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Recyclisation of carbo- and heterocyclic compounds involving malononitrile and its derivatives †

V P Litvinov

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Abstract. Published data on recyclisation reactions of carbo- and heterocycles with participation of malononitrile and recyclisation of compounds containing a malononitrile fragment or fragments with malononitrile as a synthon are surveyed, described systematically and analysed. The bibliography includes 206 references.

I. Introduction

Recyclisation of carbo- and especially heterocyclic compounds occupies an important place in organic chemistry. Recyclisation in the presence of various nucleophilic, electrophilic or dipolar reagents occurs as opening of the ring in the initial molecule and its subsequent closure. This process is often accompanied by ring expansion or contraction, introduction of a heteroatom in the ring or its replacement by another heteroatom, *etc*. Nevertheless, from the preparative viewpoint, all these complex transformations occur during a one-stage reaction, which makes possible relatively easy synthesis of compounds that are difficult to obtain by other methods or modification of heterocyclic fragments in complex, including natural, molecules. The latter is fairly important for the synthesis of new biologically active products. At present, a large number of transformations of this type are known; they include name reactions, for example, the Yur'ev, Zincke – Konig and Hafner reactions, the Dimroth, Boulton – Katritzky, Cornforth and Kost – Sagitullin rearrangements, *etc*. The problem of recyclisation is considered in numerous publications and reviews (see, for example, Refs 1 – 24).

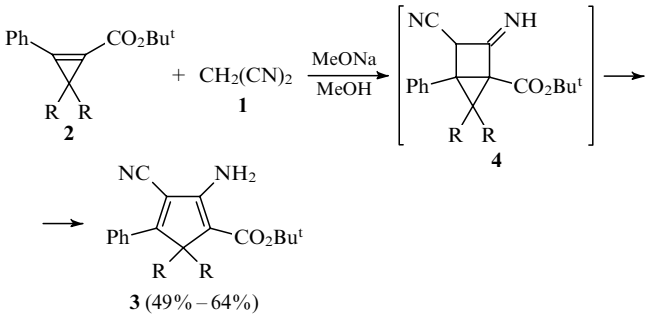
Malononitrile **1**, containing highly reactive methylene and cyano groups,[25] is of special interest as a reagent for recyclisation of carbo- and heterocyclic compounds. In this review, we consider recyclisation reactions with participation of malononitrile and its derivatives including carbo- and heterocyclic compounds with vicinal cyano groups. Primary attention is paid to the synthetic potential of these reactions and less space is given to the reaction mechanisms, because the data on the mechanisms are quite limited and often contradictory.

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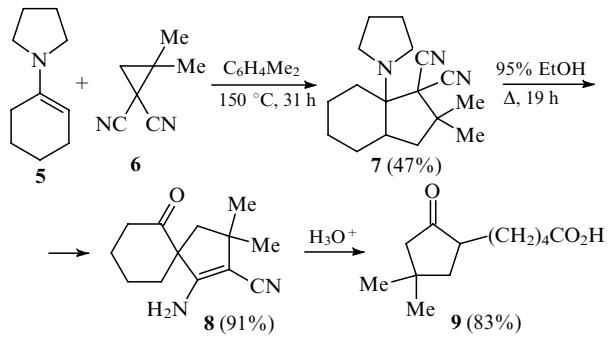
II. Recyclisation of three- and four-membered rings

In 1983, a group of German scientists found that cyclopropene derivatives **2** react with the malononitrile anion, generated by treatment of malononitrile with sodium methoxide in methanol, to give functionally substituted cyclopentadienes **3**. Bicyclic derivatives **4** were postulated as intermediates in this reaction.[26]



R = Me, Ph.

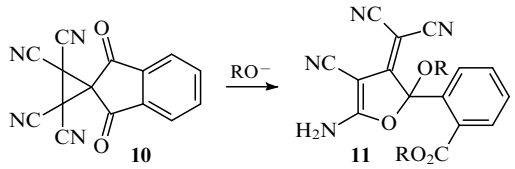
Cycloaddition of *N*-cyclohexenylpyrrolidine **5** to 2,2-dimethyl-1,1-cyclopropanedicarbonitrile **6** has been reported.[27] The reaction follows an S_N2 mechanism and yields adduct **7**. On partial hydrolysis, this product rearranges into spiro compound **8**, which is further hydrolysed to give 5-(4,4-dimethyl-2-oxocyclopentyl)pentanoic acid **9**.



The reactivity of substituted tetracyanocyclopropanes has attracted considerable attention of researchers in recent years. Thus it was found that treatment of 3,3-phthaloylcyclopropane-1,1,2,2-tetracarbonitrile **10** with nucleophiles (alcohols or ketox-

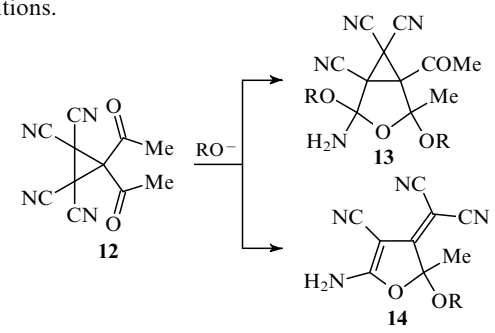
† This review is dedicated to the memory of Professor Yu A Sharanin.

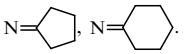
imes) induces recyclisation of the cyclopropane fragment in **10** and results in the formation of 2-alkoxy-2-(2-alkoxycarbonylphenyl)-5-amino-4-cyano-3-dicyanomethylene-2,3-dihydrofurans **11**.[28,29]



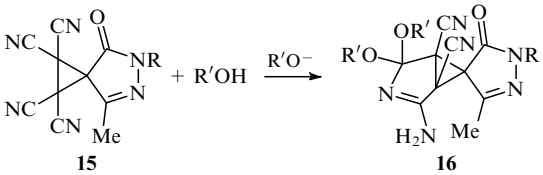
R = Me, Et, $(CH_2)_2OH$, N = CMe_2, N=.

Unlike the cyclopropane **10**, 3,3-diacetylcyclopropane-1,1,2,2-tetracarbonitrile **12** reacts with alcohols or ketoximes in the presence of catalytic amounts of the corresponding sodium alkoxides or oximates with retention of the cyclopropane ring to give substituted 3-oxabicyclo[3.1.0]hexane-1,6,6-tricarbonitriles **13**.[28,30] However, when a twofold excess of the catalyst is used, 2,3-dihydrofuran derivatives **14** are formed under similar conditions.



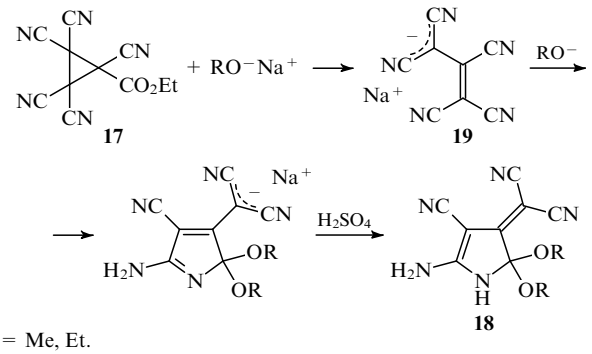
R = Me, Et, N = CMe_2, N = CMeEt, N = CMeBu, $(CH_2)_2OH$,
.

The cyclopropane ring is also retained when substituted pyrazoline-4-spirocyclopropanetetracarbonitriles **15** are treated with alcohols and ketoximes under the same conditions; this reaction affords adducts **16**.[31]



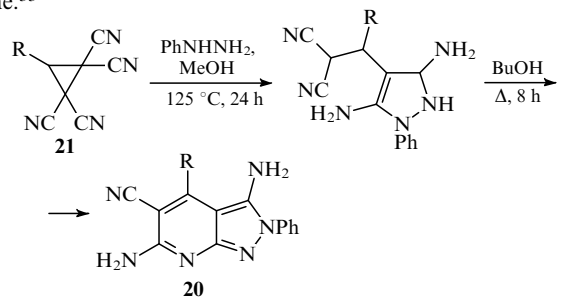
R = Pr^i, Ph; R′ = Me, Et, N = CMe_2, N = CMeEt, N=, N=.

When ethyl pentacyanocyclopropanecarboxylate **17** is made to react with alcohols in the presence of an equimolar amount of the corresponding alkoxide, it undergoes recyclisation to give 5,5-dialkoxy-2-amino-4-dicyanomethylene-2-pyrroline-3-carbonitriles **18**. The formation of a stable intermediate, sodium pentacyanopropenide **19**, was noted.[32]



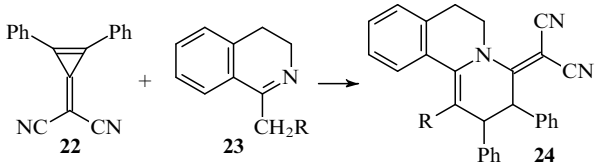
R = Me, Et.

2*H*-Pyrazolo[3,4-*b*]pyridines **21** have been prepared by recyclisation of tetracyanocyclopropanes **20** involving phenylhydrazine.[33]

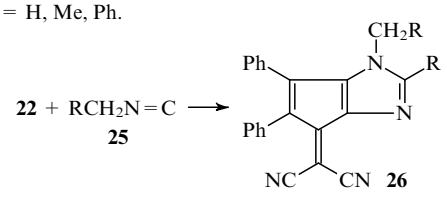


R = Me, Et, Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$.

The reaction of 3-dicyanomethylene-1,2-diphenylcycloprop-1-ene **22** with 3,4-dihydroisoquinolines **23** in ethanol is accompanied by recyclisation giving rise to 4-dicyanomethylene-2,3-diphenyl-4*H*-2,3,6,7-tetrahydropyrido[2,1-*a*]isoquinolines **24** in 73% – 78% yields.[34] Refluxing of the compound **22** with isonitriles **25** in acetonitrile results in the formation of 4-dicyanomethylene-4*H*-cyclopenta[2,3-*b*]imidazole derivatives **26** in 43% – 58% yields.[35]

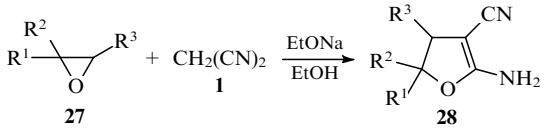


R = H, Me, Ph.



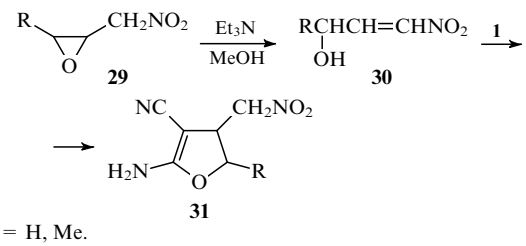
R = Ph, CO_2Et.

Various three-membered heterocycles, oxiranes,[1,36] thiiranes [1,36–38] and aziridines,[38,39] can also undergo recyclisation on treatment with nucleophiles. Thus it was found that the reaction of oxiranes **27** with malononitrile in the presence of sodium ethoxide in ethanol occurs as recyclisation yielding 2-amino-4,5-dihydrofuran-3-carbonitrile **28**.[40–42]



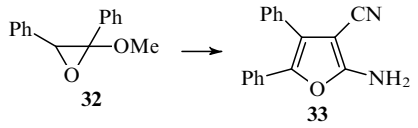
R^1 = H, Me, Et, Ph; R^2, R^3 = H, Me.

In the case of oxiranes **29**, recyclisation proceeds *via* acyclic intermediates **30**, which were treated with malononitrile after isolation. This afforded 2-amino-4-nitromethyl-4,5-dihydrofuran-3-carbonitrile **31** in yields of up to 60%.[43–45]



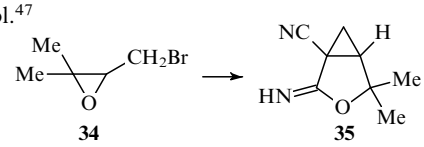
R = H, Me.

2-Methoxy-2,3-diphenyloxirane **32** recyclises in the presence of sodium malononitrile giving rise to 2-amino-4,5-diphenylfuran-3-carbonitrile **33**.[46]



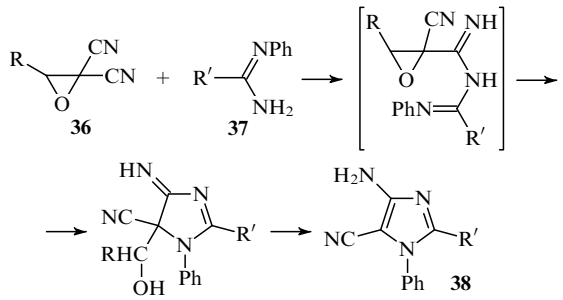
32 **33**

The γ-iminolactone **35** has been synthesised by treatment of the oxirane **34** with potassium malononitrile in *tert*-butyl alcohol.[47]



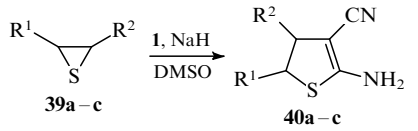
34 **35**

It has also been reported[48,49] that recyclisation of 2,2-dicyanooxiranes **36** in the presence of amidines **37** affords 4-aminoimidazole-5-carbonitriles **38**.



36 **37** **38**

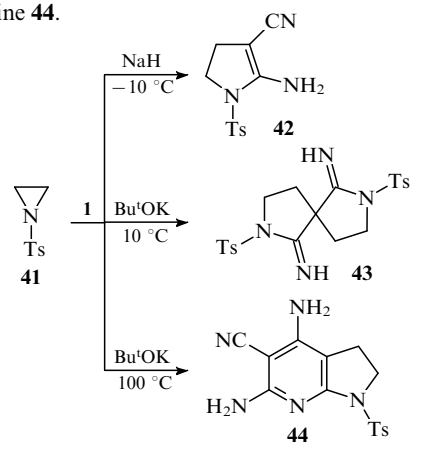
Thiiranes also enter into recyclisation reactions.[1,38,42,50–52] For example, thiiranes **39a–c** react with malononitrile in the presence of sodium hydride in DMSO giving 2-amino-4,5-dihydrothiophene-3-carbonitriles **40a–c** in 50%–62% yields. Note that in the case of the thiiranes **39a**,**b**, ring opening occurs in conformity with Krasuskii's rule, while in the case of **39c**, the ring opens against this rule.[38,50]



39a–c **40a–c**

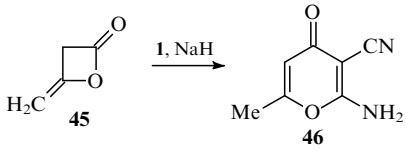
R^1 = H: R^2 = H (**a**), Me (**b**), Ph (**c**).

Recyclisation reactions for three-membered nitrogen-containing heterocycles have been reported.[42,52–54] The reaction of aziridines **41** with malononitrile in the presence of sodium hydride affords different products depending on the reaction conditions and the ratio of the reactants.[42] When the compounds **1** and **41** are taken in equimolar amounts, 2-amino-1-(toluene-*p*-sulfonyl)-4,5-dihydropyrrole-3-carbonitrile **42** is formed. The reaction with a twofold excess of the initial aziridine **41** (Bu^{t}OK, 10 °C) yields spiro compound **43**, whereas the use of a twofold excess of malononitrile and an increase in the reaction temperature to 100 °C results in the formation of 2,3-dihydropyrrolo[2,3-*b*]pyridine **44**.



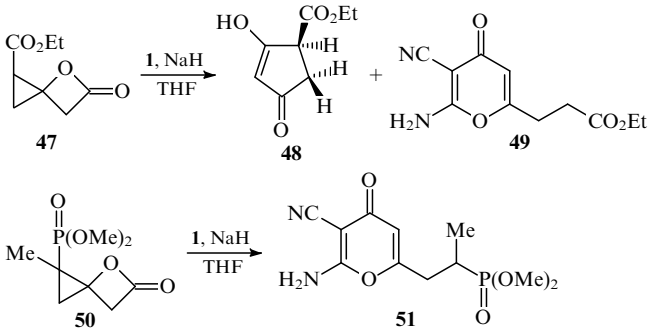
41 **42** **43** **44**

Recyclisation of four-membered heterocycles with participation of malononitrile is also known. Thus the reaction of 2-oxetanone **45** with malononitrile in the presence of sodium hydride affords 2-amino-3-cyano-6-methyl-4-pyrone **46**.[55]



45 **46**

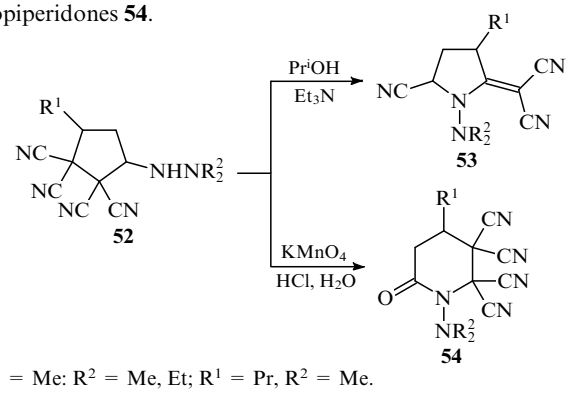
Treatment of 1-ethoxycarbonyl-5-oxo-4-oxaspiro[2.3]hexane **47** with malononitrile under similar conditions gives rise to a mixture of cyclopentenone **48** and 2-amino-4-pyrone **49** (yields 49% and 24%, respectively).[56] 1-Dimethoxyphosphoryl-1-methyl-5-oxo-4-oxaspiro[2.3]hexane **50** reacts with malononitrile under the same conditions to afford 2-amino-3-cyano-6-(2-dimethoxyphosphorylpropyl)-4-pyrone **51** in 58% yield.[56]



47 **48** **49** **50** **51**

III. Recyclisation of five-membered rings

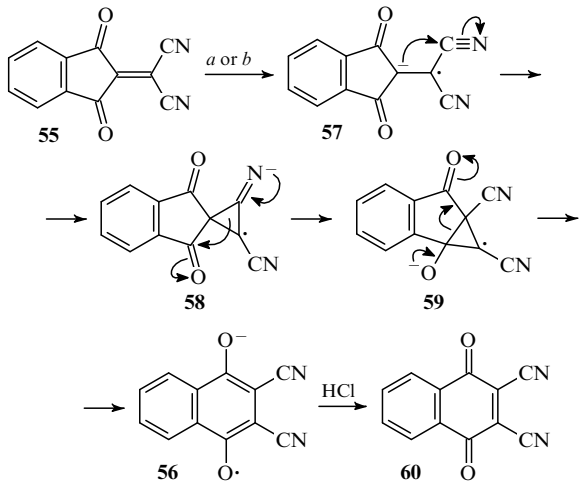
Recyclisation of tetracyanocyclopentanes **52** has been reported.[57,58] Depending on the reaction conditions, they are transformed into 2-dicyanomethylenepyrrolidines **53** or tetracyanopiperidones **54**.



52 **53** **54**

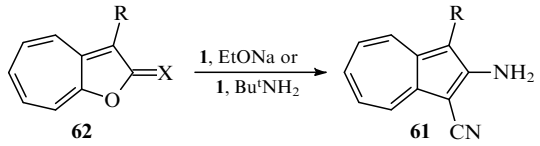
R^1 = Me: R^2 = Me, Et; R^1 = Pr, R^2 = Me.

A scheme for the transformation of 2-dicyanomethyleneindane-1,3-dione **55** into salts **56** has been proposed.[59] The transformation is attained by refluxing **55** in acetonitrile in the presence of lithium iodide or methyltriphenylphosphonium iodide or by stirring it in dry THF with finely divided sodium. The reaction scheme includes a single-electron transfer in the indanedione **55** resulting in symmetrical radical anion **57**, which cyclises to give spirocyclopropane intermediate **58**. The rearrangement of the compound **58**, accompanied by cyclopropane ring opening, and subsequent cyclisation result in the formation of cyclopropane intermediate **59**. This compound also recyclises to afford salts **56**. Treatment of the lithium or methyltriphenylphosphonium salt **56** with concentrated hydrochloric acid gives 2,3-dicyano-1,4-naphthoquinone **60** in 65% and 40% yields, respectively.[59]



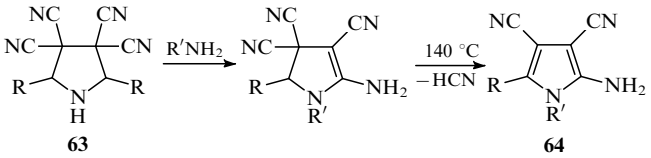
(*a*) M^+I^-, MeCN, Δ, M = Li, Ph_3PMe; (*b*) Na, THF, 20 °C, 48 h.

The review on molecular rearrangements of five-membered heterocycles[11] published in 1984 presents virtually no data on recyclisation with participation of malononitrile or recyclisation of heterocyclic systems containing malononitrile fragments. Meanwhile, an original pathway to aminoazulenes **61** consisting in recyclisation of lactones or iminolactones, 2*H*-cyclohepta[*b*]-furan derivatives **62**, on treatment with methylene active nitriles, including malononitrile, had been reported in the literature.[36,60–63]

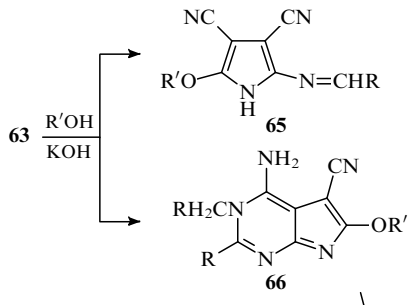


X = O, NAc; R = CO_2Et, COMe.

2,5-Disubstituted pyrrolidine-3,3,4,4-tetracarbonitriles **63** react with aromatic amines to give 2-aminopyrrole-3,4-dicarbonitriles **64**.[64] Depending on the ratio of the reactants, the reactions of the compounds **63** with primary alcohols in the presence of KOH yield either 3,4-dicyanopyrroles **65** or substituted 3*H*-pyrrolo[2,3-*d*]pyrimidines **66**.[65,66]

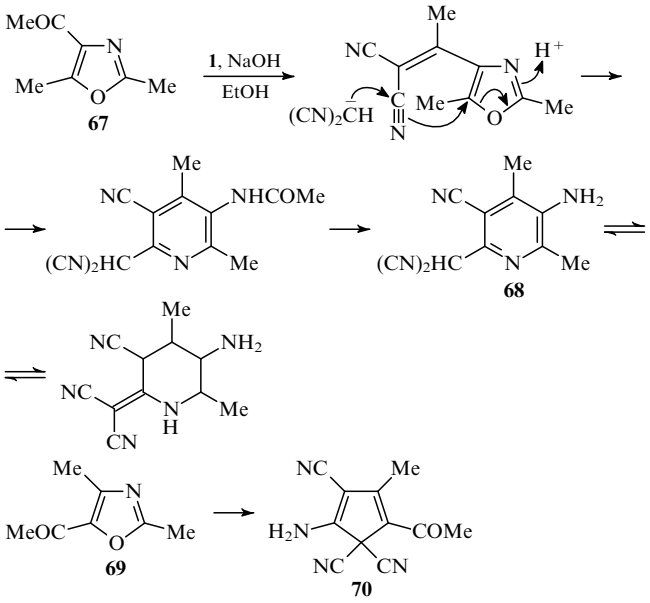


R = Ph; R′ = Ph, 3-MeC_6H_4.

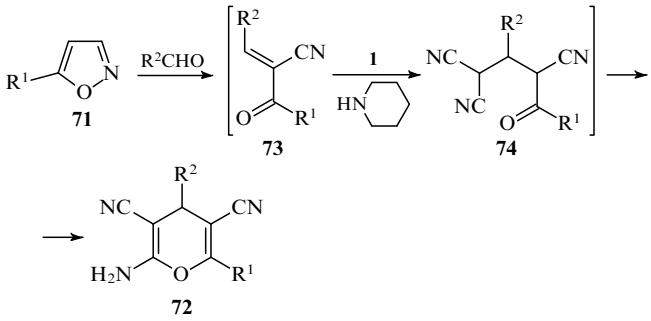


R = Ph, 4-BrC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, ; R′ = Me, Et, Pr.

4-Acetyl-2,5-dimethyloxazole **67** also reacts with malononitrile with recyclisation of the oxazole ring. This reaction results in the formation of 3-amino-6-dicyanomethyl-2,4-dimethylpyridine-5-carbonitrile **68** in 33% yield. 5-Acetyl-2,4-dimethyloxazole **69**, which is an isomer of the compound **67**, reacts with malononitrile under similar conditions being thus converted into 2-acetyl-5-amino-3-methylcyclopentadiene-1,1,4-tricarbonitrile **70** in 60% yield.[67]

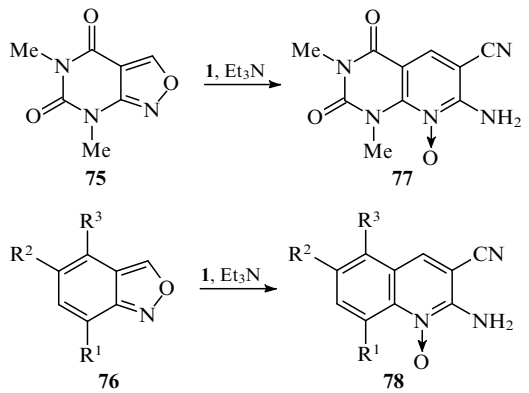


It has been noted[68–71] that isoxazoles **71** recyclise to give 2-amino-4*H*-pyran-3,5-dicarbonitriles **72**. Opening of the isoxazole ring in the compound **71** under the action of an aldehyde and EtONa in ethanol gives rise to substituted nitriles **73**. The subsequent nucleophilic attack on the compounds **73** by malononitrile followed by cyclisation of the Michael adducts **74** affords aminopyrans **72**.[69]



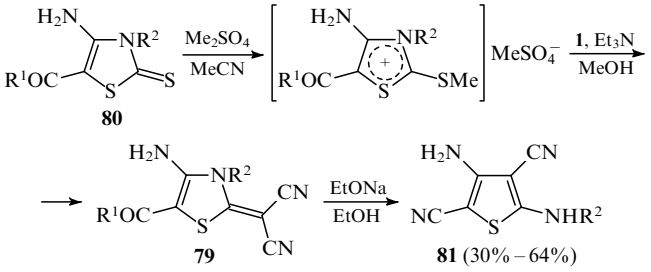
R^1 = Me: R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, Bu^t;
R^1 = Ph: R^2 = Pr^i, Bu^t, $CHEt_2$.

In turn, when fused isoxazoles **75** and **76** are made to react with malononitrile in the presence of triethylamine, the corresponding annelated 2-amino-3-cyanopyridine 1-oxides **77** and **78** are formed in high yields.[70–72]



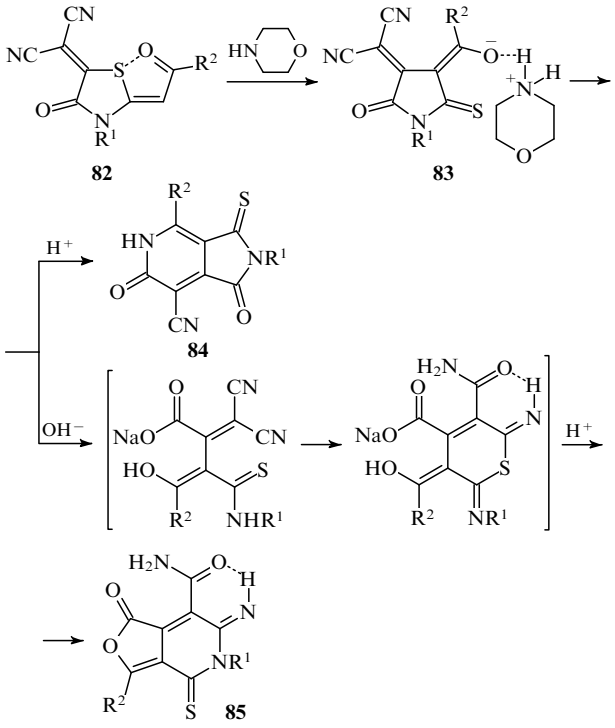
R^1 = H, Me; R^2 = H, NO_2; R^3 = H, Cl, NO_2.

Recyclisation of 4-aminothiazolin-2-ylidenemalononitriles **79**, prepared from 4-aminothiazoline-2-thiones **80**, in the presence of sodium ethoxide in ethanol giving substituted 3,5-diaminothiophene-2,4-carbonitriles **81** has been described.[73]



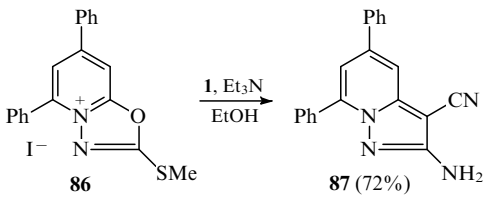
R^1 = OEt, NH_2; R^2 = Me, Ph, Bn, $CH_2CH=CH_2$.

Substituted 4-dicyanomethylenethiazolidin-5-ones **82** form complexes **83** with morpholine. Hydrolysis of these complexes with hydrochloric acid affords pyrrolo[3,4-*c*]pyridine derivatives **84**, whereas their interaction with NaOH followed by acidification gives rise to furo[3,4-*c*]pyridine derivatives **85**.[74]

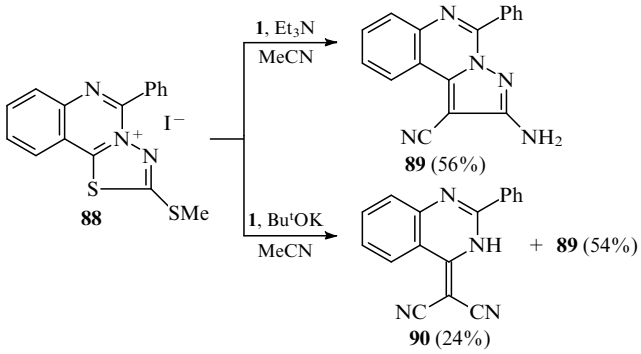


R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; R^2 = Ph, 4-MeC_6H_4.

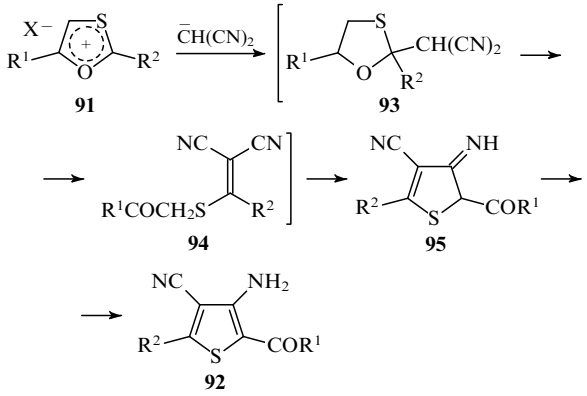
It was also shown that 2-methylthio-5,7-diphenyl-1,3,4-oxadiazolo[3,2-*a*]pyridinium iodide **86** reacts with malononitrile in ethanol in the presence of triethylamine to give 2-amino-5,7-diphenylpyrazolo[1,5-*a*]pyridine-3-carbonitrile **87**.[75]

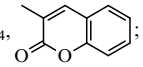


2-Methylthio-5-phenyl-1,3,4-thiadiazolo[3,2-*c*]-4-quinazolinium iodide **88** reacts with malononitrile in a similar way, with elimination of one heteroatom from the five-membered ring. Thus it was shown that the salt **88** reacts with malononitrile in dry acetonitrile in the presence of triethylamine to give 2-amino-3-cyanopyrazolo[1,5-*c*]quinazoline **89**.[76] When potassium triethylamine is replaced by potassium *tert*-butoxide, a mixture of the pyrazoloquinazoline **89** and 3,4-dihydroquinazoline **90** is formed.[76]



Recyclisation of 1,3-oxathiolium salts **91** on treatment with malononitrile has been used successfully in the synthesis of functionally substituted thiophenes **92**.[36,77–81] In the general form, the mechanism of this reaction includes the attack on the 2-position of the salt **91** by the malononitrile anion to give adduct **93**. The subsequent cleavage of the ring at the C(2)–S(3) bond in the compound **93** gives intermediate **94**, which then cyclises according to the Thorpe reaction pathway to give imine **95**; this product isomerises into more stable 3-aminothiophene **92**.

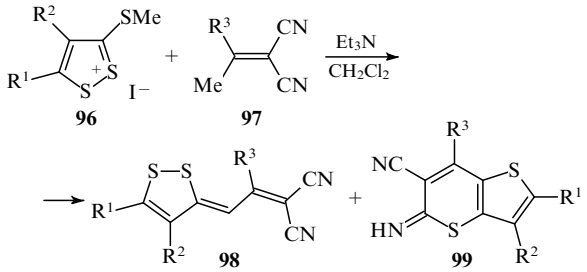


R^1 = Ph, 4-BrC_6H_4, 4-ClC_6H_4, ;

R^2 = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$.

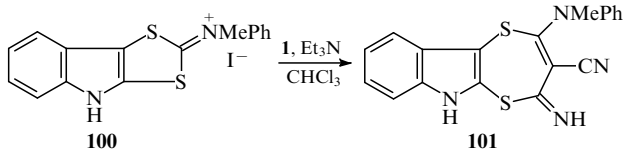
1,3-Oxathiolidene-2-immonium salts recyclise in a similar way to give functionally substituted thiophenes.[81,82]

The reaction of 3-methylthio-1,2-dithiolium iodides **96** with ylidenemalononitriles **97** in dichloromethane in the presence of triethylamine has been shown[83] to afford dithiolylidenenitriles **98** and recyclisation products — 2-iminothieno[3,2-*b*]thiopyran-3-carbonitriles **99**.



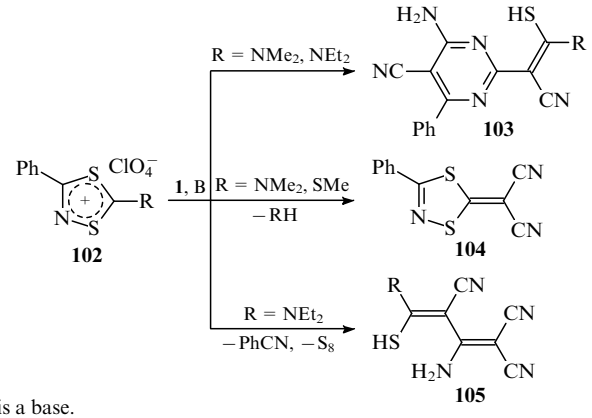
R^1 = Ph, SMe, 4-$MeOC_6H_4$; R^2 = H, 4-MeC_6H_4;
R^3 = Ph, 4-$MeOC_6H_4$.

The reaction of iodide **100** with malononitrile in the presence of triethylamine in chloroform is also accompanied by recyclisation of the dithiole fragment. Simultaneously, ring expansion occurs and 2-imino-4-(*N*-methylanilino)-2*H*-[1,4]dithiapino-[2,3-*b*]indole-3-carbonitrile **101** is formed in 83% yield.[84]



100 **101**

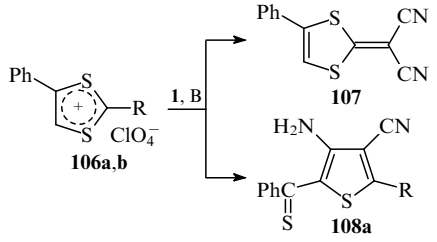
1,3,4-Dithiazolium perchlorates **102** react with malononitrile in the presence of a base (Et_3N, NaH, pyridine, γ-picoline) in EtOH, THF, CH_2Cl_2 or MeCN. Depending on the substituent at the C(5) atom, the base used and the ratio of the reactants, this gives 4-amino-2-(1-cyano-2-dialkylamino-2-sulfanylvinyl)-6-phenylpyrimidine-5-carbonitriles **103**, 2-dicyanomethylene-5-phenyl-1,3,4-dithiazole **104** or substituted 1,3-butadiene **105**.[85]



102 **103** **104** **105**

B is a base.

The pathway of the reactions of 1,3-dithiolium perchlorates with malononitrile also depends substantially on the nature of the substituents in the heterocycle and the solvent used. For example, the reaction of 2-diethylamino-4-phenyl-1,3-dithiolium perchlorate **106a** with malononitrile in the presence of a weak base (γ-picoline) results in the formation of 2-dicyanomethylene-4-phenyl-1,3-dithiole **107**, whereas in the presence of a strong base (triethylamine), 3-amino-5-diethylamino-2-thiobenzoylthiophene-4-carbonitrile **108a** is formed.[85]

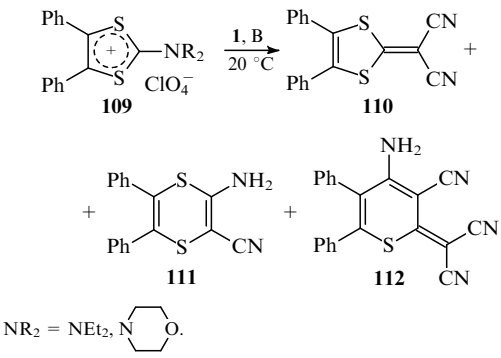


106a,b **107** **108a**

R = NEt_2 (**a**), NMe_2 (**b**).

However, when 2-dimethylamino-derivative **106b** is used as the substrate, 1,3-dithiole **107** is formed in the presence of the strong base, triethylamine.

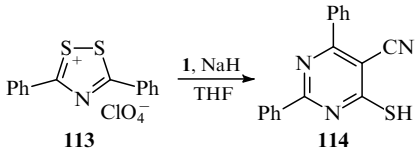
Similarly, the final products formed in the reaction of 4,5-diphenyl-1,3-dithiolium perchlorates **109** with malononitrile depend on the reaction conditions; this reaction can yield (in various proportions) 2-dicyanomethylene-4,5-diphenyl-1,3-dithiole **110**, 2-amino-5,6-diphenyl-1,4-dithiine-3-carbonitrile **111** and 4-amino-2-dicyanomethylene-5,6-diphenyl-2*H*-thiine-3-carbonitrile **112**.[85]



109 **110** **111** **112**

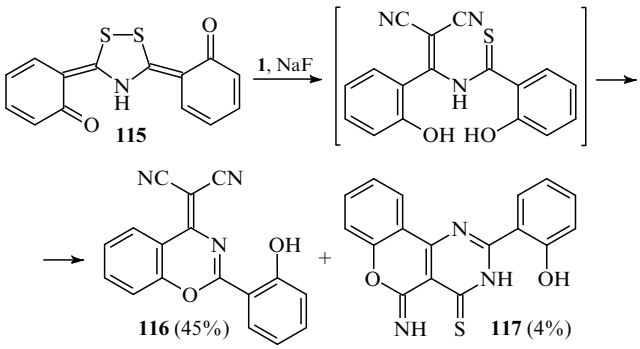
NR_2 = NEt_2, N O.

The reaction of 3,5-diphenyl-1,2,4-dithiazolium perchlorate **113** with malononitrile on refluxing in THF in the presence of sodium hydride is accompanied by recyclisation and gives 2,6-diphenyl-4-sulfanylpyrimidine-5-carbonitrile **114** in 92% yield.[86]



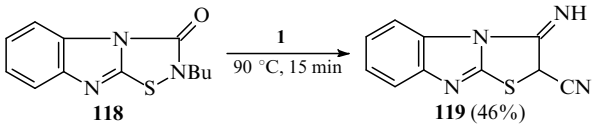
113 **114**

2-(2-Hydroxyphenyl)-4-dicyanomethylene-4*H*-1,3-benzoxazine **116** and 5-imino-2-(2-hydroxyphenyl)-1-benzopyrano-[4,3-*d*]pyrimidine-4-thione **117** have been synthesised by recyclisation of 1,2,4-dithiazolidine **115** involving malononitrile in the presence of NaF (refluxing for 2 min in a 1 : 1 DMSO : Pr_2O mixture).[87]



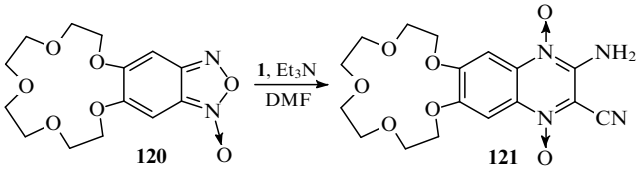
115 **116** (45%) **117** (4%)

On fusion with malononitrile (15 min, 90 °C), 2-butylbenzoimidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-one **118** undergoes recyclisation with elimination of isocyanate to give 3-imino-2,3-dihydrobenzoimidazo[2,1-*b*][1,3]thiazole-2-carbonitrile **119**.[88,89]



118 **119** (46%)

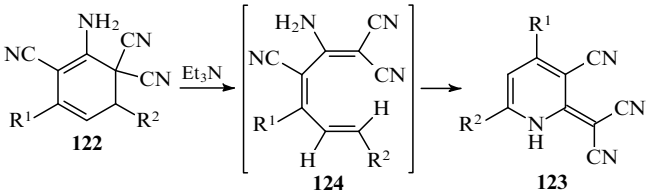
In a series of studies,[90–93] it has been found that benzofuroxans recyclise on treatment with malononitrile giving rise to substituted 2-amino-3-cyanoquinoxaline *N*,*N*-dioxides. Recyclisation of benzofuroxan-15-crown-5 **120** during the reaction with malononitrile in DMF in the presence of triethylamine, resulting in the formation of 2-amino-3-cyanoquinoxaline *N*,*N*-dioxide **121**,[93] can be cited as an example.



120 **121**

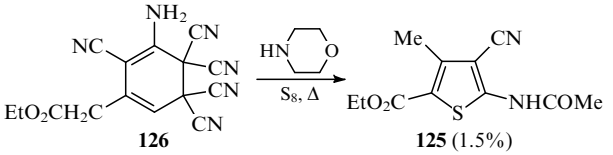
IV. Recyclisation of six-membered rings

For six-membered carbocycles containing a malononitrile fragment, base-induced recyclisation of 1-amino-1,3-cyclohexadiene-2,6,6-tricarbonitriles **122**, resulting from dimerisation of alkylidenemalononitriles, has been reported. This reaction yields 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitriles **123** and involves intermediate formation of *cis*(*trans*)-2-amino-1,3,5-hexatriene-1,1,3-tricarbonitriles **124**.[94–101]

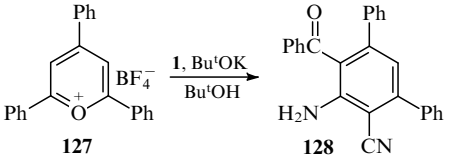


R^1 = Ph, 4-MeC_6H_4; R^2 = Ph, 4-FC_6H_4, 4-ClC_6H_4, *cyclo*-C_3H_5.

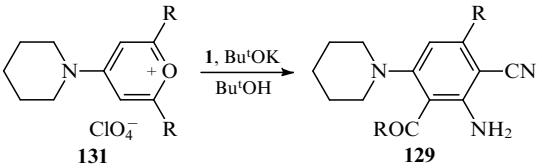
The formation of acetylaminothiophene **125** in a low yield in the recyclisation of hexa-1,3-diene **126** upon refluxing with morpholine polysulfide in ethanol for 4 h has been described.[102]



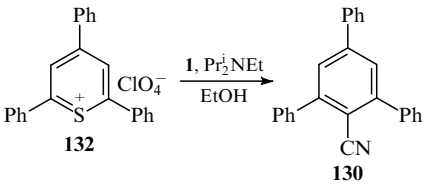
Recyclisation of six-membered heterocycles with participation of malononitrile possesses a substantially greater synthetic potential. First of all, mention should be made of recyclisation of heterocyclic compounds to carbocyclic compounds. For example, recyclisation of 2,4,6-triphenylpyrylium salt **127** during its reaction with malononitrile in *tert*-butyl alcohol in the presence of potassium *tert*-butoxide affords 2-amino-3-cyano-4,6-diphenylbenzophenone **128**, which is difficult to obtain by other methods, in a high yield.[103–106]



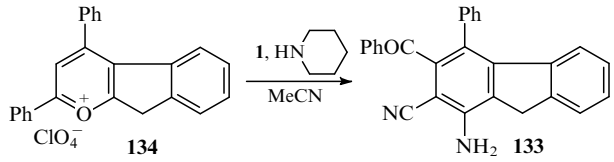
Later, this reaction was used to prepare 2-amino-3-cyano-4-methyl(or phenyl)-6-piperidylaceto(or benzo)phenones **129**[107] and 2,4,6-triphenylbenzonitrile **130**[108] from pyrylium salts **131** and 2,4,6-triphenylthiapyrylium perchlorate **132**.



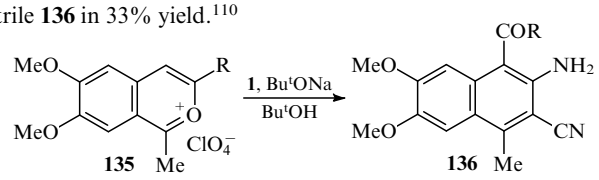
R = Me, Ph.



The synthesis of 4-amino-2-benzoyl-1-phenylfluorene-3-carbonitrile **133** in 89% yield by the reaction of 2,4-diphenyl-5*H*-indeno[2,1-*b*]pyrylium perchlorate **134** with malononitrile in acetonitrile in the presence of piperidine has been reported.[109]

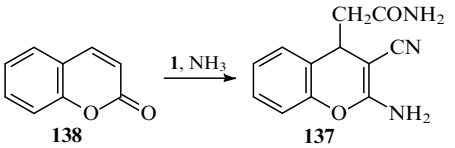


2-Benzopyrylium salt **135** undergoes similar recyclisation on treatment with malononitrile in the presence of sodium *tert*-butoxide in *tert*-butyl alcohol. This gives 2-amino-1-(3,4-dimethoxybenzoyl)-4-methyl-6,7-dimethoxynaphthalene-3-carbonitrile **136** in 33% yield.[110]

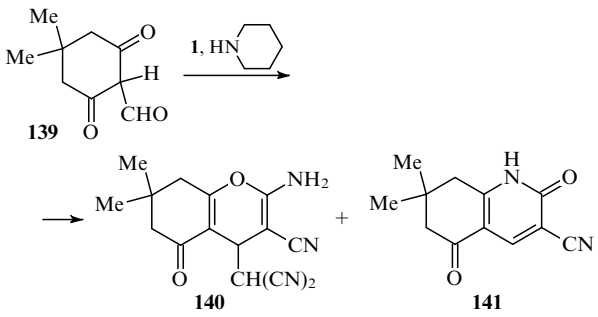


R = 3,4-$(MeO)_2C_6H_3$.

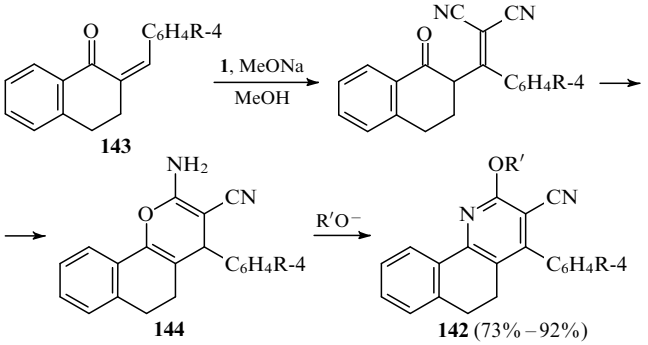
Of other examples of recyclisation of six-membered oxygen-containing heterocycles with malononitrile, the formation of (2-amino-3-cyano-4*H*-1-benzopyran-4-yl)acetamide **138** from coumarin **137** should be mentioned.[111]



It has been reported [112] that 2-formyldimedone **139** reacts with malononitrile in the presence of piperidine in methanol or ethanol to give 2-amino-4-dicyanomethyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrobenzopyran-3-carbonitrile **140** in 78% yield and 3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2(1*H*)-quinolone **141** in 20% yield.

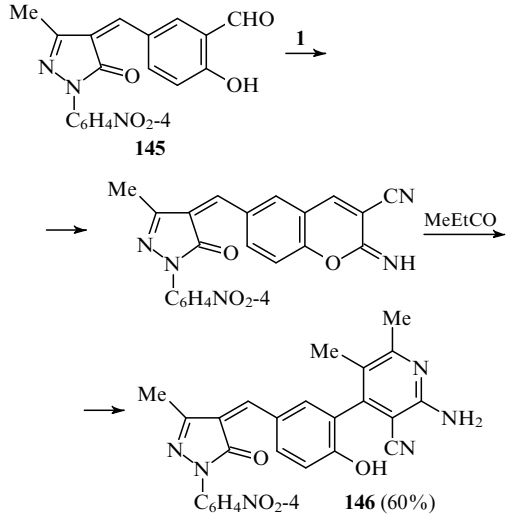


A new method for the synthesis of compounds of the benzo[*h*]quinoline series **142** has been proposed.[113] The method is based on the Michael addition of malononitrile to 2-arylidene-1-tetralones **143** in the presence of sodium methoxide in methanol. The reaction mechanism was confirmed by isolation of the reaction intermediate, 4*H*-naphtho[1,2-*b*]pyran **144**.

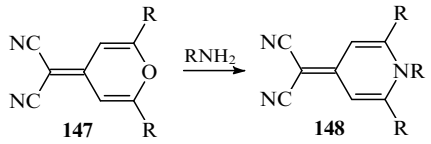


R = H, Me, Cl, OMe, NO_2; R′ = Me, Et.

The condensation of pyrazolinone **145** with malononitrile in the presence of ammonium acetate and methyl ethyl ketone on refluxing in ethanol for 3 h gives rise to substituted nicotinonitrile **146**.[114,115]

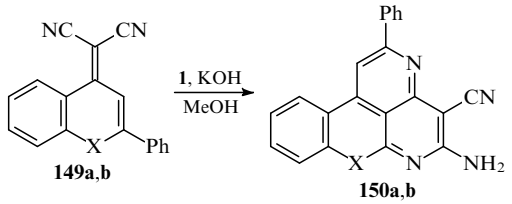


The reaction of 4*H*-pyrans **147**, incorporating a dicyanomethylene fragment, with amines is accompanied by recyclisation and results in the formation of 4-dicyanomethylene-1,4-dihydropyridines **148**.[116–118]



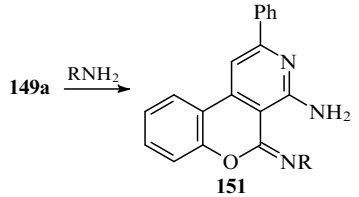
R = Alk, Ar.

However, the reactions of 4-dicyanomethylene-2-phenyl-4*H*-benzo[*b*]pyran **149a** and the corresponding thiopyran **149b** with malononitrile in methanol in the presence of KOH gives 5-amino-4-cyano-2-phenylbenzo[*b*]pyrano[4,3,2-*de*][1,6]naphthiridine **150a** or the corresponding thiopyranonaphthiridine **150b**.[119]



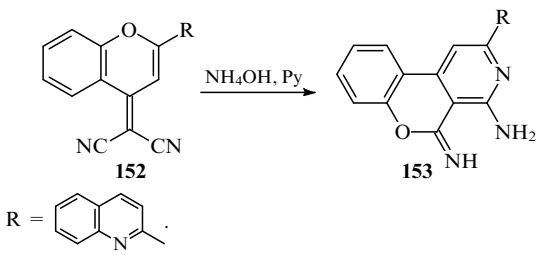
X = O (**a**), S (**b**).

The benzopyran **149a** reacts with primary amines under mild conditions giving rise to 4-amino-5-R-imino-2-phenyl-4*H*-[1]benzopyrano[3,4-*c*]pyridines **151**.[120]

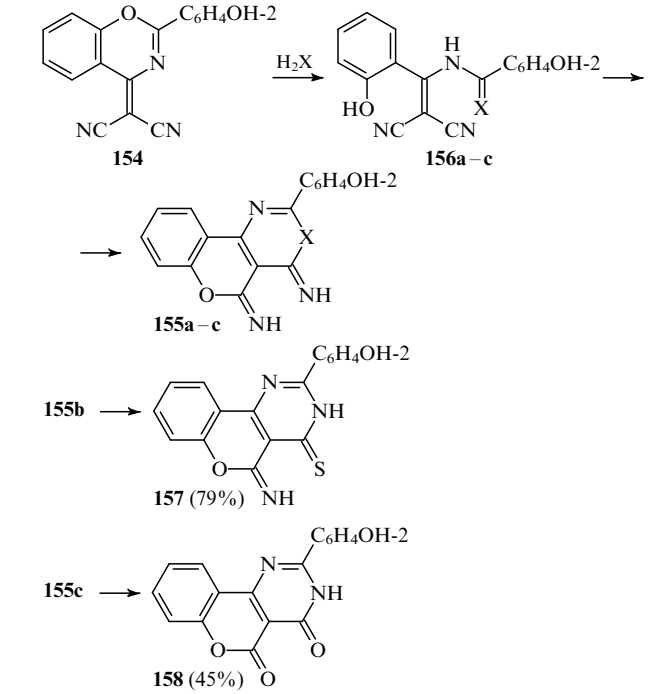


R = Ph, Bn, PhNH.

In order to synthesise analogues of the antitumour antibiotic streptonigrin, recyclisation of 4-dicyanomethylene-2-(2-quinolyl)-4*H*-[1]benzopyran **152** in pyridine in the presence of NH_4OH has been studied. This reaction gave 4-amino-5-imino-2-(2-quinolyl)-4*H*-[1]benzopyrano[3,4-*c*]pyridine **153** in 91% yield.[121]

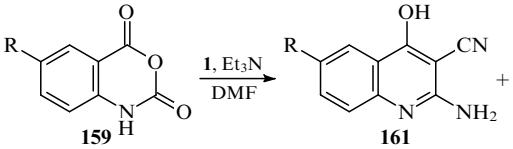


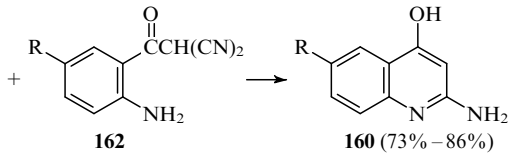
Recyclisation of 4-dicyanomethylene-2-(2-hydrophenyl)-4*H*-[1,3]benzoxazine **154** induced by various nucleophiles follows a similar pathway. Thus refluxing of the benzoxazine **154** in 2-methoxyethanol in the presence of ammonium acetate affords 2-(2-hydroxyphenyl)-4,5-diimino-3,4-dihydro-5*H*-[1]benzopyrano[4,3-*d*]pyrimidine **155a** in 91% yield.[122] The thiazine **155b** was prepared by treatment of the benzoxazine **154** with hydrogen sulfide in the presence of triethylamine, and the 1,3-oxazine **155c** was synthesised by treatment of the compound **154** with hydrochloric acid in 2-methoxyethanol. It was noted that adducts **156a–c** are formed as intermediates in this reaction; in the case of the thiazine **155b** and oxazine **155c**, the Dimroth rearrangement occurs under the reaction conditions, yielding 2-(2-hydroxyphenyl)-5-imino-4-thio-3,4-dihydro-5*H*-[1]benzopyrano[4,3-*d*]p-y-rimidine **157** and 2-(2-hydroxyphenyl)-4,5-dioxo-3,4-dihydro-5*H*-[1]benzopyranopyrimidine **158**.[122]



X = NH (**a**), S (**b**), O (**c**).

When isatic anhydride [2*H*-3,1-benzoxazine-2,4(1*H*)-dione] and its substituted derivatives **159** react with malononitrile in DMF in the presence of triethylamine and then the reaction mixture is hydrolysed with 48% HBr or 6 N KOH, they are converted into 2-amino-4-hydroxyquinolines **160**.[123,124] Compounds **161** and **162** were identified as reaction intermediates.

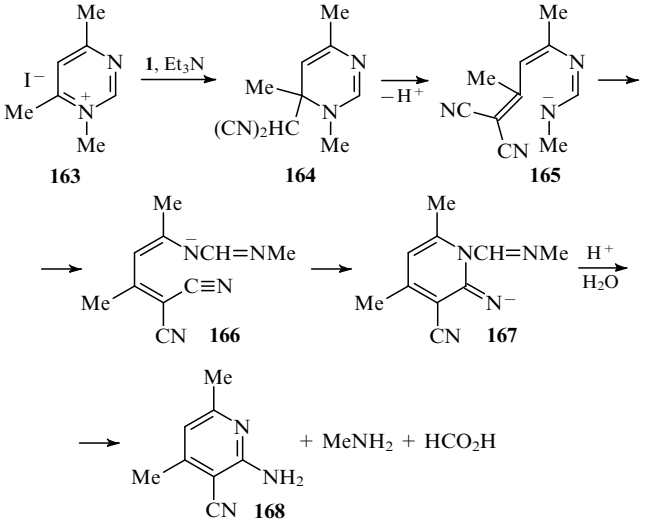




162 **160** (73% – 86%)

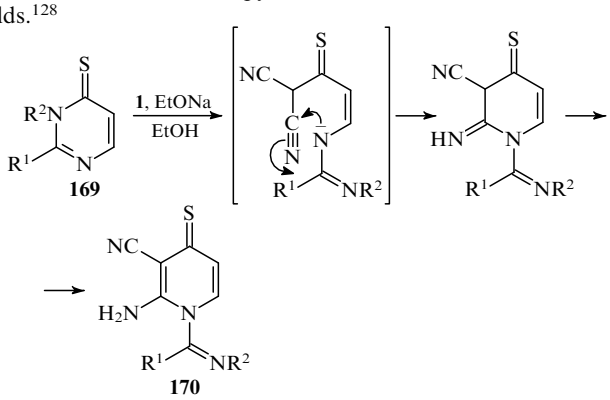
R = H, Cl, Me, OMe.

Recyclisation of pyrimidines involving malononitrile has been studied comprehensively.[19, 125–136] For the reaction of 1,4,6-trimethylpyrimidinium iodide **163**, it was found that first the 4(6)-position of the pyrimidine nucleus in the compound **163** is attacked by the malononitrile anion, which gives adduct **164**. Then the pyrimidine ring in the compound **164** is cleaved at the N(3) – C(4) bond. Due to the presence of both nucleophilic [the N(1) atom] and electrophilic [the nitrile group carbon atom] reaction sites, the intermediates **165** and **166** thus formed cyclise to give pyridine **167**. The latter is stabilised by being converted into aminopyridine **168** upon abstraction of an aminomethylene fragment as methylamine and formic acid.[125]



163 **164** **165** **166** **167** **168**

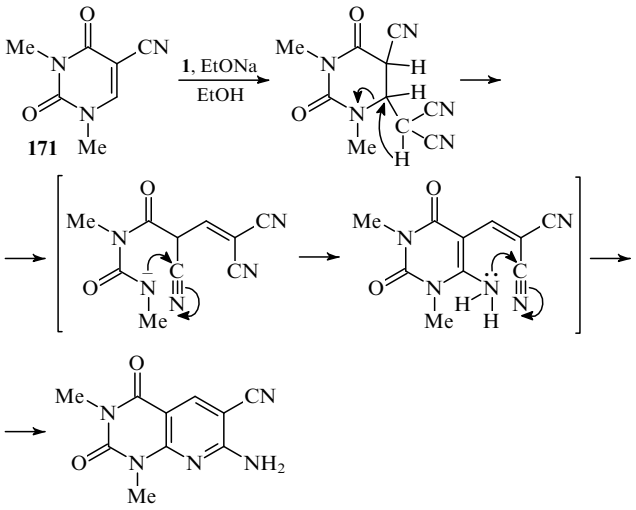
Recyclisation of 2,3-disubstituted 4(1*H*)-pyrimidinethiones **169** on treatment with malononitrile in ethanol in the presence of sodium ethoxide affords pyridinethiones **170** in 78% – 93% yields.[128]



169 **170**

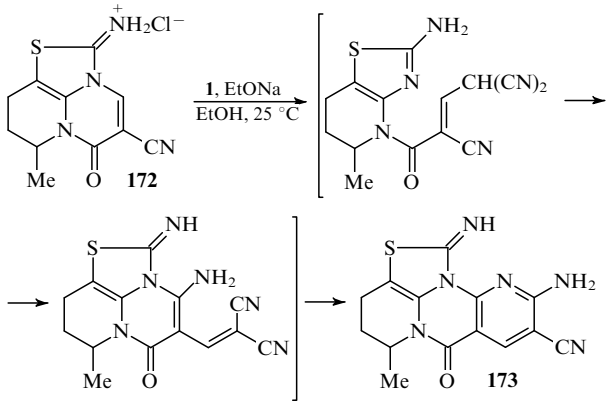
R^1 = Ph: R^2 = Ph, 3-MeC_6H_4, 4-MeC_6H_4; R^1 = R^2 = 4-MeC_6H_4.

Recyclisation of 2(1*H*)-pyrimidinediones [129] and fused pyrimidines, such as quinazolines,[132] 1*H*-pyrazolo[3,4-*d*]pyrimidines [131] and their 3-oxides [130] occurs in a similar way. The scheme for the recyclisation of pyrimidinediones can be represented in relation to the interaction of 5-cyano-1,3-dimethyluracil **171** with malononitrile.[134, 135]



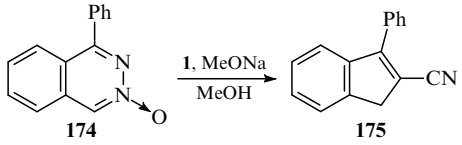
171

Recyclisation of 1-thia-2*a*,5*a*-diazaacenaphthene system **172** on treatment with malononitrile in ethanol in the presence of sodium ethoxide giving fused tetracyclic heterocyclic compound **173** in 88% yield has been described.[136]



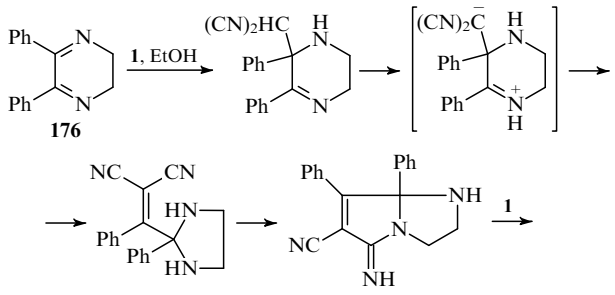
172 **173**

The recyclisation of 1-phenylphthalazine 3-oxide **174** during its reaction with malononitrile in methanol in the presence of sodium methoxide is accompanied by the loss of two nitrogen atoms and gives 3-phenylindene-2-carbonitrile **175**.[137]

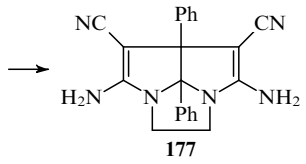


174 **175**

The recyclisation of 2,3-diphenyl-5,6-dihydropyrazine **176** occurring on refluxing with malononitrile in ethanol over a period of 1 h follows a peculiar pathway and affords 2,6-diamino-4,10-diphenyl-1,7-diazatricyclo[5.2.1.$0^{4,10}$]deca-2,5-diene-3,5-dicarbonitrile **177** in 70% yield.[138]

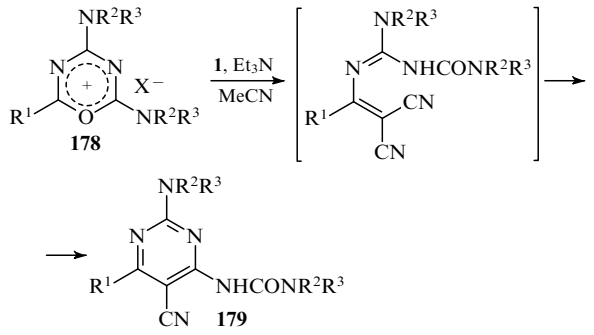


176



177

Recyclisation of 1,3,5-oxadiazinium salts **178** with participation of malononitrile carried out in acetonitrile in the presence of triethylamine has been reported. 2-Amino-6-aryl-4-carbamidopyrimidines **179** were obtained in this way in 65% – 83% yields.[139]

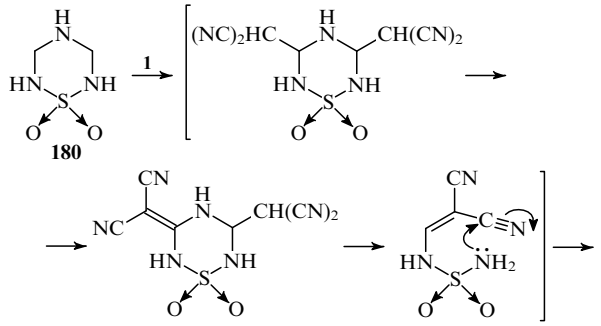


178

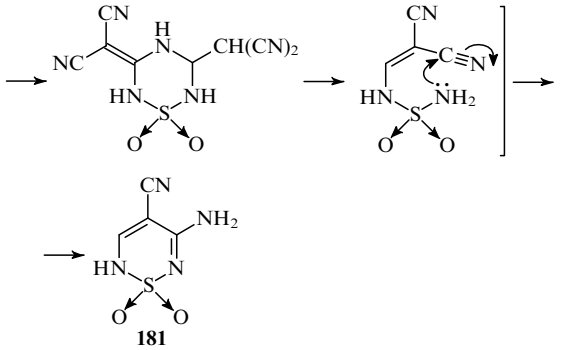
179

R^1 = Ph: R^2 = Me, R^3 = Me; R^2,R^3 = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$.

When reacting with malononitrile, 1,3,5-triazine undergoes recyclisation, similar to the transformation of pyrimidines into pyridines. This gives 4-aminopyrimidine-5-carbonitrile in 80% yield.[140, 141] Recyclisation of 4*H*-1,2,4,6-thiatriazine 1,1-dioxide **180** yielding 3-amino-4-cyano-1,2,6-thiadiazine 1,1-dioxide **181** should be classified as the same type of reaction.[142]

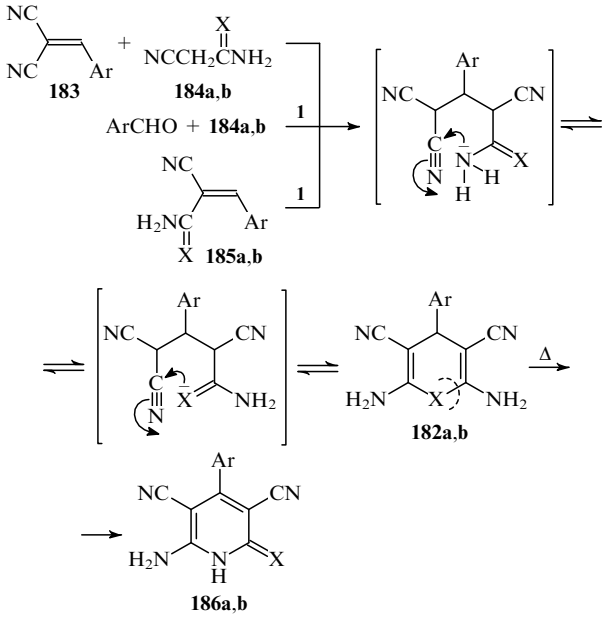


180



181

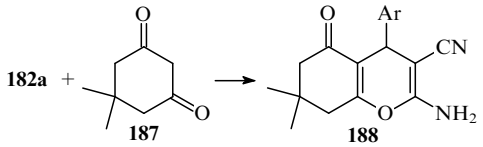
3-Cyanopyridin-2(1*H*)-ones, -thiones, -selenones and their derivatives represent an important class of heterocyclic compounds because of the diversity of their chemical transformations and the possible practical applications.[36, 76, 143 – 154] These bifunctional compounds, which contain the nitrile and the oxo – hydroxy, thione – thiol or selenone – selenol functional groups in the vicinal positions, proved to be promising starting compounds in the preparation of annelated heterocyclic systems difficult to obtain by other methods.[143, 144] The strategy of the synthesis of 3-cyano-2-pyridinones, -thiones and -selenones and their hydrogenated analogues is based, first of all, on cyclisation of functionally substituted carbonyl compounds or their derivatives with malononitrile or other derivatives of cyanoacetic acid.[155 – 164] During these studies it was found that thio(seleno)pyrans **182a**,**b** are formed in the reactions of arylidenemalononitriles **183** with cyanothio(or seleno)acetamides **184a**,**b**, or in a one-step procedure involving aromatic aldehydes, malononitrile, and the amides **184a**,**b**, or in the reactions of arylidenecyanothio(or seleno)-acetamides **185a**,**b** with malononitrile. The compounds **182a**,**b** readily recyclise to give the corresponding pyridinethiones (or selenones) **186a**,**b**.[143, 144, 155, 157, 159, 161, 164 – 179]



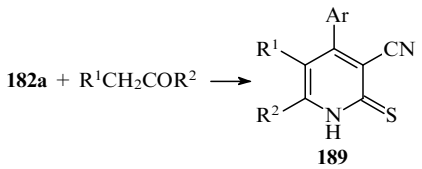
183 **184a**,**b** **185a**,**b** **182a**,**b** **186a**,**b**

X = S (**a**), Se (**b**).

According to the results of physicochemical studies, including X-ray diffraction analysis, the thio(or seleno)pyran ring in the compounds **182a**,**b** occurs in the flattened boat conformation in which the aryl substituent at the 4-position is equatorial.[159, 168, 180 – 183] The steric overcrowding of the thio(or seleno)-pyran molecules **182a**,**b** with bulky electron-withdrawing substituents hampers the bond inversion in the ring and inversion of the substituents and thus makes impossible the conformational transitions in the heterocycle at higher temperatures. Therefore, on heating, ring cleavage at the weakest bond occurs (it is denoted by a dashed line in the scheme) and the compounds **182a**,**b** are then converted into pyridinethiones(or selenones) **186a**,**b**. In some studies,[165, 184 – 186] faulty data on the structures of the thiopyrans **182a** and the pyridinethiones **186a** are presented. The structure of the thiopyrans **182a** (Ar = 4-ClC_6H_4, 4-$MeOC_6H_4$) was attributed to the corresponding pyridinethiones **186a**.[165, 168] The structures of 5-acetyl-2-amino-4-(4-methoxyphenyl)-6-methyl-4*H*-thiopyran-3-carbonitrile and 2,4-diamino-5-cyano-3-(2-furyl)-methylene-3,6-dihydropyridine-6-thione reported in the literature [185, 186] are also erroneous. In addition, it has been found that the thiopyrans **182a** recyclise on treatment with dimedone **187** to give 2-amino-4*H*-pyran-3-carbonitriles **188**, whereas on treatment with ketones, **182a** are converted into pyridinethiones **189**.[187]

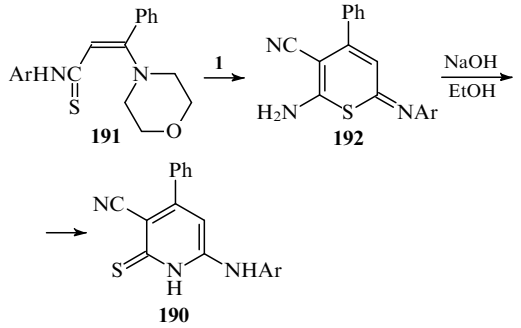


187 **188**



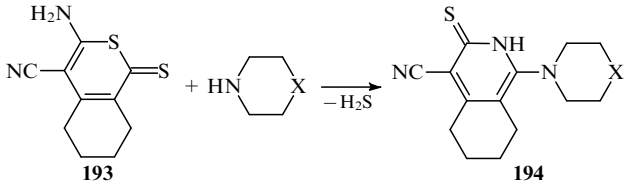
189

An original pathway to substituted pyridinethiones **190** has been proposed.[188] The reaction of β-enaminothioamides **191** with malononitrile under kinetically controlled conditions gives substituted thiopyrans **192**; on heating with a base under thermodynamically controlled conditions, these products are converted into pyridinethiones **190**, their yields being more than 80%.



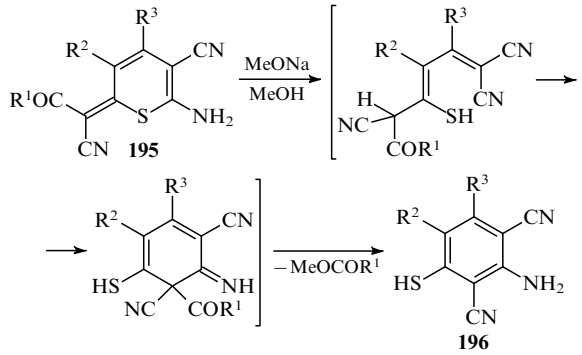
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$.

Recyclisation of 6-amino-3,4-tetramethylene-2-thiothiopyran-5-carbonitrile **193** involving organic bases affords substituted 3-cyano-4,5-tetramethylene-1,2-dihydropyridine-2(1*H*)-thiones **194**.[189]



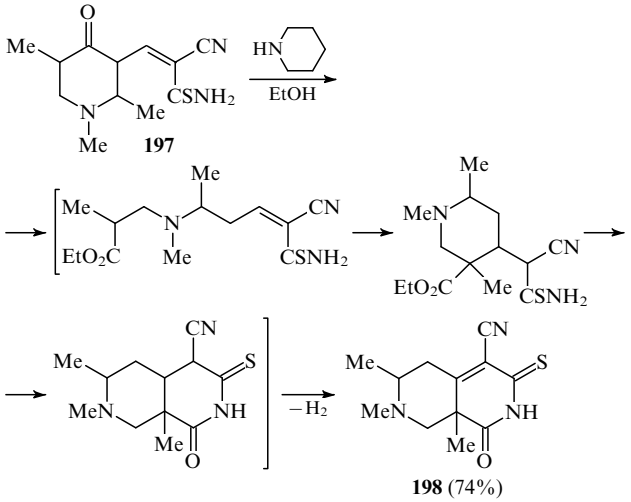
X = O, CH_2.

The ylidene-derivatives of 6-amino-2*H*-thiopyran-5-carbonitrile **195**, prepared from thiopyrylium salts, are converted into 2,6-dicyano-3-sulfanylanilines **196**; this reaction is similar to the reactions of pyrylium salts with nucleophiles.[187]



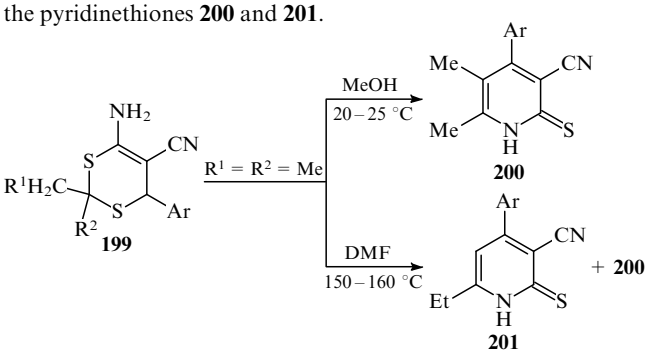
R^1 = OMe, NH_2: R^2 = Me, R^3 = Et; R^2,R^3 = $(CH_2)_4$.

In turn, piperidone **197**, containing a cyanothioacetamide fragment, recyclises on refluxing in ethanol in the presence of a catalytic amount of piperidine to give 2,7-naphthiridine **198**.[190]

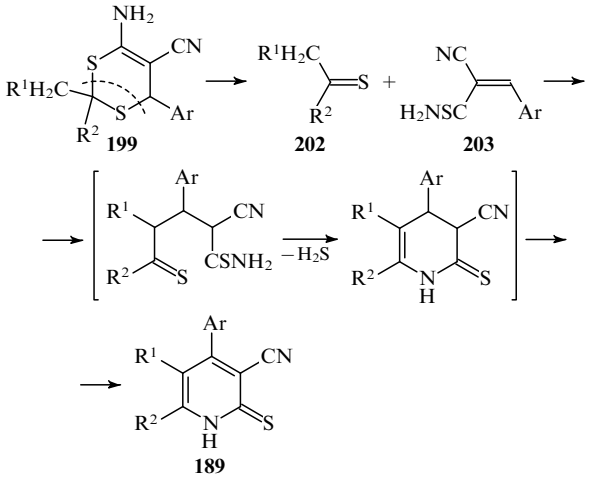


198 (74%)

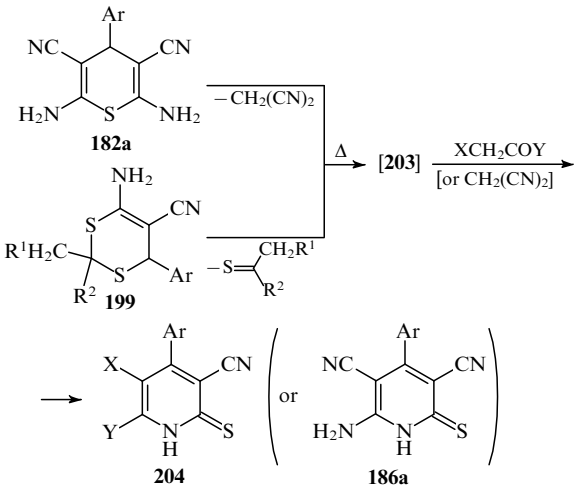
Yet another convenient route to substituted 3-cyanopyridine-2(1*H*)-thiones is recyclisation of enamino nitriles of the 1,3-dithiacyclohexene series.[191–202] In particular, it was found that 2,2-dialkyl-6-aryl-1,3-dithiacyclohex-4-enes are converted into 3-cyanopyridine-2(1*H*)-thiones **189** in high yields.[25,144,193,194] This reaction is formally accompanied by elimination of a hydrogen sulfide molecule and two hydrogen atoms, the subsequent transformations being determined by the structure of the initial substrate. The reaction conditions also have a substantial influence on its course. For example, recyclisation of 1,3-dithiacyclohex-4-ene **199** carried out in the presence of an organic base in methanol at 20–25 °C yields pyridinethione **200**, whereas heating of the compound **199** in DMF at 150–160 °C gives a mixture of the pyridinethiones **200** and **201**.



To elucidate the recyclisation mechanism, 4-amino-6-phenyl-2-cyclohexanespiro-1,3-dithiacyclohex-4-ene-5-carbonitrile **199** [Ar = Ph, R^1,R^2 = $(CH_2)_4$] was studied by X-ray diffraction analysis.[198] The results led to the conclusion that the molecules of 1,3-dithiacyclohex-4-enes **199** contain a conformationally rigid intramolecular system. Therefore, energy supplied from the outside causes rupture of the weakest bonds, S(1)–C(6) and S(3)–C(2), (shown by a dashed line in the scheme), which results in the formation of cyclohexanethione or acyclic thioketones **202** and arylidenecyanothioacetamides **203** as intermediates. The compounds **202** and **203** are finally converted into 3-cyanopyridine-2(1*H*)-thiones **189**.[25,144,194,198]

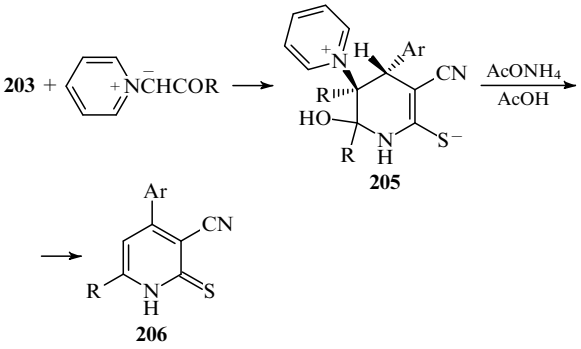


The mechanism of recyclisation of 4*H*-thiopyrans and 1,3-dithiacyclohex-4-enes **199** was confirmed by studying their cross-recyclisation with various CH acids, α-methylene ketones, 1,3-dicarbonyl compounds and their enamines, ethyl cyanoacetate and malononitrile.[25,143,144,181–183] Under thermodynamically controlled conditions, cycloelimination of heterocyclic compounds **182** and **199** occurs, yielding arylidenecyanothioacetamides **203** and either malononitrile or thioketones, respectively. The subsequent competing transformations of the amides **203** involving malononitrile or carbonyl compounds give rise to substituted pyridinethiones **204** or **186a**.



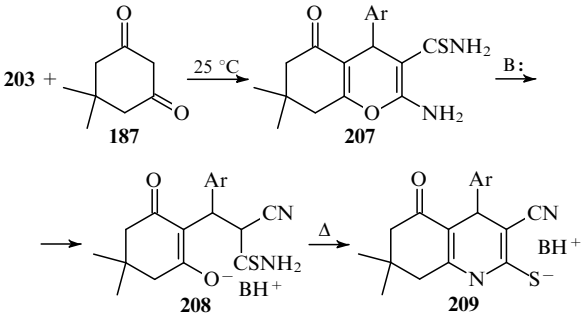
X = Alk, OAlk; Y = Alk.

To elucidate the mechanism and stereochemistry of transformations of the heterocyclic compounds **182a** and **199**, their reactions with pyridinium ylides have been studied.[144, 156, 181, 182] It was found that in this case, too, arylidenecyanothioacetamides **203** are formed as intermediates; they react stereoselectively with pyridinium ylides to give 3,4-*trans*-1,2,3,4-tetrahydropyridine-2-thiolates **205**. The latter are converted into pyridinethiones **206** on heating with ammonium acetate in acetic acid.



The results obtained demonstrated that the stereochemistry and the electronic structures of heterocyclic compounds **182a** and **199** have similar features, namely, (1) both molecules contain a planar enaminonitrile fragment with a well-developed system of p,π-conjugation; (2) they are partially hydrogenated; (3) they contain a nonplanar ring sterically overcrowded with alkyl and aryl substituents; (4) they contain one or several electron-withdrawing groups as substituents. Due to these features, when the enthalpy increases, the compounds **182a** and **199** cannot decrease their energy upon conformational transitions; instead, they undergo cycloelimination involving the weakest bonds.

The reactions of arylidenecyanothioacetamides **203** with dimedone afford substituted pyrans **207**, which recyclise in the presence of bases to give intermediates **208** and then quinolinethiolates **209**.[203–206]



V. Conclusion

The data on recyclisation of carbo- and heterocyclic compounds with participation of malononitrile and its derivatives considered here clearly demonstrate the high synthetic potential of these reactions and good prospects for using them in the syntheses of various compounds, including products that are difficult to obtain by other methods, which possess a broad spectrum of useful properties.

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