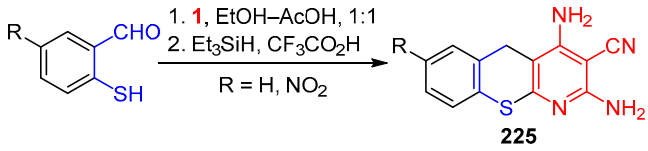
The product obtained by bromination of malononitrile dimer reacted with thioglycolic acid by a mechanism involving steps of alkylation and Thorpe–Ziegler cyclization, with the formation of 4*H*-thiopyran **224** (Scheme 112).[54]

Scheme 112



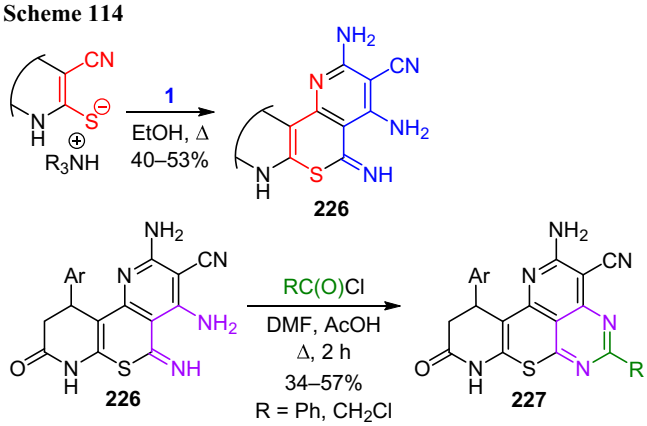
2-Mercaptobenzaldehydes reacted with dimer **1** analogously to salicylic aldehyde, forming the thio analogs of compounds **204** – thiochromeno[2,3-*b*]pyridines **225** (Scheme 113).[190]

Scheme 113



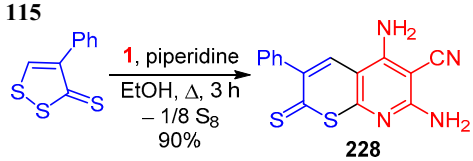
Prolonged refluxing (10–25 h) of 3-cyanopyridine-2-thiolates with malononitrile dimer (**1**) in alcohol led to the formation of cascade heterocyclization products, pyrido-[2′,3′:2,3]thiopyrano[4,5-*b*]pyridines **226** in moderate yields (Scheme 114).[251–253] Compounds **226** were found to be convenient precursors for the synthesis of polycyclic systems **227**.[253]

Scheme 114



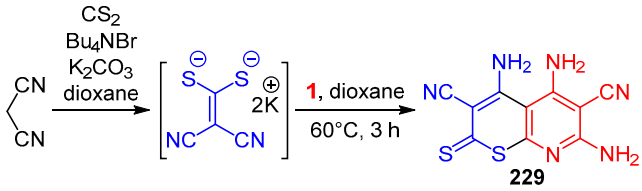
The possibility of effectively obtaining thiopyrano-[2,3-*b*]pyridine derivatives by recyclization of 1,2-dithiol-3-thiones in the presence of dimer **1** was demonstrated by the synthesis of compound **228** (Scheme 115).[254]

Scheme 115



An alternative approach to the assembly of thiopyrano-[2,3-*b*]pyridine system was based on the interaction of active methylene compounds with carbon disulfide followed by the reaction of the obtained ethene-1,1-dithiolates with dimer **1**.[59,191] Thus, a reaction of malononitrile with carbon disulfide and then with malononitrile dimer (**1**) allowed to obtain heterocyclic compound **229** in 77% yield (Scheme 116).[191]

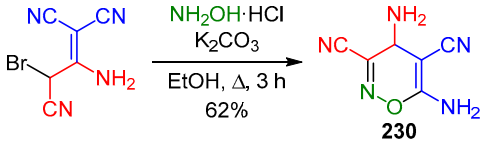
Scheme 116



5.3. Synthesis of oxazine and thiazine derivatives

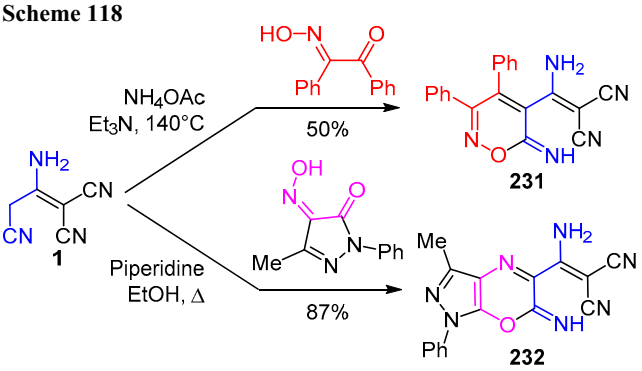
1,2-Oxazine derivative **230** was obtained in 62% yield by treatment of 2-amino-3-bromo-1,1,3-tricyanopropene with hydroxylamine (Scheme 117).[37]

Scheme 117



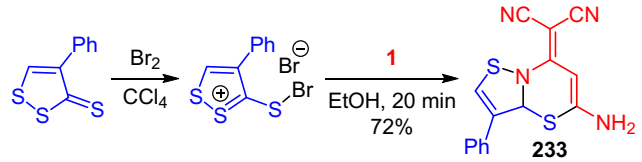
1,2-Oxazines can be obtained by condensation of malononitrile dimer with α-isonitroso ketones. For example, solvent-free fusion of benzil monooxime with dimer **1** gave oxazine **231** (Scheme 118).[255] It should be noted that this approach is not universal and the reaction is apparently sensitive to the structure of the nitroso/isonitroso component. Thus, malononitrile dimer (**1**) participated in the Ehrlich–Sachs reaction with 4-isonitrosopyrazol-5-one and, as a result of further intramolecular cyclization, representatives of a relatively rare heterocyclic system – pyrazolo[3,4-*b*][1,4]oxazines **232** were formed.[256]

Scheme 118



The possibility of assembling 1,3-thiazine ring can be illustrated by the synthesis of compound **233** through recyclization of 1,2-dithiolium bromide in the presence of dimer **1**, as described in a study by Barsy[257] (Scheme 119).

Scheme 119

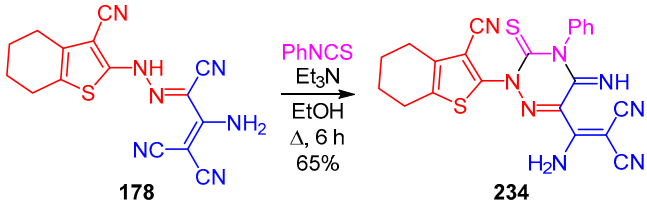


6. Miscellaneous syntheses

In this chapter we consider the syntheses of heterocycles containing three and more heteroatoms, as well as the syntheses of polycyclic systems.

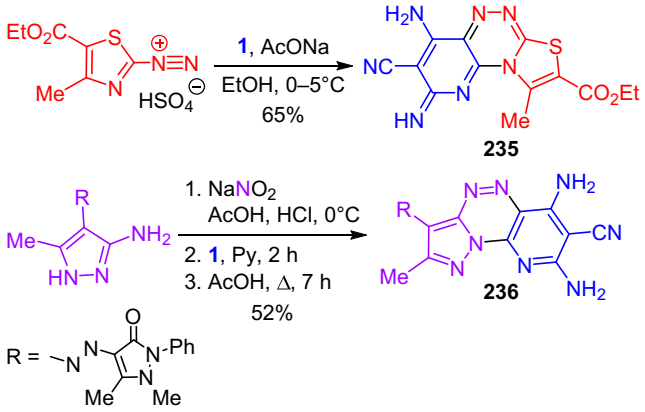
Two studies by Wardakhan[81,82] describe a series of transformations starting from hydrazone **178**, leading to the formation of polyazacyclic systems. An illustrative example would be the formation of 1,2,4-triazine **234** (Scheme 120).

Scheme 120



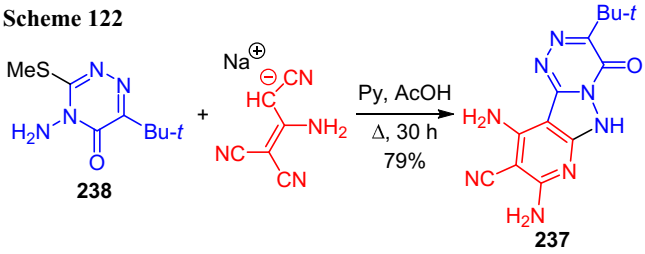
Several examples for the preparation of polycyclic systems on the basis of azo coupling products have been presented in the literature.[166,206,258,259] Thus, for instance, the azo coupling reactions of malononitrile dimer (**1**) with azolyldiazonium salts led to tricyclic products **235**[258] and **236**[259] (Scheme 121).

Scheme 121



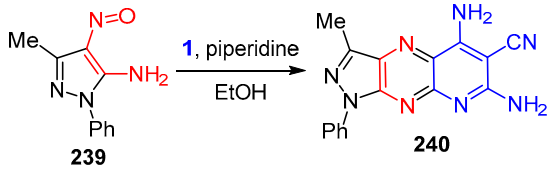
Synthesis of polyazaheterocycle **237** was accomplished using a cascade process including the steps of nucleophilic substitution (S_NAr) and two Thorpe cyclization reactions, starting from sodium salt of dimer **1** and 4-amino-1,2,4-triazine **238** (Scheme 122).[260]

Scheme 122



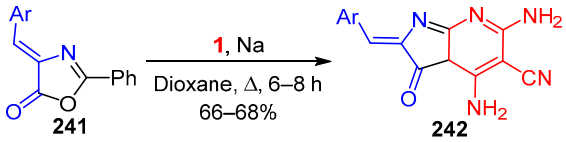
5-Amino-4-nitrosopyrazole **239** underwent Ehrlich–Sachs condensation with dimer **1**, resulting in the formation of tricyclic product **240** as a result of subsequent cascade processes (Scheme 123).[261]

Scheme 123



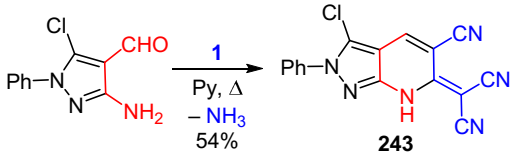
Contrary to the expectations, malononitrile dimer (**1**) did not give Michael addition products with azalactones **241**: the reaction occurred along recyclization mechanism and led to the formation of pyrrolo[2,3-*b*]pyridines **242** (Scheme 124).[262]

Scheme 124



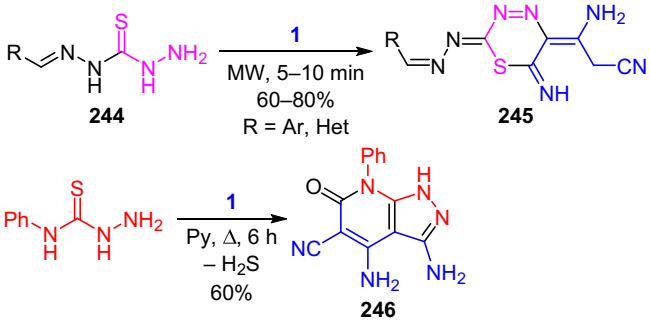
Pyrazolo[3,4-*b*]pyridine derivative **243** can be obtained by the Friedländer reaction from 3-aminopyrazole-4-carbaldehyde (Scheme 125).[263] The reaction proceeded with elimination of ammonia.

Scheme 125



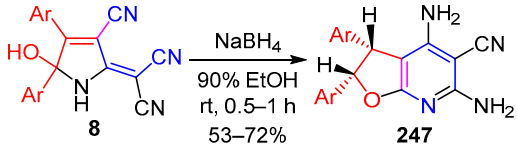
According to Aly and coworkers,[264] thiocarbohydrazones **244** reacted with malononitrile dimer (**1**) with the formation of 1,3,4-thiadiazines **245** upon refluxing in DMF medium in the presence of piperidine (10–25% yields) or under the conditions of microwave irradiation (yields 60–80%) (Scheme 126). It should be noted that, according to another source,[265] the reaction of 4-phenylthiosemicarbazide with dimer **1** proceeded along a different route and led to pyrazolopyridine **246**. Clearly, the mechanism and direction of the reactions between dimer **1** and carbothiohydrazides must be studied in greater detail.

Scheme 126



An original diastereoselective synthesis of 2,3-dihydrofuro[2,3-*b*]pyridines **247**, using the recyclization of pyrroles **8** under reducing conditions (Scheme 127) has been described in a recent work.[266]

Scheme 127

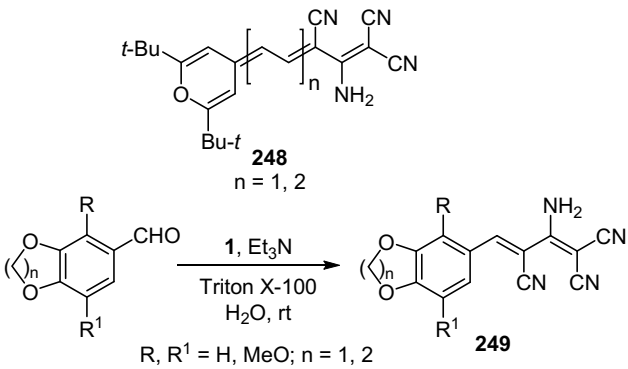


7. Practical applications of malononitrile dimer and its derivatives

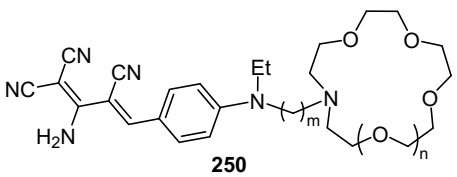
The biological activity of malononitrile dimer (**1**) was observed already in the early 1960s, when it was found that the presence of dimer **1** caused the increase of nucleoproteins in cells upon treatment with aqueous solutions of malononitrile.[267] At the same time, the antithyroid effect of dimer **1** was observed during *in vivo* experiments on rats and humans.[268] Subsequent studies showed that malononitrile dimer (**1**) in general has pronounced nootropic properties – it serves as a mimetic of nerve growth factor and promotes the regeneration of neural tissues,[269] upregulates the synthesis of RNA in neurons and neural tissues,[270] promotes the biosynthesis of neuromediator acetylcholine,[271] reduces the amnesia after electric shock,[272] stimulates the processes of learning and memory.[273] However, subsequent studies of the nootropic effects *in vivo* produced inconclusive results.[274] Thus, it has been noted in one study[274b] that the nootropic properties of malononitrile dimer were offset by the antithyroid effect.

Dimer **1** was proposed as a specific reagent for fluorimetric determination of copper at low levels.[275] Recently it was found[276] that compounds **51** serve as effective corrosion inhibitors for copper in the presence of HNO_3. Push-pull polyenes (for example, compound **248**, Scheme 128) obtained by condensation reactions of various polyenals[50,63,64,277–280] or nitrosoarenes[46–49] with dimer **1** are of interest as dyes and chromophores for the design of systems with nonlinear optical properties. A recently proposed method provides access to potentially useful fluorescent dyes – 4-arylbuta-1,3-diene-1,1,3-tricarbonitriles (for example, compounds **249**, Scheme 128), on the basis of reactions between dimer **1** and aldehydes in aqueous media in the presence of non-ionic surfactants as catalysts (62–92% yields).[281]

Scheme 128



A reaction of malononitrile dimer (**1**) and azacrown ethers containing nitrosyl or aldehyde functional groups was used for the synthesis of original chromoionophores suitable for analytical chemistry applications and in medical diagnostics.[282] The effectiveness of both the chromophoric and ionophoric parts of molecule **250** (Fig. 1) was achieved by their separation using a linker consisting of several methylene groups.



250

m = 1–3; n = 1, 2

Figure 1. Chromoionophores on the basis of malononitrile dimer.

Malononitrile dimer has found its role as active and multifunctional reagent with considerable synthetic potential, useful for solving a wide range of problems in heterocyclic chemistry. Our presented analysis of literature data, as well as another brief review focused on the chemistry of malononitrile dimer,[283] which was published during the preparation of this article reveal an abundance of synthetic applications for this reagent. Compared to the closest structural analogs – malononitrile,[3–6] cyanoacetamide,[284] cyanothioacetamide,[285] and cyanoseleno-acetamide,[286] – the molecule of 2-aminopropene-1,1,3-tricarbonitrile has several unique features that enable directed synthesis of original molecular structures with finely tuned functionality. At the same time, some of the early experimental data suffer from contradictions that should be eliminated through careful further studies, which can be recognized as an important task in this area of synthetic organic chemistry. In general, considering the analysis of all available data, we can predict further development of productive research regarding the chemistry of malononitrile dimer.

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