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Reactions of carbonyl compounds with α,β-unsaturated nitriles as a convenient pathway to carbo- and heterocycles

Yu A Sharanin (deceased), M P Goncharenko, V P Litvinov

Contents

I.	Introduction	393
II.	General regularities and classification of the reactions	393
III.	Synthesis of Michael adducts	394
IV.	Synthesis of carbocyclic compounds	400
V.	Synthesis of five-membered heterocycles	400
VI.	Synthesis of pyrans	401
VII.	Synthesis of pyridines	409

Abstract. Published data on the methods for synthesis of carbo- and heterocyclic compounds based on reactions of α,β-unsaturated nitriles with carbonyl compounds and activated phenols are surveyed. It is demonstrated that all these reactions occur *via* nucleophilic addition of the carbanion generated from a carbonyl compound to the double bond of an unsaturated nitrile (the Michael reaction). The main routes of transformation of the adducts into carbo- and heterocyclic compounds are considered. The methods for regioselective preparation of fused 4*H*-pyrans or 1,4-dihydropyridines by varying conditions of cyclisation of Michael adducts are discussed. The bibliography includes 249 references.

I. Introduction

Reactions of carbonyl compounds with α,β-unsaturated nitriles can yield carbo- and heterocycles that are difficult to synthesise by other methods. Unsaturated nitriles activated by electron-withdrawing substituents react with carbonyl compounds under mild conditions; in some cases, this makes it possible to isolate intermediate compounds and to conduct highly regio- and stereoselective reactions that require simple experimental equipment. The use of initial compounds with various substituents in the molecules permits the synthesis of a broad range of heterocyclic derivatives including substituted 4*H*-pyrans, pyridines, 2-pyridones, and pyridine-2-thiones. It should be noted that the compounds produced in this way contain easily modifiable functional groups, and, therefore, they present interest for fine organic synthesis and for the chemistry of pesticides and medicines. The reactions of carbonyl compounds with ylidene derivatives of malononitrile, cyanoacetamide, and ethyl cyanoacetate have been considered in several reviews [1–6] and monographs.[7–9] However, due to the vigorous development of this field of organic chemistry, the information available from these sources needs to be supplemented. In this review, we generalise and describe systematically the data on the methods for the synthesis of carbo- and heterocycles based on reactions of carbonyl compounds with unsaturated nitriles.

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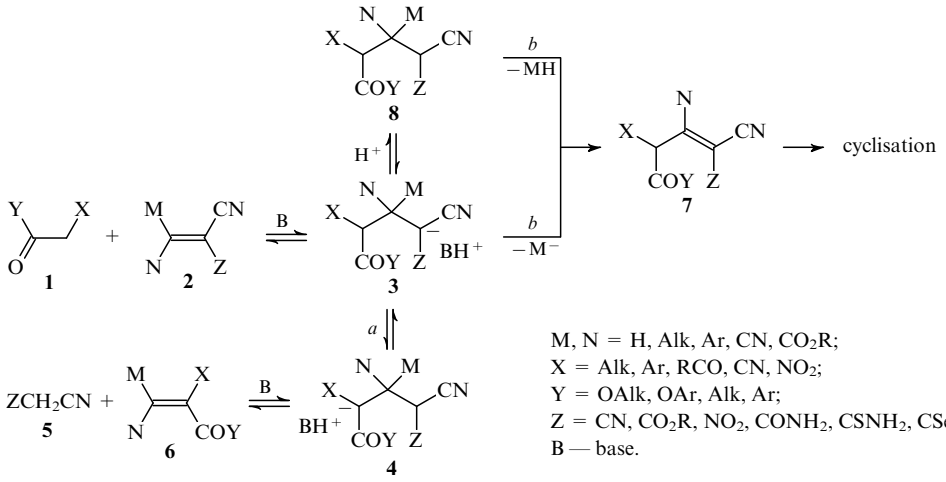
II. General regularities and classification of the reactions

Reactions of carbonyl compounds **1** with α,β-unsaturated nitriles **2** occurs most often as the Michael nucleophilic addition of the methylene group of the carbonyl compound to the activated double bond of the nitrile. The reaction involves a base, the role of which is to generate the corresponding carbanion. In addition, the base stabilises the resulting adduct as salt **3**. This process is generally illustrated by Scheme 1.[10]

The resulting salt **3** or **4** can undergo a number of subsequent transformations, their routes depending on the structures of the initial reagents and on the particular conditions. Thus, the reaction in question possesses great synthetic potential, because its regioselectivity can be modified by varying the substituents and reaction conditions. In some cases, the process follows pathway (*a*) with elimination of nitrile derivative **5** and formation of α,β-unsaturated dicarbonyl compounds **6**, *i.e.* **1** and **5** exchange their methylene fragments. This reaction is reversible, and heterocyclic compounds can be synthesised both by reaction of **1** with **2** and **5** with **6**. If one of the substituents (for instance M) is a good leaving group, it is eliminated giving rise to a multiple bond [path (*b*)]. The alkene **7** thus formed, depending on its structure, is either removed from the reaction area or undergoes intramolecular cyclisation to give carbo- or heterocyclic compounds. Acidification of the salt **3** gives adduct **8**, which can be converted into the nitrile **7** upon elimination of MH.

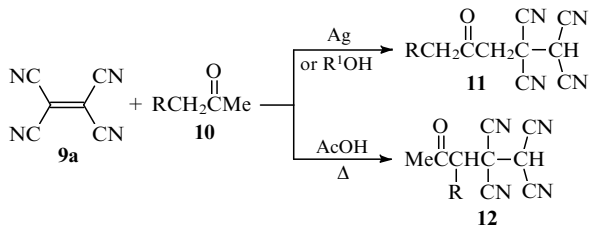
The most frequently encountered variant of the subsequent transformations of the compounds **3** and **8** is intramolecular cyclisation.[11] Depending on the natures of substituents X, Y, and Z, this can afford diverse, as a rule six-membered, carbo- and heterocycles. Some of the adducts **3**, **7**, and **8**, can be isolated, especially those derived from cyclic dicarbonyl compounds or tetracyanoethylene, which cyclise under more rigorous conditions. These adducts can also eliminate a nucleofugal fragment.

Scheme 1

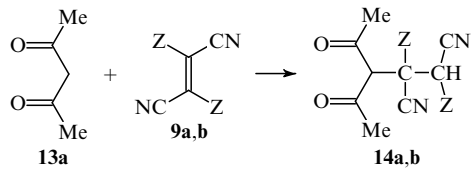


III. Synthesis of Michael adducts

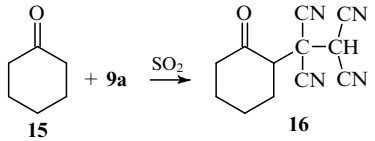
In this Section the formation of stable Michael adducts in the reactions of carbonyl compounds with unsaturated nitriles is described, the conditions and stereochemical aspects of these reactions are generalised, and decomposition of these adducts with elimination of nucleofugal groups is considered. The Michael adducts derived from carbonyl compounds and tetracyanoethylene (TCE) are the most stable.[3,4] It has been found that reaction of TCE **9a** with ketones **10** catalysed by 'molecular silver' or alcohols occurs selectively involving the methyl group and yields acyclic adducts **11**.[12] To activate the methylene group and obtain the isomeric product **12**, the reaction needs to be conducted with heating in the presence of acetic or trichloroacetic acid.[12] The structures of the adducts **11** and **12** were confirmed by their cyclisation into pyridines and pyrans under the action of acids.[13]



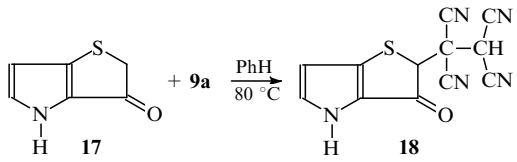
Acetylacetone **13a** reacts with TCE in the presence of silver in benzene at room temperature to give easily cyclisable adduct **14a** in 70% yield.[14] When the same compounds react in ethanol without a catalyst, the yield of **14a** is 88%.[10] Dicyanofumarate **9b** gives similar adducts **14b**.[10]



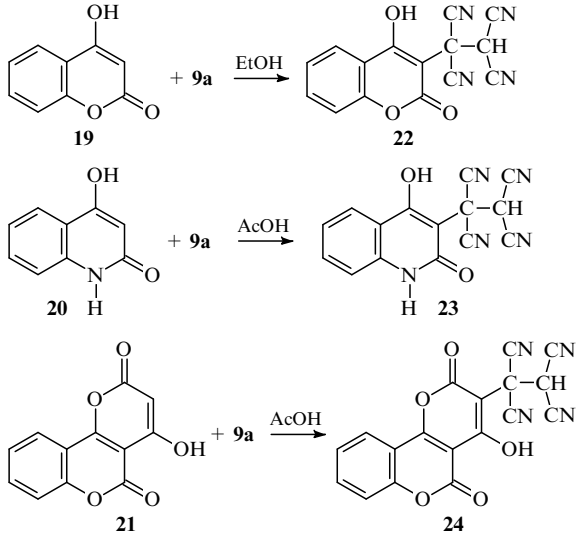
Data on isolation of stable products of addition of cyclohexanone **15** to TCE in the presence of SO_2 have been reported; the yield of adduct **16** reaches 95%.[3]



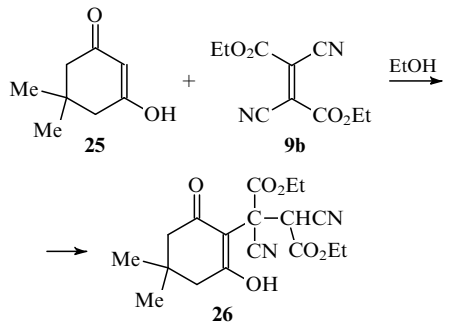
4*H*-Thieno[3,2-*b*]pyrrol-4-one **17** reacts with TCE in boiling benzene giving rise to stable adduct **18**, which has been reported [15] not to undergo subsequent cyclisation.



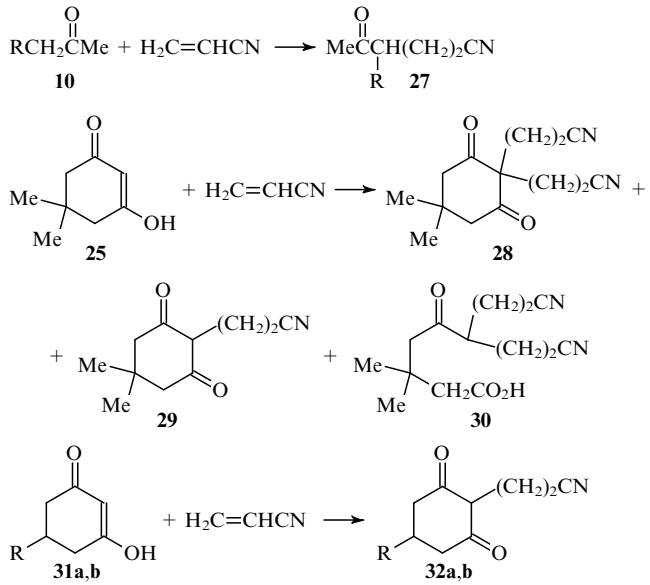
Tautomeric forms of cyclic 1,3-dicarbonyl compounds, such as 4-hydroxycoumarin **19**, 4-hydroxy-2-quinolinone **20**, and (4-hydroxy-2,5-dioxo-2*H*,5*H*-pyrano)[3,2-*c*][1]benzopyran **21**, also react with TCE to give stable Michael adducts. The adduct **22** was prepared in ethanol, while compounds **23** and **24** were synthesised in glacial acetic acid.[16]



The reaction of the dicyanofumarate **9b** with dimedone **25** results in the formation of adduct **26** existing in the enol form.[10]

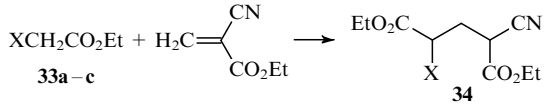


Under the Michael reaction conditions, the ketones **10** are cyanoethylated by acrylonitrile at the methylene group yielding stable compounds **27**, which are intermediates in the synthesis of cyclic diketones (see Section IV).[17] The addition of dimedone **25** to acrylonitrile in boiling dioxane gives rise to stable Michael adducts **28** and **29** and acid **30**, the latter being the major product. However, variation of the reaction conditions permits the adduct **28** to be prepared in 85% yield. Alkaline hydrolysis of this adduct in a 10% solution of potassium carbonate affords the acid **30** in 74% yield.[18] The reaction of cyclohexanone **31a** or its methyl analogue **31b** with acrylonitrile affords adducts **32** in yields of more than 60%.[20] The structure and chemical properties of these products, in particular, cyclisation to give pyridines, have been studied.[19,20]



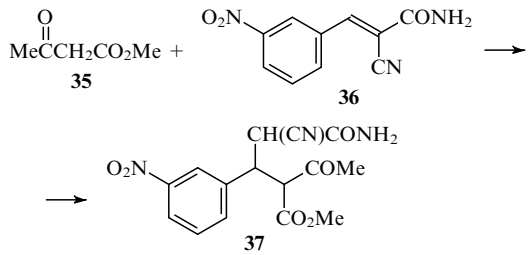
R = H (**a**), Me (**b**).

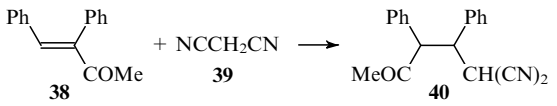
Ethyl acetoacetate **33a** adds to ethyl 1-cyanoacrylate in the presence of highly basic secondary amines yielding adduct **34**.[21] Ethyl cyanoacetate **33b** and ethyl nitroacetate **33c** behave in a similar way.



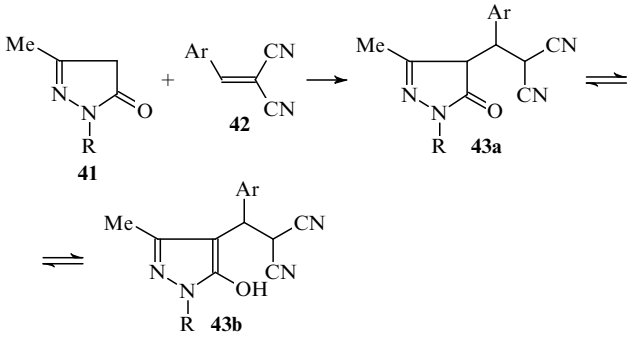
X = AcO (**a**), CN (**b**), NO_2 (**c**).

Arylidene derivatives of malononitrile and its analogues are widely used in reactions with carbonyl compounds. The Michael adducts formed in these reactions are normally unstable and readily undergo intramolecular cyclisation. However, the reaction of methyl acetoacetate **35** with 2-cyano-3-(3-nitrophenyl)acrylamide **36** in methanol in the presence of piperidine affords stable Michael adduct **37** in 88% yield.[22] Similar open-chain products are formed when unsaturated ketone **38** is made to react with malononitrile **39**; adduct **40** does not cyclise even in sodium alkoxide solutions.[23]

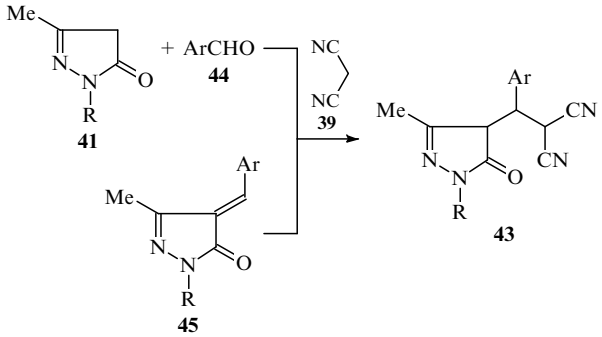




Apparently due to steric rigidity, heterocyclic carbonyl compounds are more readily converted into Michael adducts than acyclic 1,3-dicarbonyl compounds. The reaction of N-substituted 3-methyl-5-pyrazolones **41** with arylidenemalononitriles **42** can serve as an example of a well studied reaction of this type. A large number of adducts **43** with various aryl substituents have been synthesised in this way.[11,24–27] It was found that in DMSO solutions these compounds exist mostly in the enol form **43b**.[25]

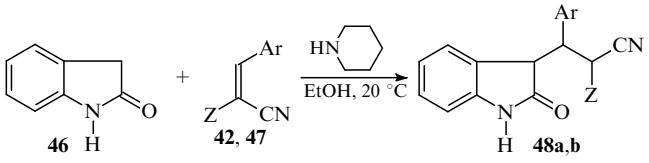


The adducts **43** have also been obtained by condensation of aromatic aldehydes **44**, malononitrile **39**, and pyrazolones **41**[27] and by the addition of malononitrile **39** to 4-arylidene-3-methyl-5-pyrazolones **45**.[25,27]



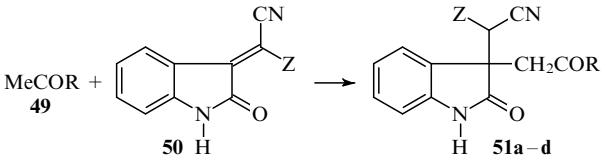
In addition, adducts of the type **43** are formed upon interaction of benzylidenemalononitrile **42** with 3-hetaryl-substituted 5-pyrazolone derivatives.[28]

Stable Michael adducts are also produced when oxindole **46** reacts with arylidene derivatives of malononitrile **42** or cyanoacetamide **47**.[29] The adducts **48** do not cyclise into the corresponding pyrans even on treatment with strong bases; this was attributed[29] to the low degree of enolisation of the indoline fragment.



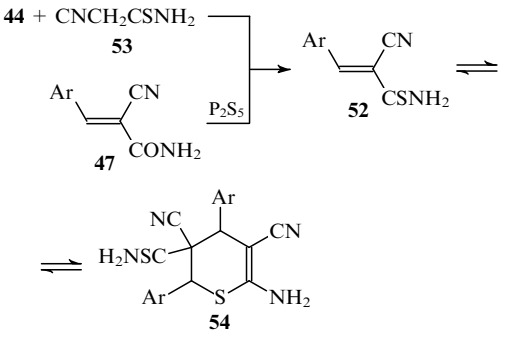
Z = CN (**42**, **48a**); Z = $CONH_2$ (**47**, **48b**).

Apparently, this also accounts for the fact that adducts **51a–d** formed from ketones **49** and 3-cyanomethylidene derivatives of oxindole **50** are quite stable and do not cyclise to pyrans without preliminary reduction.[30]

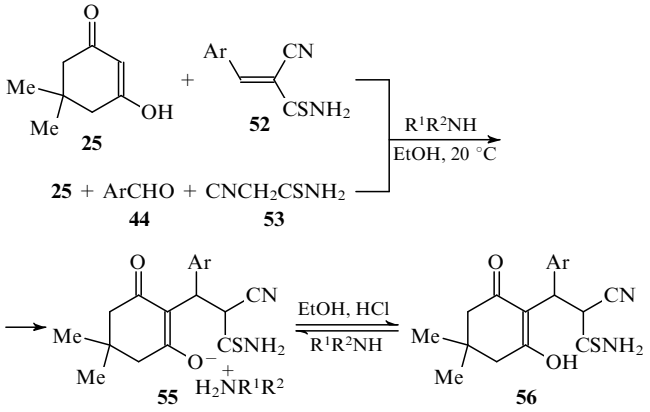


Z = CO_2Et, R = Ph (**a**); Z = CN, R = Me (**b**);
Z = CO_2Et, R = Me (**c**); Z = CN, R = Ph (**d**).

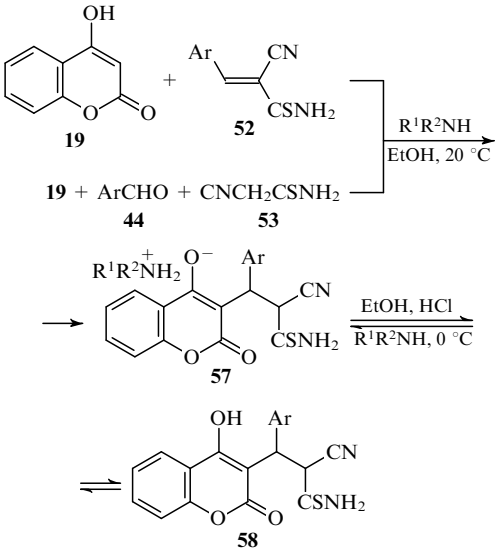
The reaction of dicarbonyl compounds with arylidene derivatives of cyanothioacetamide also possesses great synthetic potential. In this case, the presence of several reaction centres ensures the existence of various routes for cyclisation of the intermediate Michael adducts and, as a consequence, the possibility of regiocontrolled synthesis of a number of oxygen-, nitrogen-, and sulfur-containing heterocycles. Arylidenecyanothioacetamides **52** are prepared by reactions of the aromatic aldehydes **44** with cyanothioacetamide **53**[31,32] or by reactions of the corresponding amides **47** with phosphorus pentasulfide in pyridine.[33] They tend to dimerise according to the Diels–Alder reaction pattern to give 2*H*-thiopyrans **54**, which exist in solutions as a ring–chain equilibrium with the compounds **52**; this equilibrium shifts to the left on increasing the temperature.[32] Some thioamides **52** have been reported to exhibit tuberculostatic activities.[33]



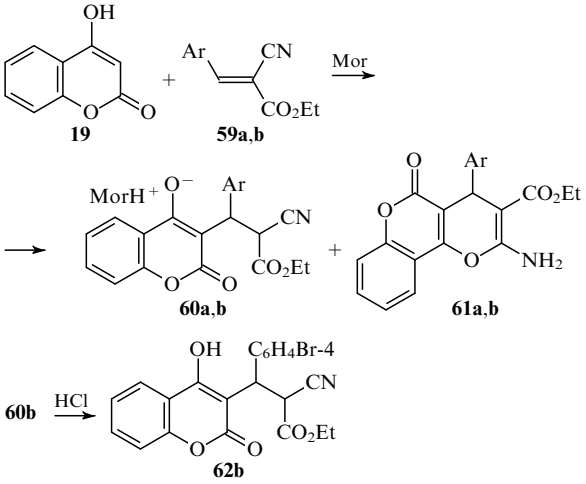
The reaction of dimedone **25** with arylidenecyanothioacetamides **52** in the presence of an equimolar amount of secondary amines in anhydrous ethanol at 20–25 °C affords Michael adducts, which are isolated from the reaction mixture as poorly soluble enol salts **55**.[34–36] The corresponding aromatic aldehydes **44** and cyanothioacetamide **53** can be used in this reaction, instead of the compounds **52**, under the same conditions.[36] On treatment with hydrogen chloride in ethanol at 0 °C, these salts are reversibly converted into free adducts **56**, which exist solely in the enol form.[36]



4-Hydroxycoumarin **19** reacts with arylidenecyanothioacetamide **52** in a similar way. When the reaction is carried out in ethanol in the presence of equimolar amounts of secondary amines at 20–25 °C, salts **57** are formed; these salts are also produced when 4-hydroxycoumarin **19** reacts with the aromatic aldehydes **44** and cyanothioacetamide **53**.[37] When gaseous hydrogen chloride is passed through an ethanolic solution containing the salts **57**, they are reversibly converted into compounds **58**.[37]

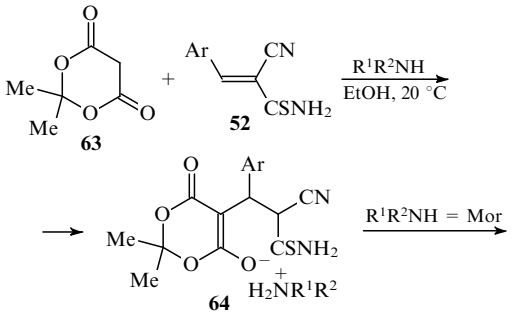


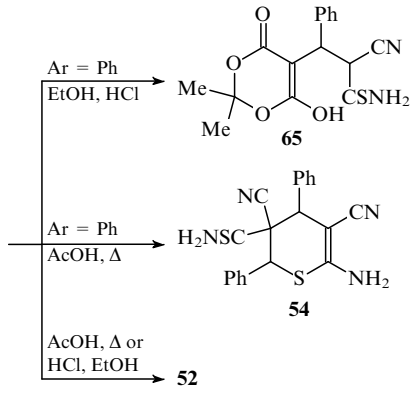
When 4-hydroxycoumarin **19** is made to react with ethyl arylidenecyanoacetates **59** in the presence of an equimolar amount of morpholine, a mixture of enolates **60** and the products of their subsequent cyclisation, 4*H*-pyrans **61**, is formed; according to the data of NMR spectroscopy, the salts **60** predominate in this mixture. The free enol **62b** was prepared by treatment of the compound **60b** with hydrogen chloride.[37]



Mor is morpholine; Ar = C_6H_5 (**a**); 4-BrC_6H_4 (**b**).

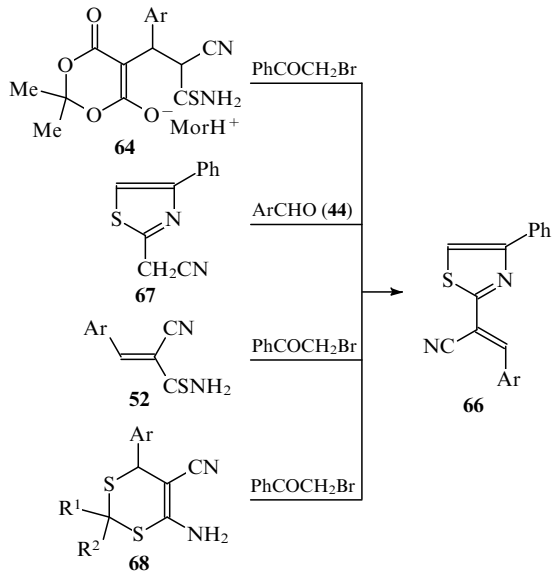
Meldrum's acid (isopropylidene malonate **63**), which is formally a cyclic 1,3-dilactone and a structural analogue of dimedone, is widely used in organic synthesis.[38] Being a relatively strong CH acid (pK_a = 4.97),[39] Meldrum's acid is not enolysed in the solid state or in solution.[40,41] Like dimedone, it reacts with arylidenecyanothioacetamides **52** to give enolates **64**.[42]





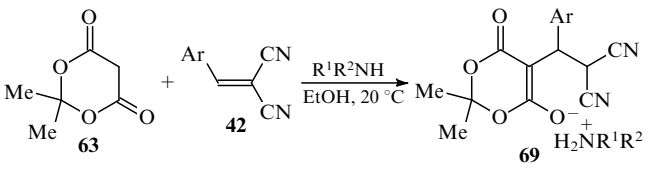
Unlike the salts **55** and **57**, which can be converted into the free enols **56** and **58** by acidification, compounds **64** decompose on treatment with hydrogen chloride in ethanol at 0 °C or on heating in acetic acid to give the initial thioamides **52**. However, in the case of the morpholinium salt **64** (Ar = Ph), free Michael adduct **65** has been prepared.[42] Heating of the same salt in acetic acid affords thiopyran **54** resulting from dimerisation of benzylidenecyanothioacetamide.[32]

The compounds **64** react with phenacyl bromide according to the Hantzsch reaction pattern with elimination of Meldrum's acid and formation of thiazole derivatives **66**. The same compounds have been synthesised by treatment of the thioamides **52** with phenacyl bromide.[42]



Arylthiazolylcyanoethylenes **66** have previously been obtained by reactions of 2-cyanomethylthiazoles **67** with the aromatic aldehydes **44**,[43] or phenacyl bromide with 4-amino-6-aryl-5-cyano-1,3-dithiacyclohexenes **68**.[44] The latter reaction has served as evidence for the intermediate formation of the thioamides **52** during thermal decomposition of dithiacyclohexenes **68** (see Section VII).[45,46]

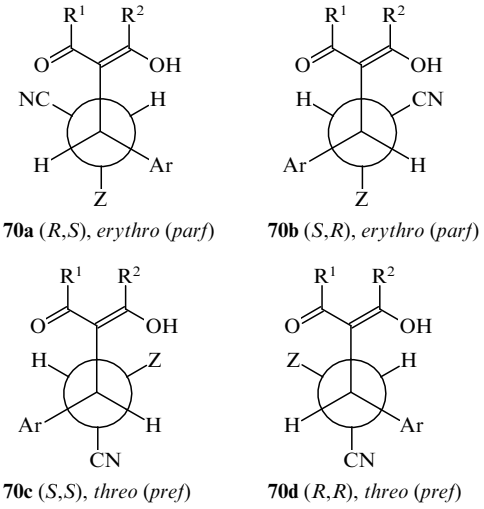
The reaction of Meldrum's acid **63** with arylidenemalononitriles **42** in ethanol in the presence of secondary amines also gives rise to Michael adducts formed as salts **69**.[42] A similar reaction of dimedone and 4-hydroxycoumarin affords fused 4*H*-pyrans (see Section VI).



When cyclic 1,3-dicarbonyl compounds are made to react with arylidenecyanothioacetamides, the Michael adducts are usually isolated as enol salts of secondary amines. In the case of acyclic 1,3-dicarbonyl compounds, the intermediate adducts cyclise without isolation to the corresponding pyridines (see Section VII).

Based on the spin-spin coupling constants, ^3J = 11.5–12.5 Hz, of the methine protons in the compounds **55**–**58**, **60**, **62**, **64**, **65**, and **69**, it was found that the dihedral angles φ between these protons are 158–165°, which corresponds to the antiperiplanar conformation.[36,37,42]

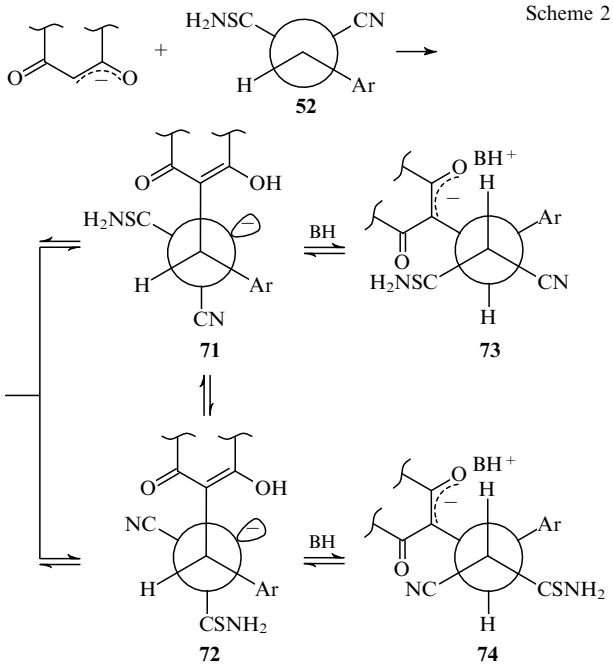
It is known that the selectivity of any reaction is determined by the symmetry of the transition state; therefore, when diastereoisomeric activated complexes are formed, they react at different rates.[47] The Michael addition of dicarbonyl compounds to unsaturated nitriles of the types **42**, **47**, **52**, or **59** results in the appearance of two asymmetric centres; thus, the reaction system is diastereotopic. Since the attack on the diastereotopic sides of the molecule could give unequal amounts of diastereoisomers, due to the difference between the free energies of the corresponding transition states, this reaction is, in principle, diastereoselective and can afford two pairs of diastereoisomeric adducts, **70a**,**b** and **70c**,**d**. The substituent Z is usually represented by ester, amide, thiocarbamoyl, and other similar groups, which, according to the succession rule, are senior with respect to the cyano group. In this case, the stereoisomers **70a** and **70b** constitute an enantiomeric pair of the *erythro*-type (*parf*) diastereoisomers, whereas the isomers **70c** and **70d** belong to the *threo*-type (*pref*).[48,49] The predominant formation of one or another stereoisomer depends on the particular conditions.

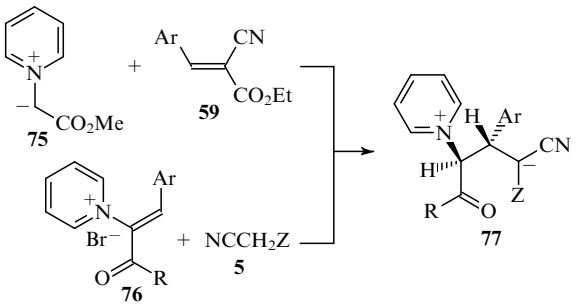


The addition of a dicarbonyl fragment to the double bond in the compounds **52** existing as *E* isomers[32,50] gives intermediate carbanions **71** and **72**. It is known that the inversion of configuration in carbanions occurs relatively easily[51] and that the *E*/*Z* isomerisation of arylidenecyanoacetates occurs exactly at this stage.[52] Apparently, the carbanions **71** and **72** are also able to isomerise to each other. The protonation of the carbanions **71** and **72** gives isomers represented by projections **73** and **74**, respectively. Evidently, the course of cyclisation depends not only on thermodynamic factors but also on the spatial structure of the adducts. Therefore, intramolecular cyclisation of *erythro*- and *threo*-diastereoisomers yields different compounds: pyrans or pyridines (see Sections VI and VII, respectively, Scheme 2).

It is known that pyridinium ylides are good reagents for transferring the methylenecarbonyl function to an activated C=C bond.[53] When pyridinium ylides **75** react with the unsaturated nitriles **59**, or the nitriles **5** react with unsaturated ketones **76**, Michael adducts **77** are formed.[53–55]

Scheme 2



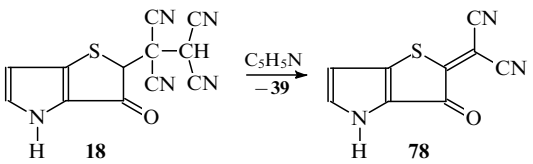


Z = CN, CO_2Et.

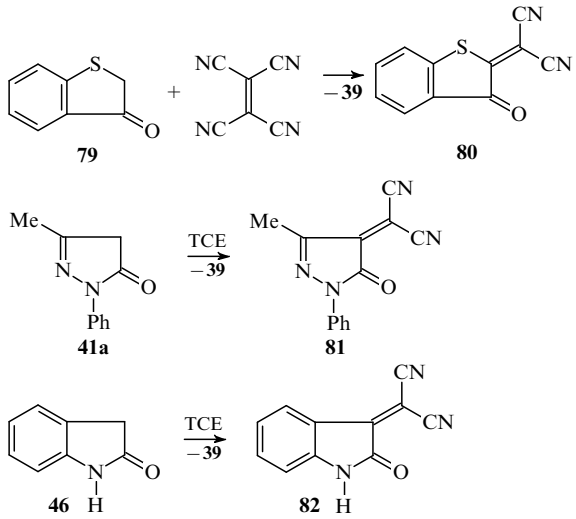
Based on conformational analysis using the magnitudes of the spin-spin coupling constants of methine protons, ^3J = 11.2–11.8 Hz, it was shown that the adducts **77** also exist only in the antiperiplanar conformation. The reactions of unsaturated nitriles with pyridinium ylides have been considered in more detail in a review.[56]

A possible route for subsequent transformations of Michael adducts is decomposition accompanied by elimination of an easily leaving group [57] [Scheme 1, pathway (*a*)] and resulting in various rearrangements and exchange of methylene components.[57–59] The Michael adducts derived from unsaturated nitriles also tend to undergo retro-reactions, and, consequently, the reactions of ylidene derivatives of cyanoacetetic acids with nucleophiles typically involve dynamic equilibria of the type **1** + **2** ⇌ **3** ⇌ **4** ⇌ **6** + **5** (see Scheme 1).[60] These transformations have been considered in detail.[61]

The adducts formed from cyclic carbonyl compounds and TCE tend to eliminate malononitrile **39**. Thus on treatment with pyridine, the adduct **18** is cleaved to afford compound **78**.[15]

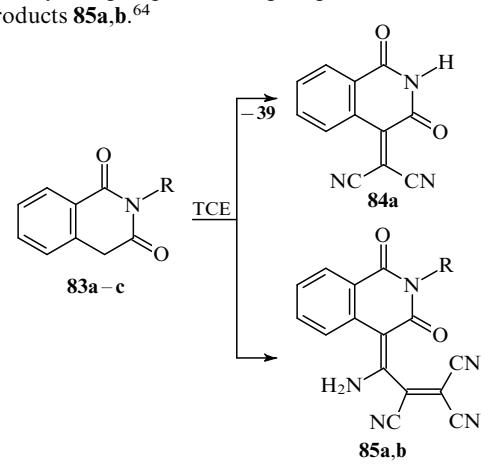


Benzo[*b*]thiophen-3-one **79** reacts with TCE giving rise to unsaturated nitrile **80** without intermediate isolation of the Michael adduct.[15] The reaction of the pyrazolone **41a** with TCE also results in the formation of the corresponding dicyanomethylidene derivative **81**.[62] 2-Indolinone **46** reacts with TCE in a similar way and gives dicyanomethylideneindolinone **82**.[63]



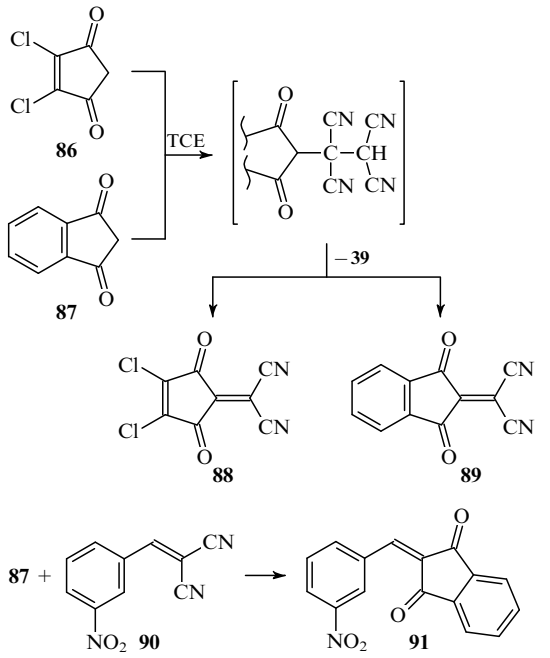
TCE is tetracyanoethylene.

The behaviour of imides **83** in the reaction with TCE depends on the nature of the substituent at the nitrogen atom. For R = H, the reaction occurs according to the Michael pathway followed by elimination of malononitrile **39** to give compound **84a**. However, in the presence of an alkyl substituent, the nucleophilic methylene group in the compound **83** attacks the electrophilic carbon atom of a cyano group in TCE giving rise to the Thorpe reaction products **85a**,**b**.[64]

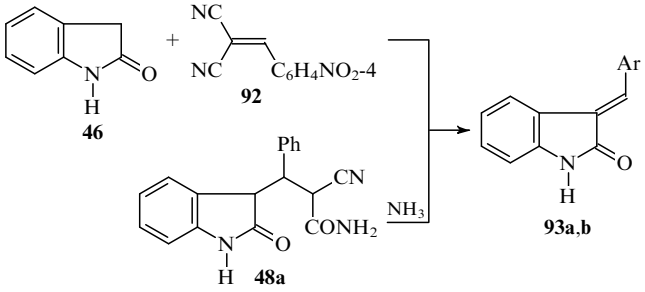


R = H (**83a**), Me (**83b**, **85a**), Et (**83c**, **85b**).

Cyclic diketones such as 4,5-dichlorocyclopent-4-ene-1,3-dione **86** [65] and 1,3-indanedione **87** [66] also react with TCE according to the Michael pathway. The products **88** and **89** thus formed contain an electron-deficient double bond. The compound **88** has been used to prepare charge-transfer complexes.[65] The reaction of indanedione **87** with 3-nitrobenzylidenemalononitrile **90** gives rise to unsaturated diketone **91**.[11]

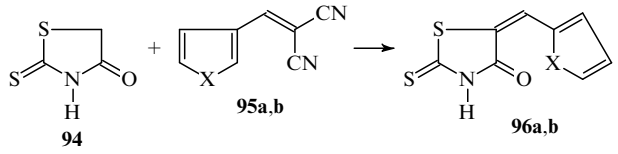


The reaction of 4-nitrobenzylidenemalononitrile **92** with indolinone **46** affords compound **93a**.[29] When other arylmethylidenemalononitriles are introduced into this reaction, stable Michael adducts **48** are produced;[29] one of them (**48a**) is converted into non-substituted unsaturated ketone **93b** on treatment with ammonia.[29]



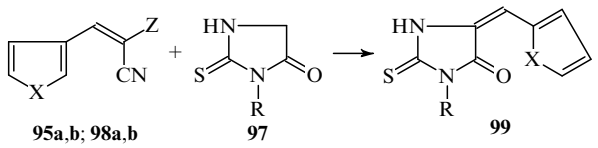
Ar = 4-$NO_2C_6H_4$ (**a**), Ph (**b**).

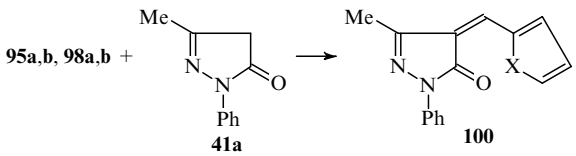
The reactions of thiazolidine derivative **94** with furylidene- and thienylidene-malononitriles **95a**,**b** giving unsaturated ketones **96a**,**b** in 90% yield have been reported.[67]



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

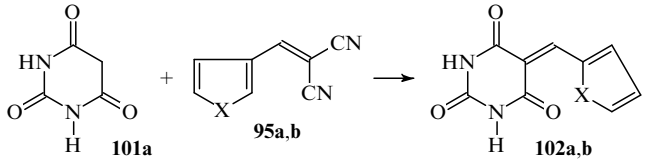
3-R-2-Thiohydanthoins **97** having a similar structure and 3-methyl-1-phenylpyrazolone **41a** react with **95a**,**b** and **98a**,**b** to give products **99** and **100**. It has been suggested [68] that during this reaction, the reactants exchange their methylene components.





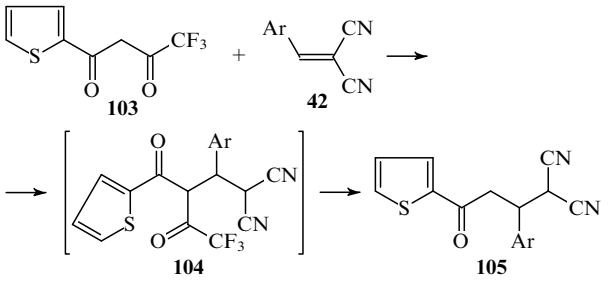
X = O, Z = CN (**95a**); X = S, Z = CN (**95b**);
X = O, Z = CO_2Et (**98a**); X = S, Z = CO_2Et (**98b**).

It has been shown that on refluxing in ethanol with barbituric acid **101a** and triethylamine, substituted furylidenemalononitriles **95a**,**b** are converted into compounds **102**.[69] By varying reaction conditions, one can obtain 2-aminopyrano[2,3-*d*]pyrimidines (see Section VI).

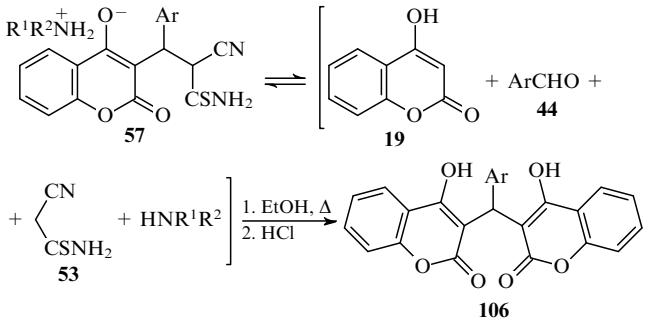


X = O (**a**), S (**b**).

An interesting reaction occurs between arylidenemalononitriles **42** and 1,1,1-trifluoro-3-(2-thenoyl)acetone **103**. The Michael adducts **104** formed intermediately undergo acidic cleavage with elimination of trifluoroacetic acid and are thus converted into substituted dicyanopropanes **105**,[11,70] which can be used to synthesise substituted pyridines.[70]

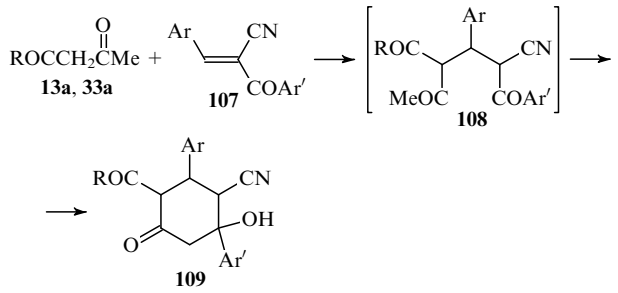


It has been mentioned above that the salts of adducts formed by Meldrum's acid and arylidenecyanothioacetamides **64** enter into a retro-reaction induced by acids and resulting in regeneration of the thioamides **52**. This is in agreement with the known data indicating that Michael adducts are stabilised by bases.[60] On heating in ethanol, the dimedone and Meldrum's acid derivatives are finally converted into derivatives of hydrogenated pyridine (Section VII). In the case of the salts **57** prepared from 4-hydroxycoumarin the cyclisation is hampered, and, as a result, the retro-reactions prevail. Prolonged refluxing of the salts **57** in ethanol followed by acidification has given aryl-substituted dicoumarins **106**;[37] these compounds have also been synthesised by the reaction of 4-hydroxycoumarin **19** with aromatic aldehydes **44**.[71,72] The chemical properties of the compounds **106** and their analogues have been studied.[73,74] It was found that they possess a moderate anticoagulant activity and inhibit oxidative phosphorylation in liver mitochondria.[75] The structure of a dicoumarin **106** (Ar = Ph) has been studied by X-ray diffraction analysis.[76]



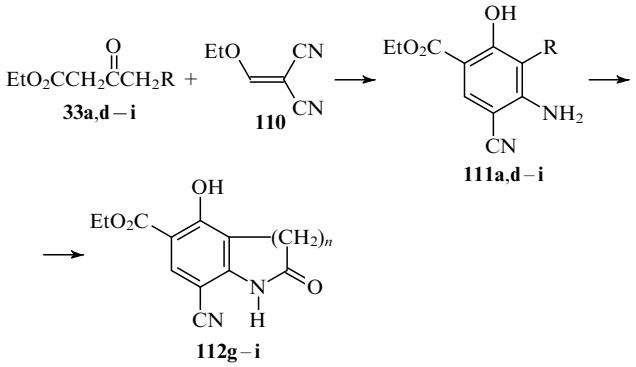
IV. Synthesis of carbocyclic compounds

Carbocyclic compounds are formed in those cases where at the stage of cyclisation of the adducts **7** and **8** (see Scheme 1), the carbon atom of the methyl, methylene, or methine group, activated by electron-withdrawing substituents, acts as the nucleophilic centre, while the carbonyl or nitrile carbon atom acts as the electrophilic centre.[7] The reactions of 1,3-dicarbonyl compounds **13a** and **33a** with substituted nitriles **107** occur *via* cyclisation of the intermediate Michael adducts **108** at the aryl group and afford compounds **109**.[23, 77]



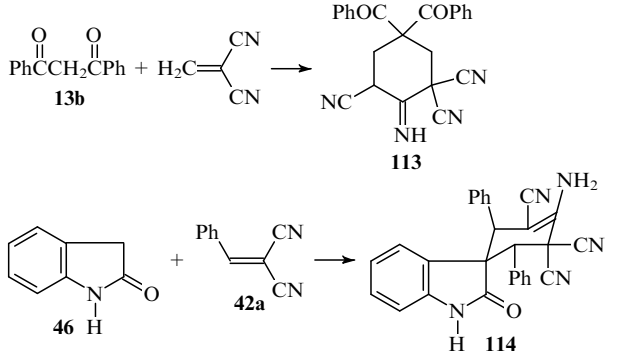
R = Me (**13a**), OEt (**33a**).

The dicarbonyl compounds **33a**,**d**–**f** react with ethoxymethylidenemalononitrile **110** to give substituted anilines **111**.[78–80] When the compounds **33g**–**i** with R = $(CH_2)_nCO_2Et$, n = 1, 2, 3, are introduced into this reaction, subsequent condensation is possible, resulting in the formation of fused heterocyclic compounds **112**.[80]

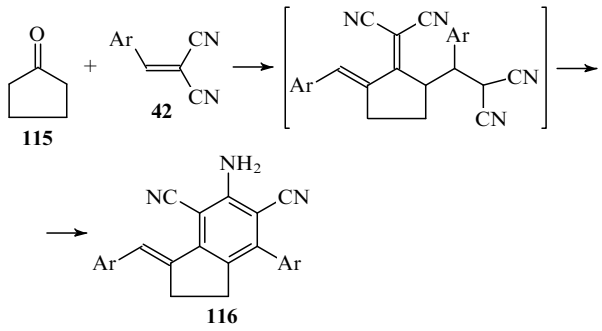


R = H (**a**), Me (**d**), Et (**e**), Ph (**f**), EtO_2CCH_2 (**g**),$EtO_2C(CH_2)_2$ (**h**), $EtO_2C(CH_2)_3$ (**i**).

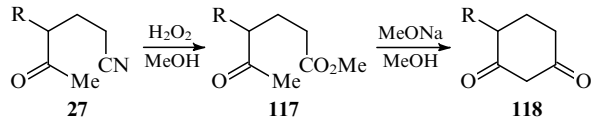
In some cases, the intermediate Michael adducts can add to a second molecule of the starting unsaturated nitrile, and the resulting bis-adduct can undergo Thorpe cyclisation. This route is realised, for example, in reactions of dibenzoylmethane **13b** with 1,1-dicyanoethylene [1] and oxindole **46** with benzylidenemalononitrile **42a**.[29] The resulting compounds **113** and **114** contain six-membered carbocycles.



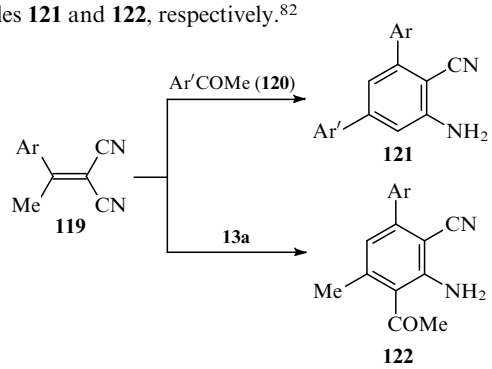
Cyclopentanone **115** also adds two molecules of an unsaturated nitrile giving rise to fused anilines **116**.[81]



On treatment with hydrogen peroxide in methanol, the adducts **27** are converted into esters **117**, refluxing of which in the presence of sodium methoxide leads to their cyclisation yielding substituted cyclohexanediones **118**.[17]



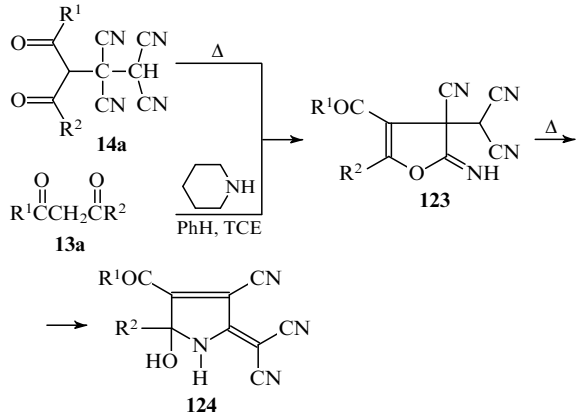
Unsaturated nitriles **119** react with substituted acetophenones **120** or with acetylacetone **13a** to give arylated 2-aminobenzonitriles **121** and **122**, respectively.[82]

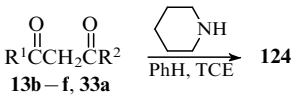


V. Synthesis of five-membered heterocycles

With an appropriate arrangement of the reaction centres, Michael adducts like 1,4-dioxo nitriles cyclise to give five-membered heterocycles, furans and pyrroles. Thus the adduct **14a** is converted into substituted 2-iminofuran **123** even during recrystallisation from a mixture of acetone and petroleum ether. The reaction of acetylacetone **13a** with TCE **9a** in benzene in the presence of pyridine affords immediately the imine **123**.[14]

On heating, 2-iminofuran **123** undergoes rearrangement accompanied by migration of the dicyanomethyl group to give dihydropyrroles **124**. The pyrroles **124** are also produced when ethyl acetoacetate **33a** or various acyclic 1,3-diketones **13b**–**f** (except for acetylacetone) react with TCE in the presence of piperidine. No furans **123** were produced in these reactions.[14]

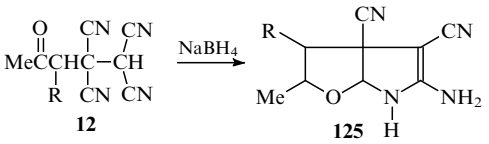




13b–f, 33a **124**

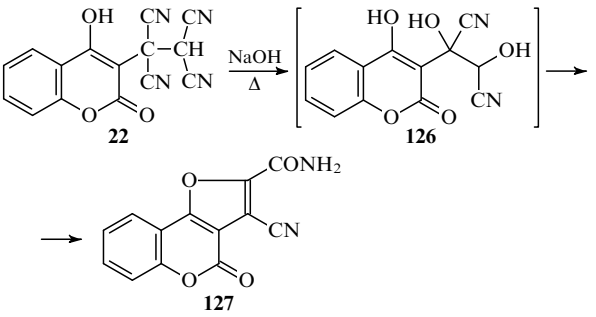
$R^1 = R^2 =$ Me (**13a**, **14a**); $R^1 = R^2 =$ Ph (**13b**);
$R^1 = R^2 =$ Et (**13c**); $R^1 =$ Me, $R^2 =$ Ph (**13d**);
$R^1 = CHMe_2$: $R^2 =$ Me (**13e**), $CHMe_2$ (**13f**); $R^1 =$ OEt, $R^2 =$ Me (**33a**).

It has been reported [83] that during the reduction with sodium tetrahydroborate, acyclic adducts of the type **12** cyclise to substituted tetrahydrofuro[2,3-*b*]pyrroles **125**.



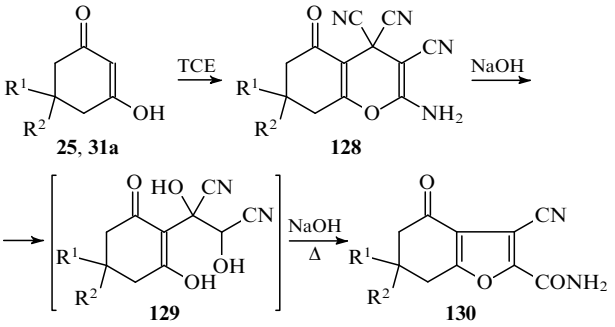
12 **125**

When the adduct **22** is refluxed in an alkaline solution, two cyano groups are substituted to give intermediate **126**, which cyclises with simultaneous hydrolysis of one more cyano group giving rise to furobenzopyranone **127**.[16]



22 **126** **127**

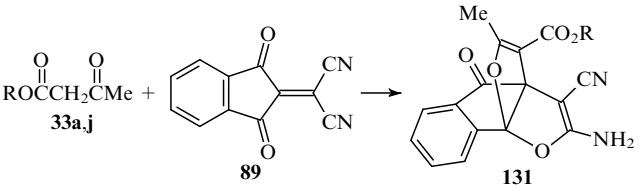
Pyrans **128**, obtained by the interaction of dimedone **25** or cyclohexanedione **31a** with TCE, react with alkali with opening of the pyran ring to give intermediates **129**, which are then converted into fused furans **130** in a similar way.[84]



25, **31a** **128** **129** **130**

$R^1 = R^2 =$ Me (**25**), H (**31a**).

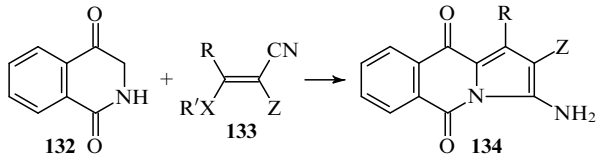
2-(Dicyanomethylidene)-1,3-indanedione **89** reacts with alkyl acetoacetates **33a,j** on refluxing in ethanol. This results in the formation of propellanes **131** in moderate yields.[85]



33a,**j** **89** **131**

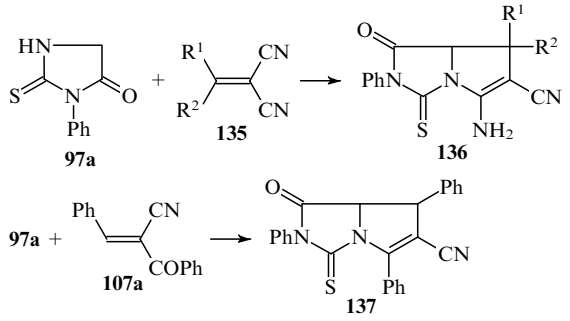
R = Et (**33a**), Bu^t (**33j**).

The reactions of isoquinolinedione **132** with unsaturated nitriles **133** containing an easily leaving group R^1X (X = O, S) result in the formation of pyrrolo[1,2-*b*]isoquinolinediones **134**. Cyclisation occurs under mild conditions without isolation of intermediate adducts. The compound **134** was found to possess antiphlogistic activity.[86]



132 **133** **134**

3-Phenyl-2-thiohydantoin **97a** reacts with a large number of ylidenemalononitriles **135** giving rise to substituted pyrrolo[1,2-*c*]imidazoles **136**.[87] However, for unsaturated nitriles containing a benzoyl group, for example, for **107a**, the cyclisation was reported [87] to involve the CO group instead of CN and to yield pyrrolo[1,2-*c*]imidazole **137**.



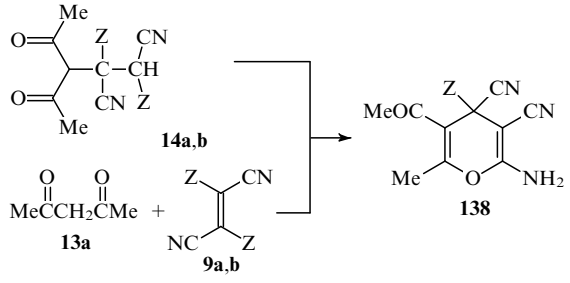
97a **135** **136** **107a** **137**

VI. Synthesis of pyrans

Cyclisation of the Michael adducts of the type **7** and **8** (see Scheme 1) giving a pyran ring occurs in those cases where the oxygen atom in δ-hydroxy or δ-oxo nitriles acts as the nucleophilic centre.[7] As a rule, this affords 4*H*-pyrans. A carbonyl fragment can serve as the electrophilic centre in place of the nitrile group. Depending on the structures of the initial compounds, the formation of pyrans in the reactions under consideration can occur without intermediate Michael reaction between the reactants. The mild conditions needed for these reactions, high yields of products, and also potential biological activities of the resulting 4*H*-pyrans account for the considerable interest aroused by these objects and for the large number of publications on this topic, which have been surveyed in monographs and reviews.[1,7,88]

There are two main approaches to the synthesis of the compounds in question, namely, interaction of nitriles with α,β-unsaturated ketones [23,88] and interaction of carbonyl compounds with α,β-unsaturated nitriles. This section is devoted to the latter approach. However, in each particular case, the most efficient preparative method can be chosen for the synthesis of pyrans, because the above structures can occur in equilibrium (**5** + **6** ⇌ **3** ⇌ **1** + **2** in Scheme 1) [10,60,61] and these reactions have common intermediates.

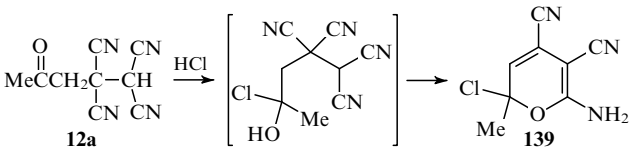
The acyclic adducts **14a**,**b**, prepared by the addition of acetylacetone to TCE or dicyanofumarate, readily cyclise to the corresponding 4*H*-pyrans **138** on refluxing in petroleum ether.[10] The same products are formed when acetylacetone **13a** reacts with nitriles **9a**,**b** in acetonitrile.



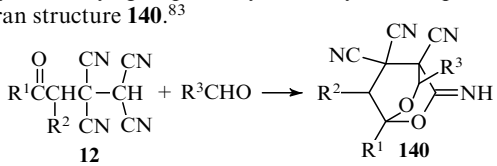
14a,**b** **13a** **9a**,**b** **138**

Z = CN (**a**), CO_2Et (**b**).

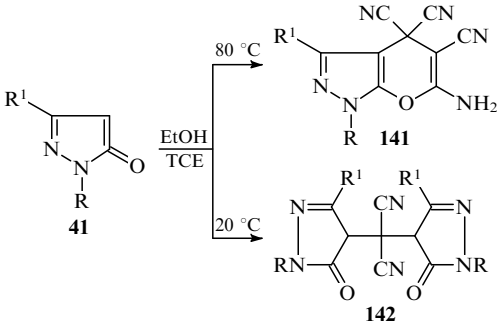
The adduct **12a** synthesised from acetone and TCE cyclises into the 2*H*-pyran **139** under the action of hydrogen chloride.[13]



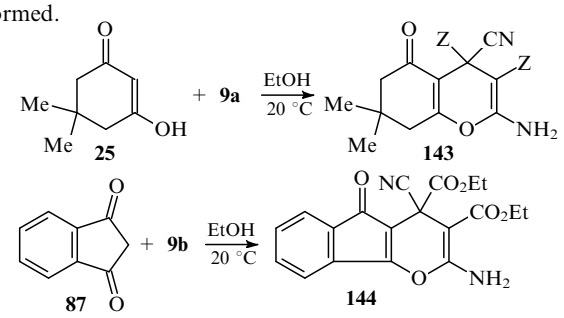
The compounds **12**, which are formed when ketones add to TCE (see Section III), can react with aldehydes at the terminal dicyanomethyl group; this yields bicyclic compounds with the pyran structure **140**.[83]



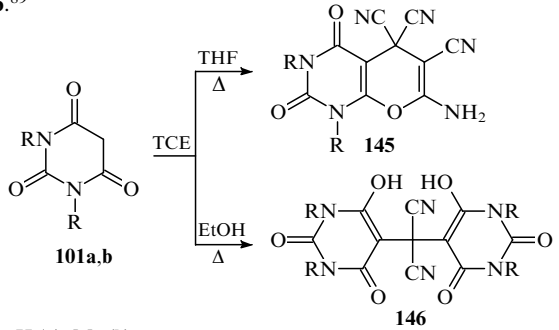
Refluxing of pyrazolones **41** with TCE in ethanol results in the formation of pyrano[2,3-*c*]pyrazoles **141**. This reaction carried out without heating yields bis-adducts **142**.[89] Apparently, in this case, the rate of elimination of malononitrile from the intermediate Michael adduct is higher than the rate of cyclisation.



When dimedone **25**[10, 84] reacts with TCE **9a**, or indanedione **87**[10] reacts with dicyanofumarate, fused pyrans **143** and **144** are formed.

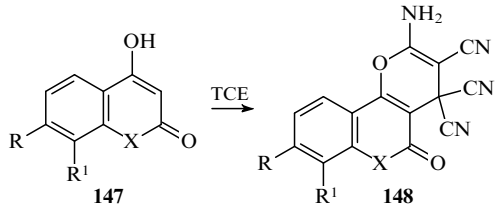


Barbituric acids **101a**,**b** react with TCE in boiling THF to give fused 4*H*-pyrans **145**.[89] It is of interest that the same reaction carried out in ethanol results in the formation of bis-adducts **146**.[89]

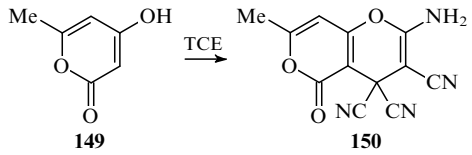


R = H (**a**), Me (**b**).

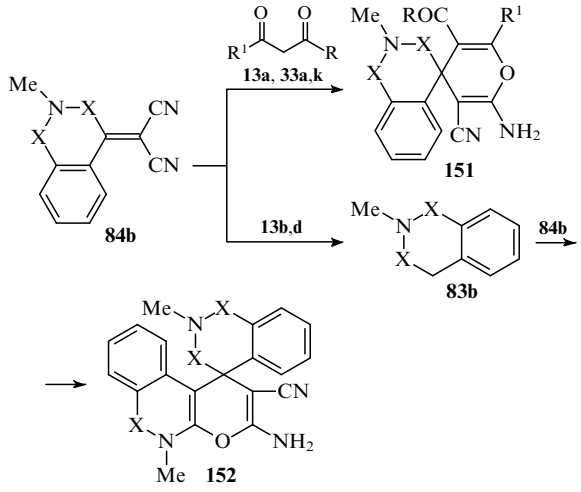
4-Hydroxycoumarin **19** and 4-hydroxy-2-quinolinone **20** can be regarded as completely enolysed cyclic 1,3-dicarbonyl compounds. As noted above, they form Michael adducts **22** and **23** upon reactions with TCE.[16] Later, it has been found that the reaction of the substituted coumarins **147** (X = O) and quinolinones **147** (X = NR) with TCE permits the synthesis of fused pyrans **148** in one step without isolation of the adducts of the type **22** and **23**.[63] Like 4-hydroxycoumarin, triacetic acid lactone **149** also reacts with TCE giving rise to fused pyran **150**.[89]



X = O, NR.

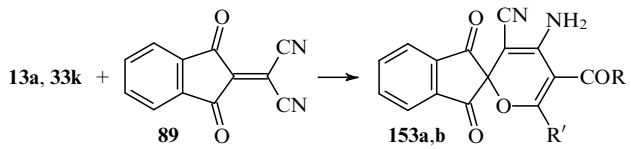


The reactions of carbonyl compounds with dicyanomethylidene derivatives of carbo- and heterocyclic compounds make it possible to synthesise spiro-derivatives of pyrans, which are difficult to obtain by other methods. Thus reactions of 3-dicyanomethylidene-1-methylisoquinoline-2,8-dione **84b** with acetylacetone **13a**, ethyl acetoacetate **33a**, and ethyl benzoylacetate **33k** gave spiropyrans **151**.[90] When dibenzoylmethane **13b** or benzoylacetone **13d** is used as the dicarbonyl compound, the reaction starts with elimination of malononitrile from the compound **84b** giving homophthalimide **83b**. The latter reacts with excess **84b** to yield spiropyran **152**.[90]



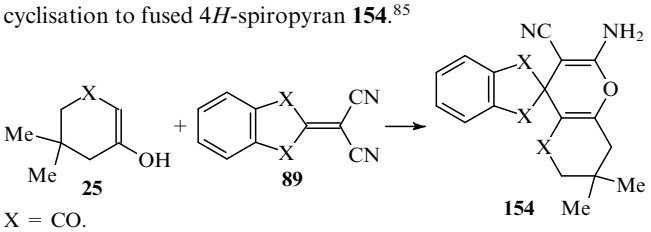
X = CO; R = R^1 = Me; R = OEt: R^1 = Me, Ph.

2-Dicyanomethylidene-1,3-indanethione **89** reacts with acetylacetone **13a** and ethyl benzoylacetate **33k** giving rise to substituted 2*H*-pyrans **153a**,**b**.[85]



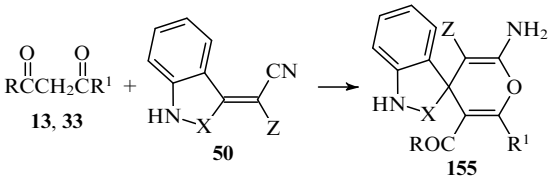
R = R^1 = Me (**13a**, **153a**); R = Et, R^1 = Ph (**33k**, **153b**).

Unlike acyclic dicarbonyl compounds, dimedone adds to the unsaturated nitrile **89** according to Michael; this is followed by cyclisation to fused 4*H*-spiropyran **154**.[85]



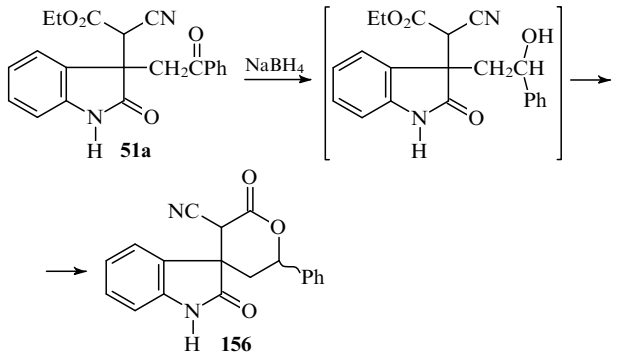
X = CO.

The reactions of 3-cyanomethylidene **50** with a broad range of dicarbonyl compounds of the types **13** and **33** lead to the synthesis of substituted spiropyrans **155** without isolation of intermediate Michael adducts.[91] Similar results have been obtained in another study.[85]

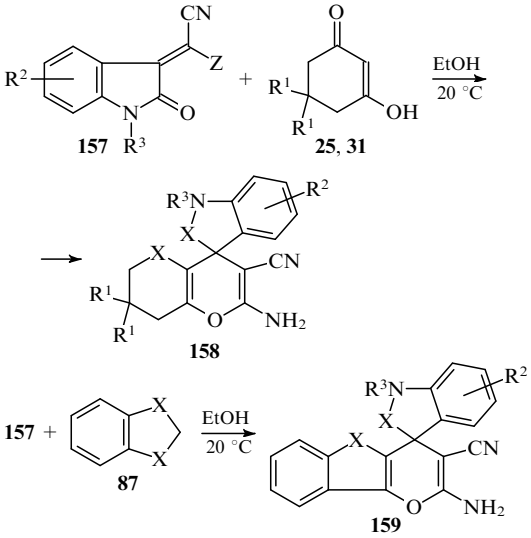


R = Alk, Ar; R^1 = Alk, Ar, OAlk; X = CO; Z = CN, CO_2Et.

On reduction with sodium tetrahydroborate, the adduct **51a** cyclises giving rise to substituted hydrogenated spiropyran **156**, which has been isolated as a mixture of two diastereoisomers in a ratio of 3 : 1.[30]

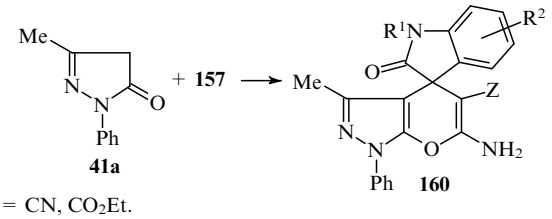


Cyclic 1,3-dicarbonyl compounds — substituted 1,3-cyclohexanediones **25**, **32** and indanedione **87**[92] — react with 3-cyanomethylidene-2-oxoindoles **157** to give spiropyrans **158** and **159**, respectively.



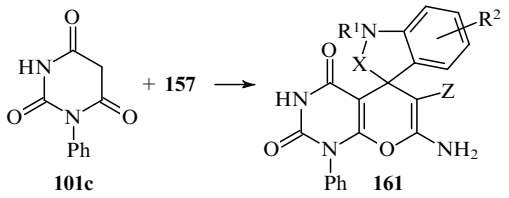
R^1 = Me (**25**), H (**31**); Z = CN; X = CO.

The addition of the pyrazolone **41a** to substituted 3-cyanomethylidene-2-oxindole **157** results in the formation of spiropyrans **160**.[91,93] Some fluoro-substituted derivatives of **160**, for example, those with R^2 = 5-F or 4-CF_3, exhibit herbicide properties.[93]



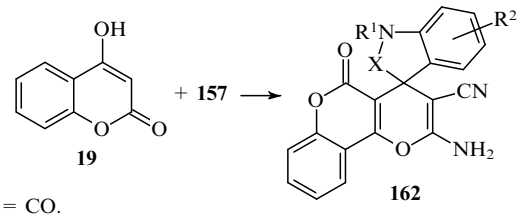
Z = CN, CO_2Et.

Barbituric acids also react with 3-cyanomethylideneindolinones **157** to give spiropyrans.[91,94] In the case of 1-phenylbarbituric acid **101c**, the reaction with fluorine-containing **157** gives rise to spiro compounds **161**.[95]



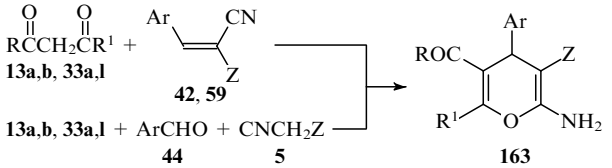
Z = CN, CO_2Et; X = CO.

3-Dicyanomethylidene-2-oxindoles **157** with 4-hydroxycoumarin **19** afford the corresponding spiropyrans **162**.[92]



X = CO.

Arylidene derivatives of malononitrile and ethyl cyanoacetate smoothly react with 1,3-dicarbonyl compounds containing a highly reactive methylene group yielding 2-amino-4*H*-pyrans. In this case, the intermediate Michael adducts immediately undergo intramolecular cyclisation. The reaction is normally carried out in ethanol at room temperature using catalytic amounts of organic bases. The simplicity and convenience of this route to substituted 2-amino-4-aryl-4*H*-pyrans **163** have been demonstrated in relation to the interaction between ethyl acetoacetate **33a** and the unsaturated nitriles **42**.[96] Later, ethyl oxaloacetate **33l**[97] and other acyclic dicarbonyl compounds such as acetylacetone **13a** and dibenzoylmethane **13b**[11] were also introduced in the reactions with the unsaturated nitriles **42** and **59**. The aromatic aldehydes **44** and functional derivatives of malonic acid (Z = CN, CO_2Et) can be used instead of the nitriles **42** and **59**; in many cases, this results in simpler preparative procedures.[96]



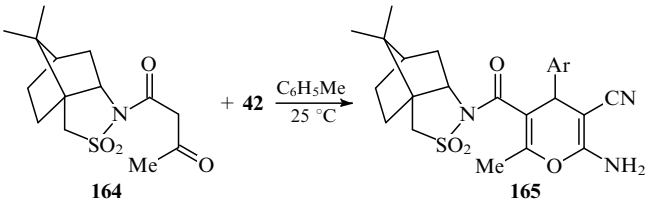
R = R^1 = Me (**13a**); R = R^1 = Ph (**13b**); R = OEt: R^1 = Me (**33a**), R^1 = CO_2Et (**13l**); Z = CN (**42**), CO_2Et (**59**).

This reaction has been extended to hetaryl-substituted derivatives of the unsaturated nitriles **42** and **59**. In particular, 1,3-dicarbonyl compounds have been made to react with thiophene[98] and pyridine[99] derivatives and with quaternised pyridines.[100] The structure of the pyrans obtained in this way, namely, 3-(2-amino-

3,5-dicarbethoxy-6-methyl-4(4*H*)-pyranyl-1-methylpyridinium iodide, was studied by X-ray diffraction analysis.[100] It was found that the pyran ring has a boat conformation in which the O and C atoms emerge from the plane of the boat 'bottom'.

The formation of furyl-substituted pyrans **163** upon interaction of 2-furylidenemalononitriles with ethyl 4-chloro-3-oxobutyrate[101] or acetylacetone[102,103] has been reported. In several studies,[104–108] syntheses of pyrans based on reactions of the unsaturated nitriles **42** and **59** with ethyl acetoacetate or acetylacetone have been reproduced.

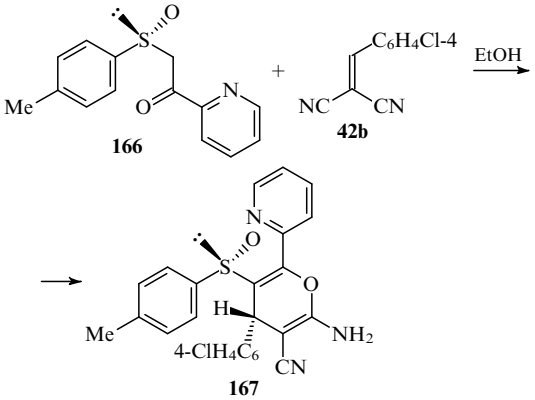
The use of optically active esters of acetoacetic acid in the reactions with arylidenemalononitriles was a step forward on the way to the synthesis of chiral 4*H*-pyrans. Thus reaction of esters derived from acetoacetic acid and (1*R*,2*S*,5*R*)-(−)-menthol, (1*S*)-*endo*-(−)-borneol, or ethyl (*S*)-(−)-lactate with benzylidene- and *m*-nitrobenzylidene-malononitriles **42a** and **90** affords the pyrans **163** containing an optically active substituent. The yields of the mixture of diastereoisomers was 73%–98%;[109] however, the diastereoisomeric excess was no more than 10% and the mixture could not be separated. The reactions of the arylidenemalononitriles **42** with chiral acetoacetylsulfamide **164** are much more stereoselective. Thus pyrans **165** are formed as mixtures of diastereoisomers with a diastereoisomeric excess of 60%–70%. In some cases, this mixture has been separated into individual isomers, and it turned out that all the major isomers are characterised by the same configuration at the newly formed C(4) chiral centre in the pyran fragment. X-Ray diffraction study has shown that in the minor isomer of **165** (Ar = Ph), this atom has the *S*-absolute configuration.



164 **165**

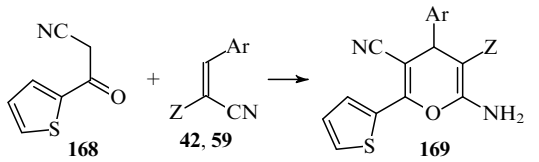
A much higher degree of asymmetric induction has been observed for the reactions of the unsaturated nitriles **42** and **59** with β-oxosulfones and sulfoxides yielding 5-R-sulfinyl- and 5-R-sulfonyl-substituted pyrans.[110] The reaction of the optically active β-oxo sulfoxide **166** with 4-chlorobenzylidenemalononitrile **42b** gives the single enantiomer **167** in 86% yield. According to X-ray diffraction analysis, the C(4) and S atoms in this compound have the (*R*,*R*) absolute configuration. In 5-sulfinyl-substituted analogues of the pyran **167**, the oxygen atoms and the proton of the RSOC(5)C(4)HAr structural fragment are always *syn*-arranged.

The researchers[110] believe that this high degree of asymmetric induction is due to the fact that the electron-withdrawing reaction centre approaches from the side opposite to the *p*-tolylsulfinyl substituent. However, thermodynamic control of the stereoselectivity in this process also cannot be ruled out.



166 **42b** **167**

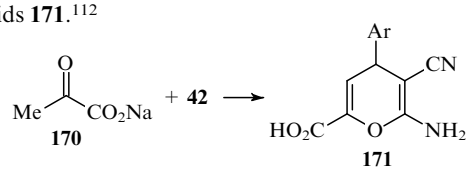
Apart from 1,3-dicarbonyl compounds, α-cyano ketones can also serve as convenient synthons for the synthesis of pyrans. The reaction of 2-thenoylacetonitrile **168** with the nitriles **42** and **59** giving rise to 5-cyanopyrans **169** provides an example.[111]



168 **42, 59** **169**

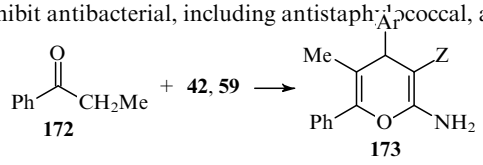
Z = CN (**42**), CO_2Et (**59**).

Sodium pyruvate **170** possesses sufficient CH acidity to be involved in the Michael reaction with the arylidenemalononitriles **42**. Refluxing in ethanol for 3 h in the presence of sodium ethoxide results in the formation of derivatives of 4*H*-pyran-2-carboxylic acids **171**.[112]



170 **171**

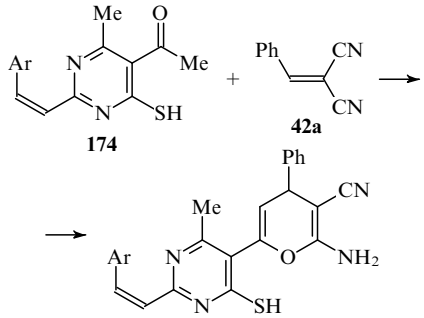
The possibility of synthesising 6-phenyl-substituted 4*H*-pyrans **173** from alkyl aryl ketones has been demonstrated by performing the reaction of the propiophenone **172** with the nitriles **42** and **59**.[113] Some of the compounds **173** have been reported to exhibit antibacterial, including antistaphylococcal, activities.[113]



172 **173**

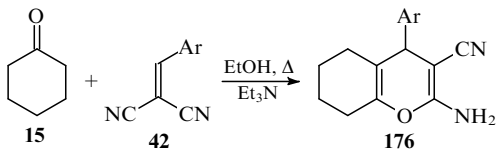
Z = CN (**42**), CO_2Et (**59**).

Acetyl derivatives of heterocyclic compounds can be involved in the Michael reaction as CH acids. A study of the reaction of 5-acetyl-substituted pyrimidines **174** with benzylidenemalononitrile **42a** has shown[114] that despite the fact that **174** are polyfunctional compounds, the reaction is highly chemoselective and results in the formation of pyrans **175** in 50%–55% yields.

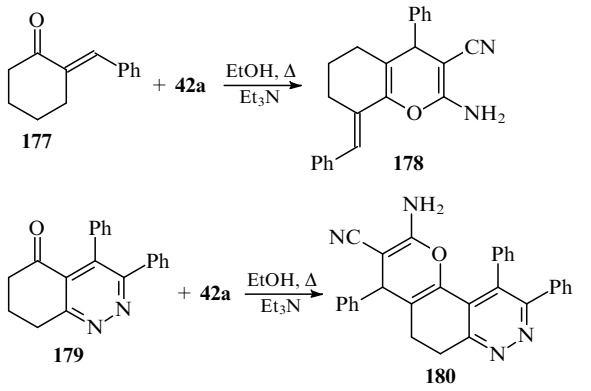


174 **42a** **175**

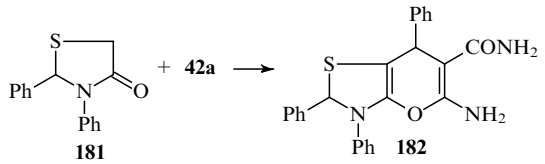
Cyclic ketones serve as the starting compounds for the preparation of fused pyrans. To obtain substituted tetrahydrobenzo[*b*]pyrans **176** from cyclohexanone and the nitriles **42**, it is sufficient to reflux the reactants in ethanol in the presence of triethylamine for 10 min.[115] 2-Benzylidenecyclohexanone **177** enters into this reaction under similar conditions to give pyrans **178**.[112] When substituted tetrahydrocinnolin-5-one **179** is made to react with benzylidenemalononitrile **42a**, polyfused pyran **180** is produced.[116]



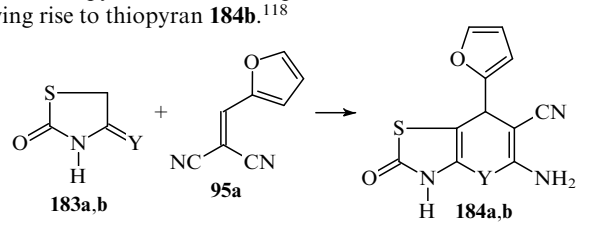
15 **42** **176**



Five-membered heterocyclic carbonyl compounds also react with unsaturated nitriles giving rise to fused 4*H*-pyrans. Thus thiazolone **181** reacts with benzylidenemalononitrile **42a** upon refluxing in ethanol for 6 h in the presence of triethylamine. It has been noted [117] that this reaction is accompanied by hydrolysis of the cyano group and affords 3-carbamoyl-substituted pyran **182**.

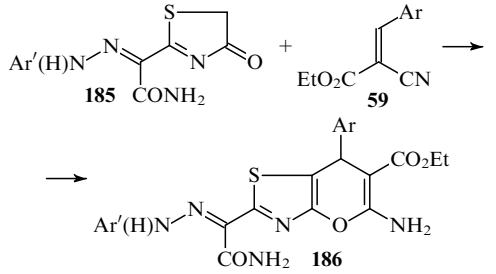


The reaction of compound **183a** with furylidenemalononitrile **95a** affords pyran **184a**.[118] Compound **183b** reacts in a similar way giving rise to thiopyran **184b**.[118]

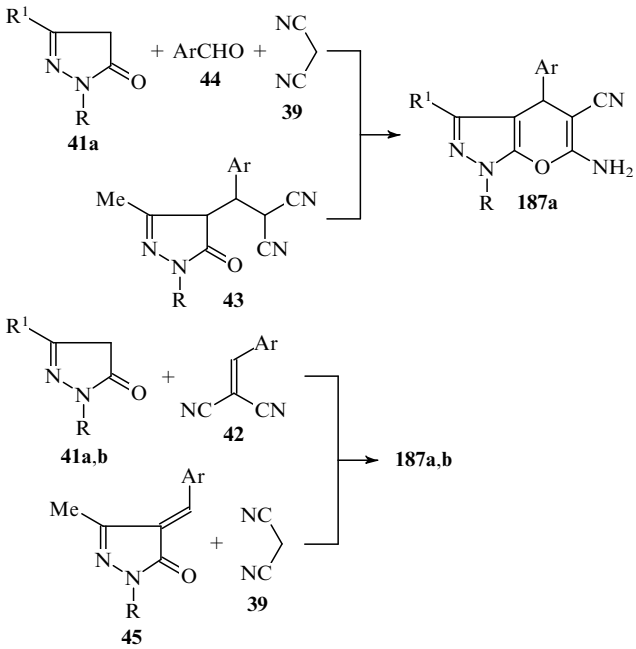


Y = O (**a**), S (**b**).

Thiazolone derivatives **185** react with ethyl arylidenecyanoacetates **59** with the formation of 2-aminopyrans **186**.[119, 120]

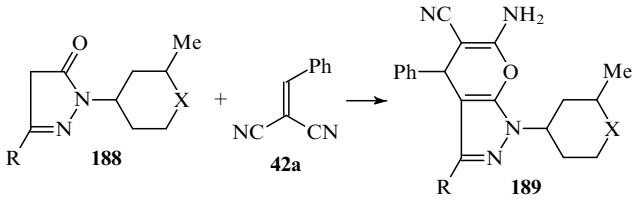


Among the reactions of carbonyl compounds with unsaturated nitriles, the transformation of 3-methylpyrazol-5-ones **41** yielding pyranopyrazoles **187** deserves special attention. The simplicity of the experiment and the high yields and the potential biological activity of the reaction products [28, 121] account for the large number of publications dealing with this topic. The synthetic capacity of the reactions of the pyrazolones **41** with arylidenemalononitrile **42** giving stable Michael adducts **43** was considered in Section III. On treatment with bases, the resulting adducts cyclise to pyrans **187**. The latter have also been isolated when the compounds **41** have been heated with **42** in the presence of morpholine.[11, 24–27] The aromatic aldehydes **44** and unsaturated ketones **45** react with malononitrile **39** or with the pyrazolones **41** under conditions described by the researchers cited above [24, 27] to give aminopyrans **187**. 3-Trifluoromethylpyrazol-5-ones react with the nitriles **42** in a similar way; on boiling in ethanol with piperidine, they are converted into 5-trifluoromethyl-substituted pyrans **187b**.[122]



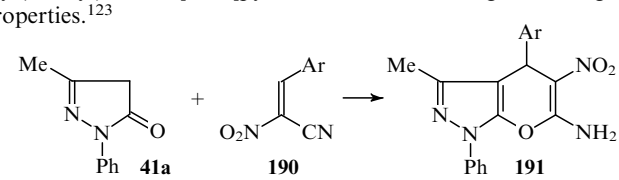
R[1] = Me (**a**), CF_3 (**b**).

The use of 1-heteryl-substituted pyrazolones **188** in the reaction with benzylidenemalononitrile **42a** permits the synthesis of 1-heterylpyrano[2,3-*c*]pyrazoles **189**, which exhibit antimutagenic activity.[28] In the absence of bases, it is possible to isolate intermediate Michael adducts of the type **43**.

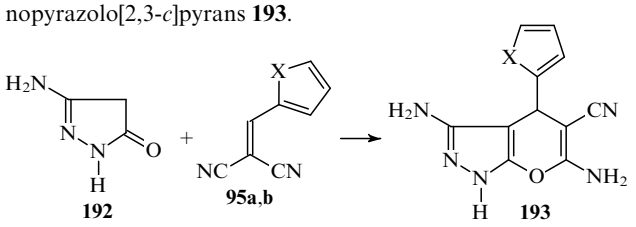


R = Me, Ph; X = O, S.

The reaction of arylidenenitroacetonitriles **190** with the pyrazolone **41a** results in the formation of difficultly accessible 4-aryl(hetaryl)-3-nitro[2,3-*c*]pyrazoles **191** exhibiting antiallergic properties.[123]

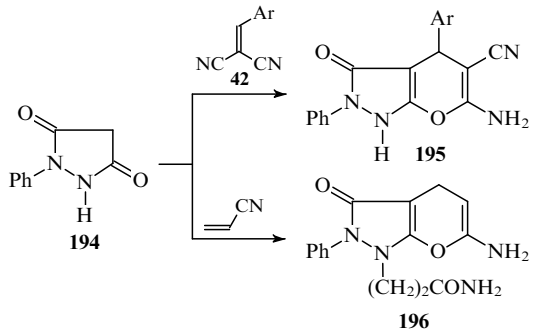


It has been reported [68] that 3-aminopyrazolone **192** reacts with 2-furyl- and 2-thienyl-substituted derivatives **95a**,**b** to give 5-aminopyrazolo[2,3-*c*]pyrans **193**.

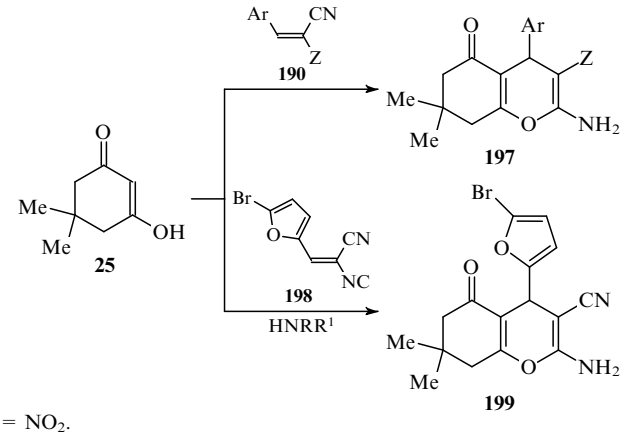


Y = O (**a**), S (**b**).

Pyrazoline-3,5-dione **194** reacts with aryl-substituted unsaturated nitriles **42** similarly to the pyrazolone **41** to yield fused 2-amino-4*H*-pyrans **195**.[68, 124] Acrylonitrile forms bis-adduct **196**.[124]

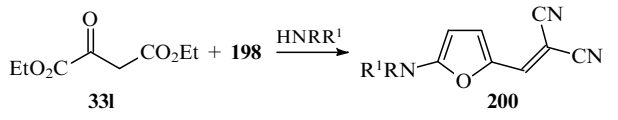


Cyclic 1,3-diketones are strong CH acids and are substantially enolysed.[125] Enolisation is important for the formation of the pyran ring,[7] and cyclic 1,3-dicarbonyl compounds are widely known as convenient reagents for the synthesis of fused 4*H*-pyrans. Thus a number of fused 4*H*-pyrans **197** containing a nitro group have been obtained by reactions of dimedone **25** with aryl (or hetaryl) derivatives of nitroacetonitrile **190**.[123, 126–128] Some of them were found to exhibit antiallergic properties.[123] When dimedone **25** reacts with 5-bromofurfurylidenemalononitrile **198** in the presence of secondary amines, substituted pyran **199** is formed in 95% yield.[97]

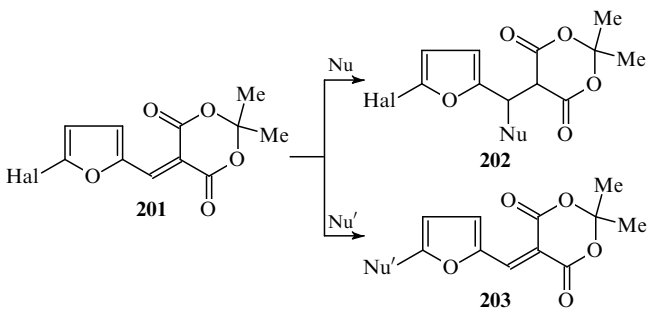


Z = NO_2.

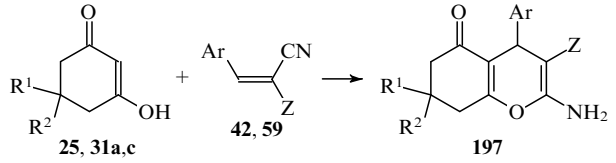
Oxalacetate **33l** does not react with the nitrile **198** under these conditions; in this case, only the bromine atom is substituted by a secondary amine residue. The rate of nucleophilic substitution in the furan nucleus in this system proves to be higher than the rate of Michael addition and, hence, the nitriles **200** are formed.



These findings are consistent with the available data on nucleophilic reactions in the series of furylidene derivatives **201**.[129] It was shown that hard nucleophiles (Nu) enter into the addition reaction to give adducts **202**. In the case of soft nucleophiles (Nu′), the halogen in the furan ring undergoes nucleophilic substitution, and this gives furylidene derivatives **203**.

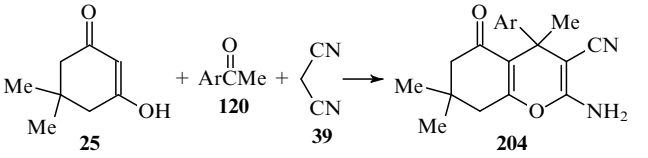


Numerous representatives of substituted tetrahydro-4*H*-benzo[*b*]pyrans **197**[11, 26, 130–132] have been prepared by interaction of 1,3-cyclohexanediones with the aryl(or hetaryl)-substituted α,β-unsaturated nitriles **42** and **59**. It was found that some compounds of the type **197** possess fungicidal activities.[130]

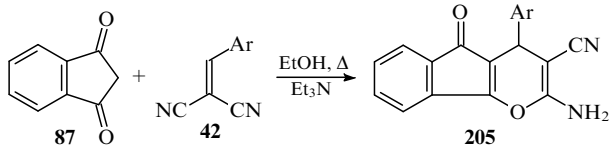


$R^1 = R^2 = Me$ (**25**); $R^1 = R^2 = H$ (**31a**); $R^1 = Ph$, $R^2 = H$ (**31c**); Z = CN (**42**), CO_2Et (**59**).

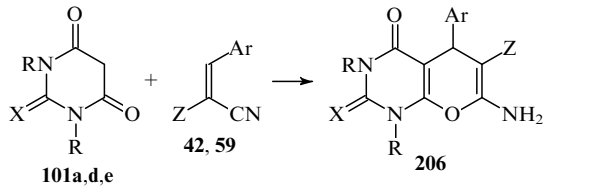
Fused pyrans of the type **197** can also be obtained by the reaction of dimedone with aromatic aldehydes and malononitrile.[133] The reaction of dimedone with the substituted acetophenones **120** and malononitrile affords 4-methyl-substituted pyrans **204**.[133]



1,3-Indanedione **87** reacts with arylidenemalononitriles **42** to give fused pyrans **205**. The reaction requires a 20-min heating in ethanol in the presence of triethylamine.[112]



It has been mentioned above that the reaction between barbituric acid and arylidenemalononitriles in boiling ethanol affords the compounds **102** resulting from elimination of malononitrile. However, at room temperature in dioxane, barbituric acid **101a** reacts with the nitriles **42** or **59** giving rise to substituted 2-aminopyrano[2,3-*d*]pyrimidines **206**.[134, 135] The compounds **206** are also formed in the reaction with 2-thiobarbituric acid **101d**[119] and 1,3-diphenyl-2-thiobarbituric acid **101e**.[136]

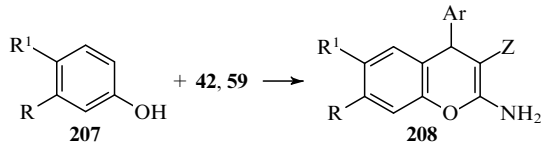


R = H: X = O (**a**), S (**d**); R = Ph, X = S (**e**); Z = CN (**42**), CO_2Et (**59**).

In this Section, we also present numerous examples of reactions of unsaturated nitriles with phenols, which can be regarded as completely enolysed ketones.[125]

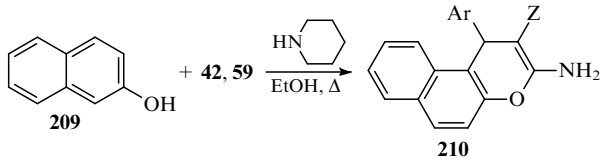
It is known that interaction of activated phenols (resorcinol, *m*-aminophenol, phloroglucinol) with α,β-unsaturated nitriles under the conditions of the Hoesch reaction[137] does not involve the cyano group. The phenols add to the double bond giving β-arylpropionitriles or products of their subsequent cyclisation ('anomalous Hoesch reaction'[138]). Thus in the presence of acid catalysts, cyanoethylation of substituted resorcinol derivatives results in the formation of 3,4-dihydrocoumarins.[138–141] Arylidene derivatives of malononitrile **42** and the cyanoacetate **59** react with phenols **207** under conditions of basic catalysis on short-term heating in ethanol. This affords substituted 4*H*-benzo[*b*]pyrans

208 in 65% – 90% yields.[142, 143] On refluxing in ethanol for 15 min in the presence of piperidine, non-substituted phenol also gives pyrans **208** (R = R′ = H).[144]



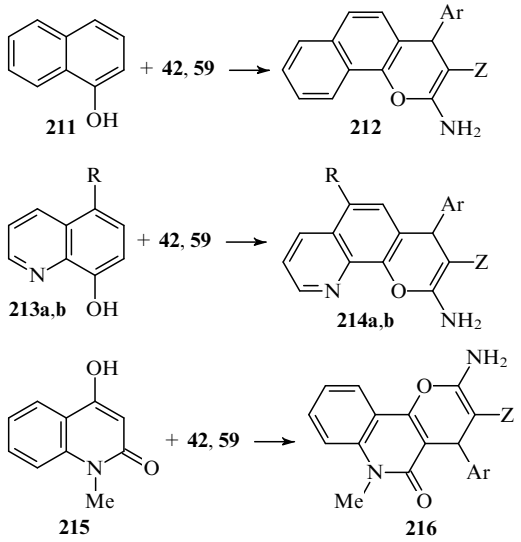
R = OH, NH_2; R^1 = H, Alk; Z = CN (**42**), CO_2Et (**59**).

Under similar conditions, 2-naphthol **209** reacts with the nitriles **42** and **59** to give substituted 4*H*-naphtho[2,1-*b*]pyrans **210**.[143, 145] In this case, the arylidenemalononitriles **42** can be replaced by a mixture of the corresponding aromatic aldehydes and malononitrile.[146]



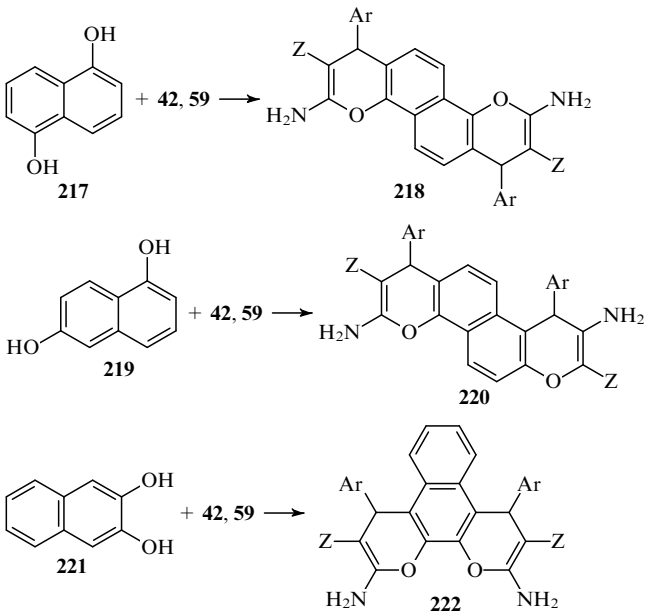
Z = CN (**42**), CO_2Et (**59**).

1-Naphthol **211** reacts with the nitriles **42** and **59** on a short-term heating in ethanol in the presence of a base giving rise to the corresponding fused pyrans **212** in 65% – 85% yields.[144, 147, 148] 8-Hydroxyquinoline **213** behaves in a similar way and upon the reaction with **42**, it is converted into pyrans **214** in yields of up to 80%.[144] When 2-aminosulfo-derivatives of 8-hydroxyquinoline **213b** are made to react with the nitriles **42** and **59**, the corresponding aminosulfonyl-derivatives **214b** are produced.[149] Under similar conditions, 4-hydroxy-1-methyl-2-quinolinone **215** reacts with the nitriles **42** and **59** affording fused pyrans **216**, their yields ranging from 80% (Z = CO_2Et) to 90% (Z = CN).[144]



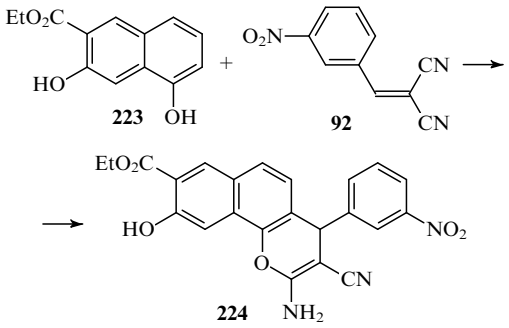
R = H (**a**), $R^1_2NSO_2$ (**b**); Z = CN (**42**), CO_2Et (**59**).

Dihydroxynaphthalenes are capable of condensing with two molecules of **42** or **59** to give naphthodipyrans. Thus 1,5-dihydroxynaphthalene **217** was converted into naphtho-[1,2-*b*:5,6-*b*′]dipyrans **218**,[147, 150] 1,6-dihydroxynaphthalene **219** into naphtho[1,2-*b*:6,5-*b*′]dipyrans **220**,[150] while 2,3-dihydroxynaphthalene **221** and the nitriles **42** and **59** form naphtho[1,2-*b*:3,4-*b*′]dipyrans **222**.[150, 151]



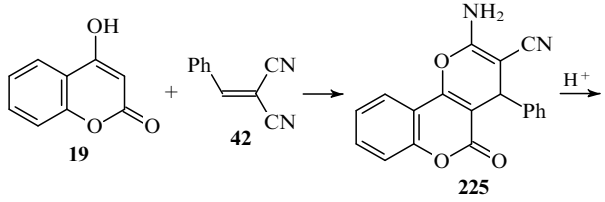
Z = CN (**42**), CO_2Et (**59**).

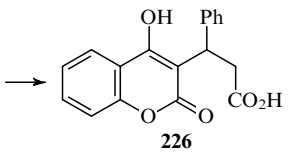
The reaction of ethyl 3,5-dihydroxynaphthalene-2-carboxylate **223** with 3-nitrophenylmethylidenemalononitrile **92** occurs selectively giving rise to naphtho[1,2-*b*]pyran **224**.[152]



Among fused pyrans — derivatives of 2-naphthol, dihydroxynaphthalenes, hydroxyquinolines, and hydroxyisoquinolines, — compounds with high antiproliferative activities have been found.[153] Some of them have been recommended for treatment of immune disorders and also for a number of diseases such as rheumatoid arthritis, atherosclerosis, cirrhosis, cancer, *etc.*[152, 153]

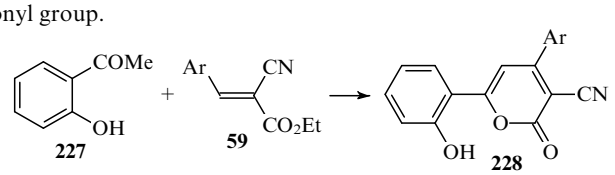
On refluxing with benzylidenemalononitrile **42a** in pyridine [154] or water,[155] 4-hydroxycoumarin **19** is converted into 4*H*-pyran **225**, which undergoes acid hydrolysis being thus converted into compound **226** serving as the intermediate in the synthesis of a rodent poison, warfarin. The pyran **225** is also formed when benzylidenemalononitrile **42a** is made to react with 4-hydroxycoumarin **19** in ethanol at room temperature in the presence of an equimolar amount of a base; Michael adducts were not isolated in this reaction.[37]





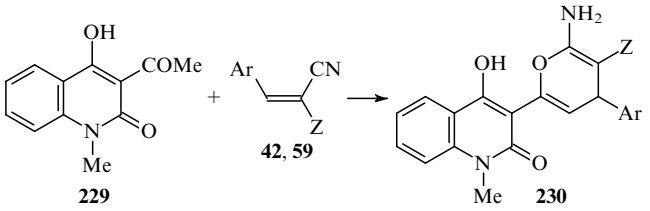
226

The reactions of *C*-acetyl-derivatives of phenols with unsaturated nitriles involve the methyl group of the acetyl fragment. For example, 2-hydroxyacetophenone **227** reacts with the nitriles **59** giving 2*H*-pyran-2-ones **228**, which result from intramolecular cyclisation of the intermediate Michael adduct at the ethoxycarbonyl group.



227 **59** **228**

To the contrary, the reaction of 3-acetyl-4-hydroxy-1-methyl-2-quinolinone **229** with the nitriles **42** and **59** yields only 2-amino-4*H*-pyrans **230**,[149] *i.e.* cyclisation involves the cyano group.

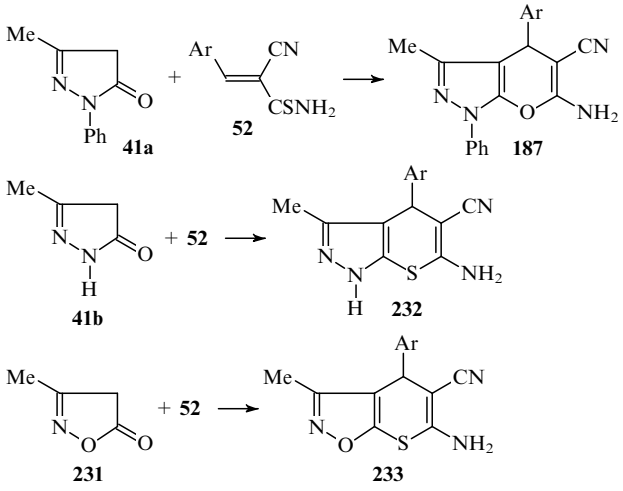


229 **42**, **59** **230**

Z = CN (**42**), CO_2Et (**59**).

The formation of the pyrans **61a**,**b** upon the reaction of 4-hydroxycoumarin with arylidenecyanoacetates **59** has been considered previously (see Section III).

Arylidenecyanothioacetamides **52** can also serve as convenient intermediates in the synthesis of 4*H*-pyrans and their derivatives. It has been reported[156] that the reaction of the phenyl-substituted pyrazolone **41a** with thioacetamides **52**, like the reaction with the nitriles **42**, affords the pyrans **187**. However, when the thioamides **52** are made to react with the pyrazolone **41b** or with isoxazolone **231**, thiapyrans **232** and **233**, respectively, are produced.

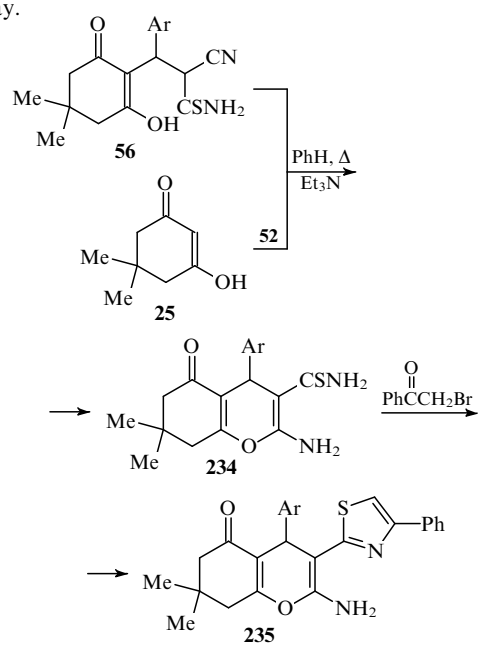


41a **52** **187**

41b **232**

231 **233**

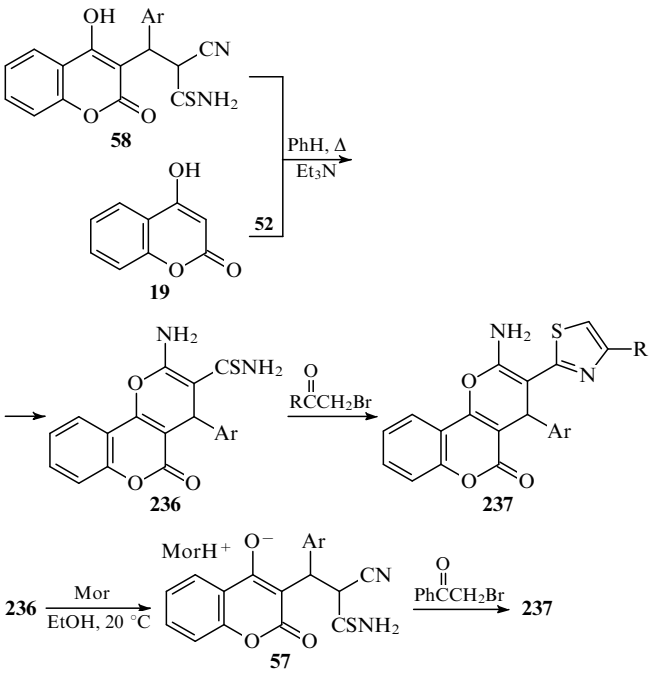
As has been noted in Section III, the interaction of cyclic 1,3-dicarbonyl compounds (dimedone, 4-hydroxycoumarin, and Meldrum's acid) with arylidenecyanothioacetamides results in the formation of Michael adducts, which can cyclise according to various pathways depending on the reaction conditions. Thus on refluxing in benzene with a catalytic quantity of triethylamine, the adducts are converted into fused 3-thiocarbamoyl-4*H*-pyrans **234**. However, reaction of the arylidenecyanothioacetamides **52** with dimedone **25** under the same conditions is a more convenient route to the pyrans **234**.[36,157] The thiocarbamoyl group in the pyrans **234** can be modified according to the Hantzsch reaction pattern on treatment with phenacyl bromide in DMF. Substituted 3-(4-phenylthiazol-2-yl)-4*H*-pyrans **235** were synthesised in this way.



56 **25** **234** **235**

Evidently, a necessary condition for the intramolecular cyclisation to occur is close arrangement of the reaction centres, the OH and CN groups. Consideration of the projections presented in Section III (**71**–**74**) shows that conditions favourable for the cyclisation to pyrans are realised in the conformation **74**. Since the yields of the pyrans **234** in this reaction reach 90%,[36] it is assumed that under these conditions, the conformers **73** undergo the reverse reaction with regeneration of the initial compounds **25** and **52**.

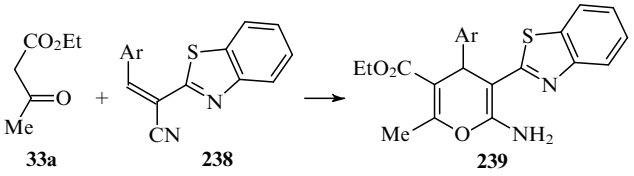
The adducts **58** prepared from 4-hydroxycoumarin cyclise to fused 2-amino-3-thiocarbamoyl-4*H*-pyrans **236** on boiling in benzene with triethylamine. Higher yields of the pyrans **236** (up to 73%) can be attained when the reactants **19** and **52** react directly with each other.[37]



58 **19** **236** **237** **57**

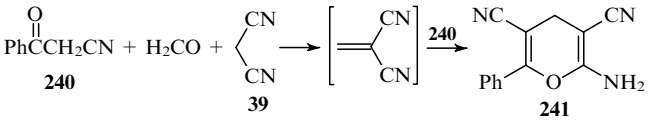
Treatment of the pyrans **236** with α-haloketones resulted in the synthesis of the corresponding 3-(4-phenylthiazol-2-yl)-4*H*-pyrans **237**.[37] The pyran ring in the compounds **236** can be cleaved by secondary amines; this gives the acyclic salts **57**, which are converted into the pyrans **237** on treatment with phenacyl bromide.[37]

Reactions of arylbenzothiazolylcyanoethylenes **238** with ethyl acetoacetate **33a** afford benzothiazolyl-substituted pyrans **239**.[158]



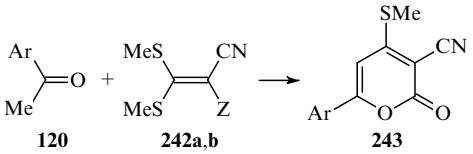
33a **238** **239**

The synthesis of pyrans based on alkylidene derivatives of malonic acids has not been adequately elaborated yet. A three-component reaction between benzoylacetonitrile **240**, formaldehyde, and malononitrile **39** in ethanol in the presence of triethylamine should be mentioned.[159] Apparently, this reaction involves intermediate formation of 1,1-dicyanoethylene, which then reacts with the ketone **240** to give pyran **241** having no substituent at the 4-position.[159]



240 **39** **241**

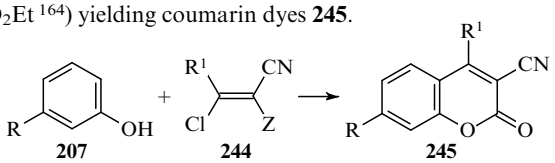
In some cases, unsaturated nitriles contain easily leaving groups such as methylthio, halo, or trichloromethyl groups. As has been noted in Section II, the products of addition of carbonyl compounds to these nitriles can eliminate a readily leaving fragment and then cyclise. Several syntheses of pyrans based on this approach have been reported. Thus the 2,2-di(methyl-thio)methylidene derivatives of malononitrile or cyanoacetate **242a**,**b** react with the acetophenones **120** with elimination of the methylthio group to give pyran-2-ones **243**.[160–162]



120 **242a**,**b** **243**

Z = CN (**a**), CO_2Et (**b**).

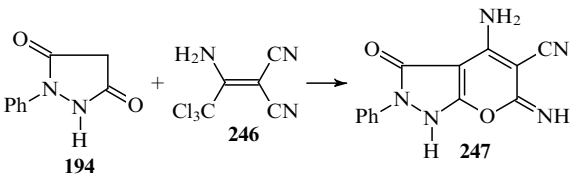
Substituted *m*-aminophenols (or resorcinol) **207** react with β-chloro-substituted unsaturated nitriles **244** (Z = CN[163] or CO_2Et[164]) yielding coumarin dyes **245**.



207 **244** **245**

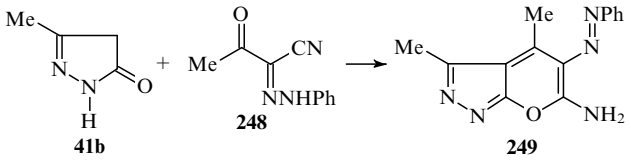
R = OH, Me_2N, Et_2N; Z = CN, CO_2Et.

The reaction of pyrazoline-3,5-dione **194** with trichloro-substituted nitrile **246** is accompanied by elimination of chloroform and gives rise to substituted 6-iminotetrahydropyrano-[2,3-*c*]pyrazole **247**.[124]



194 **246** **247**

Although the phenyl-substituted aetylacetonitrile **248** is formally also an α,β-unsaturated nitrile, it does not enter into the Michael reaction with carbonyl compounds. The addition of the pyrazolone **41b** involves the carbonyl group of **248** and results in the formation of fused 2*H*-pyrans **249**.[165]

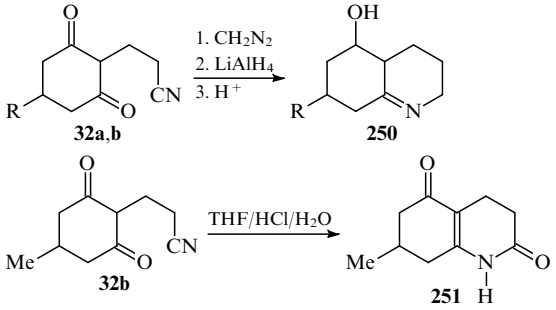


41b **248** **249**

VII. Synthesis of pyridines

The reactions of carbonyl compounds with α,β-unsaturated nitriles opens the way to the synthesis of pyridine derivatives that are difficult to obtain by other methods. It is clear that pyridines can be formed if the intermediate adducts undergo cyclisation involving a nucleophilic nitrogen atom, in particular, the nitrogen of the nitrile group. A more widely used variant is incorporation of the nitrogen atom from ammonium acetate or enamine. The method for the synthesis of pyridones and pyridinethiones with participation of amides and thioamides seems promising. The reactions resulting in the synthesis of 2-aminopyridines have been considered in detail and systematised in a monograph.[8] Published data on the synthesis of 3-cyano-2(1*H*)-pyridones, -pyridinethiones, and -pyridineselenones have been surveyed in a review.[166] In this Section, we consider the characteristic features of the preparation of pyridines based on reactions of carbonyl compounds with unsaturated nitriles.

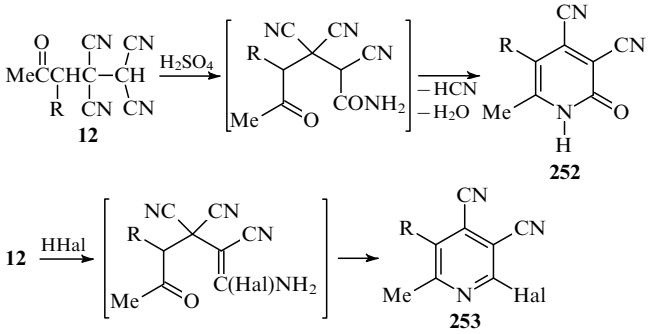
The reduction of the nitrile group in the adducts **32** by lithium aluminium hydride results in the generation of an amine and, as a consequence, in the formation of hydrogenated quinolines **250**.[19] The cyano group in the adduct **32b** is hydrolysed with subsequent cyclisation giving rise to hydrogenated quinoline **251**, which has been used as the starting compound in a 14-stage synthesis of 12-epilycopodine.[20]



32a,**b** **250** **32b** **251**

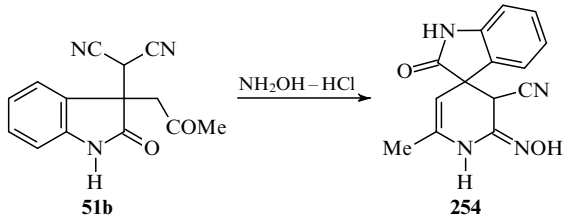
R = H (**a**), Me (**b**).

On treatment with acids, the adducts **12** cyclise to substituted 3,4-dicyano-2(1*H*)-pyridones **252**. The reaction includes hydrolysis of the cyano group followed by cyclisation of the resulting amide.[13] Treatment of the compounds **12** with hydrogen halides affords 2-halopyridines **253** according to the known mechanism of dinitrile cyclisation.[13,83]



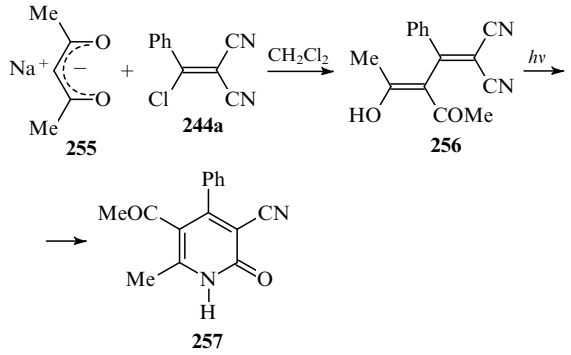
12 **252** **253**

The adduct **51b** has been converted into spiro-compound **254** upon the reaction with hydroxylamine.[30]



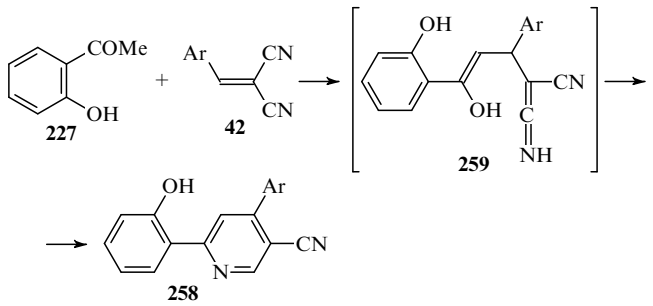
51b **254**

Sodium acetylacetonate **255** reacts with the chloro-substituted derivative of malononitrile **244a** giving rise to the *cis*-isomer of the substitution product **256**, which transforms into the *trans*-isomer on exposure to UV radiation in methanol; the latter cyclises *in situ* to 3-cyano-2(1*H*)-pyridone **257**.[167]



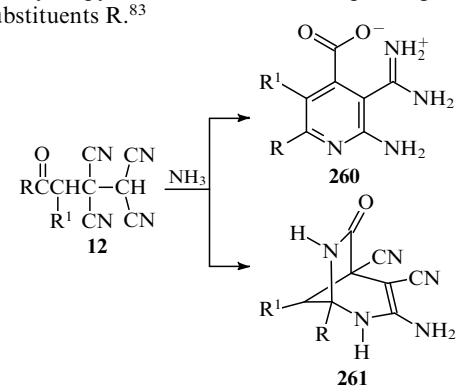
255 **244a** **256** **257**

The formation of pyridines **258** upon cyclisation of intermediates **259** resulting from interaction of 2-hydroxyacetophenone **227** with the nitriles **42** has been reported.[149]



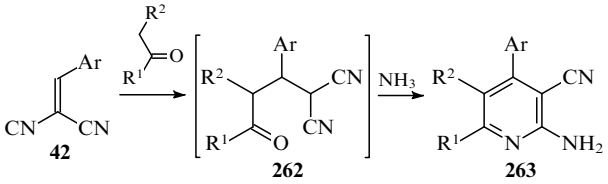
227 **42** **259** **258**

Ammonia can also be used as the source of nitrogen needed to close a pyridine ring. Thus treatment of the adducts **12** with ammonia yields either 2-aminopyridines in the betaine form **260** or bicyclic pyridine derivatives **261**, depending on the nature of the substituents R.[83]



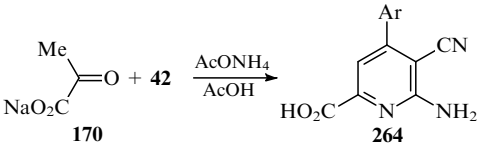
12 **260** **261**

Among the numerous methods for the synthesis of 2-aminopyridines,[8] we would like to mention interaction of the unsaturated nitriles **42** with carbonyl compounds in the presence of ammonium acetate. The aromatic aldehydes **44** and malononitrile **39** can be used instead of **42**.[168] It has been reported[169] that the interaction between these compounds yields the nitrile **42**, to which carbonyl compounds then add. Treatment of Michael adducts **262** with ammonia induces their cyclisation to pyridines **263**. Among this series of reactions, the synthesis of alkyl-substituted pyridines **263** (R^1, R^2 = H, Alk) from the nitriles **42** and aliphatic ketones has been studied.[170] Substituted acetophenones (R^1 = Ar′, R^2 = H) have also been used;[169] in this case, the reactions were conducted with heterocyclic derivatives of malononitrile such as 5-methoxy-2,3-diphenylbenzo[*b*]furan-6-ylidenemalononitrile[171] and 5-nitrobenzo[*b*]thiophen-2-ylidenemalononitrile.[172] The compounds **263** containing a bipyridine fragment (Ar = pyridyl) and possessing cardiotonic properties have been prepared from pyridinecarbaldehyde, the appropriate ketone, and ammonium acetate.[173]



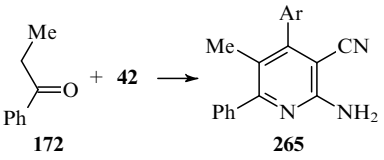
42 **262** **263**

Refluxing of sodium pyruvate **170** with the nitriles **42** and ammonium acetate in acetic acid affords derivatives of α-picolinic acid **264**.[112]



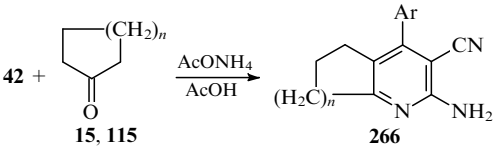
170 **264**

It has been shown for propiophenone **172** that alkyl aryl ketones react with the nitriles **42** forming either the pyrans **173** (Section VI) or 2-aminopyridines **265**. The latter are formed when the reactants are refluxed in acetic acid with ammonium acetate.[113]



172 **265**

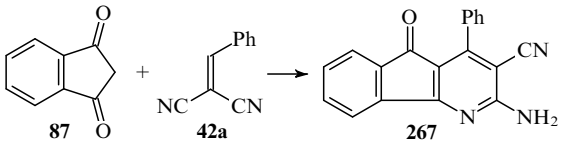
Cyclopentanone **115** and cyclohexanone **15** react with the nitriles **42** yielding the corresponding pyridines **266** (n = 1, 2).[169]



15, **115** **266**

n = 1 (**115**), 2 (**15**).

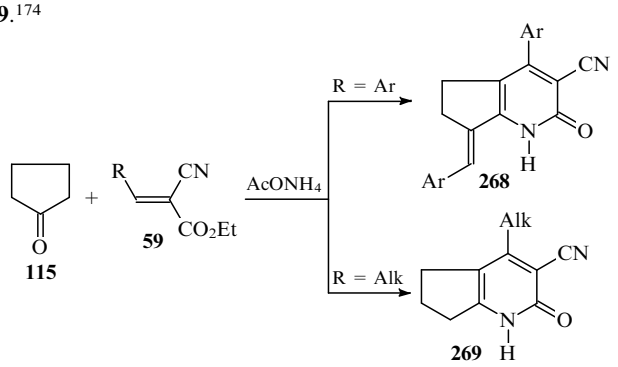
When 1,3-indanedione **87** is refluxed with benzylidenemalononitrile **42a** and ammonium acetate in acetic acid, fused 2-aminopyridines **267** are produced.[112]



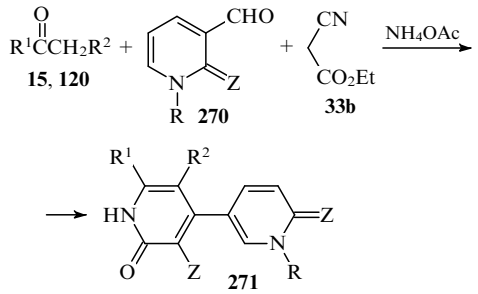
87 **42a** **267**

The introduction of aryl(alkyl)idene derivatives of ethyl cyanoacetate into reactions with carbonyl compounds and ammonium acetate makes it possible to synthesise substituted 3-cyano-2(1*H*)-pyridones. When cyclopentanone **115** reacts with

arylidene derivatives of the cyanoacetate **59** in the presence of ammonium acetate, 7-arylidene-2-pyridones **268** are formed. Evidently, in this case, a second molecule of the cyanoacetate is cleaved under the reaction conditions,[60] and the aromatic aldehyde formed *in situ* enters into the condensation. The alkyl-derivatives **59** do not undergo this cleavage and form pyridones **269**.[174]

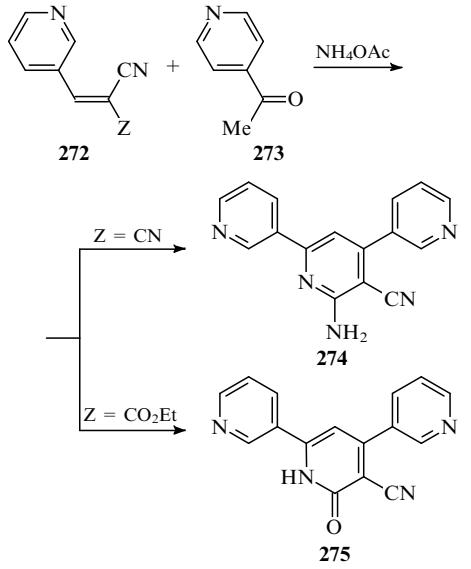


The condensation of the cyanoacetate **33b** and compounds **270** — 3-formyl-2(1*H*)-pyridones (Z = O), -pyridinethiones (Z = S), and -pyridinoselenones (Z = Se) — with cyclohexanone **15** and the substituted acetophenones **120** in the presence of ammonium acetate gives rise to bipyridine derivatives **271**.[175] Substituted 2-chloro-3-formylquinolines have also been used as the aldehyde constituent for the preparation of hetarylpyridines of the type **271**.[176]

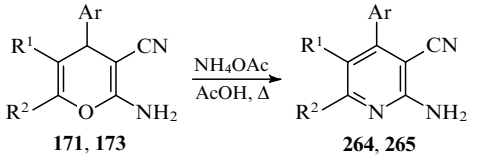


R^1 — R^2 = $(CH_2)_4$ (**15**); R^1 = Ar, R^2 = H (**120**); Z = O, S, Se.

Refluxing 3-pyridylidenemalononitrile **272** (Z = CN) or ethyl 3-pyridylidenecyanoacetate (Z = CO_2Et) with 3-acetylpyridine **273** and ammonium acetate affords derivatives of the alkaloid nicotelline **274** or **275**, respectively.[177]

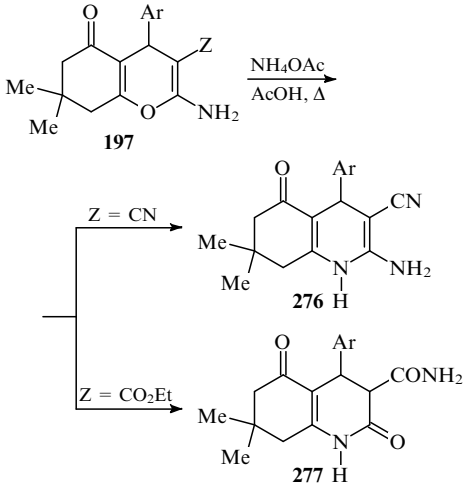


The formation of a pyran ring upon intramolecular interaction of hydroxy and cyano groups is reversible.[7] Therefore, under certain conditions, for example, under the action of nucleophiles, the pyran ring can be cleaved. Thus 2-aminopyridines **264**[112] and **265**[113] are formed when the pyrans **171** and **173** are treated with ammonium acetate in boiling acetic acid.

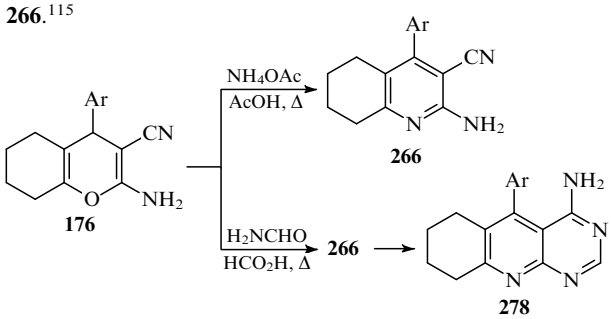


R^1 = H, R^2 = CO_2H (**171**, **264**); R^1 = Me, R^2 = Ph (**173**, **265**).

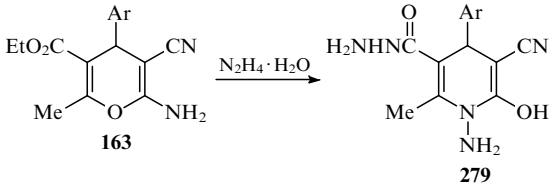
It has been reported[132] that the fused pyrans **197** (Z = CN), prepared from dimedone and arylidenemalononitriles, recyclise in a similar way giving rise to 2-amino-3-cyanohexahydroquinolines **276**. 3-Ethoxycarbonyl-substituted pyrans **197** (Z = CO_2Et) are converted under these conditions into 3-carbamoylhexahydro-2(1*H*)-quinolinone derivatives **277**.[132]



The fused pyrans **176** recyclise on treatment with ammonium acetate to give tetrahydroquinolines **266**. Formamide can also act as a nucleophile in this reaction. When **176** are heated in formamide in the presence of formic acid, pyrido[2,3-*d*]pyrimidine derivatives **278** are produced *via* the intermediate quinolines **266**.[115]

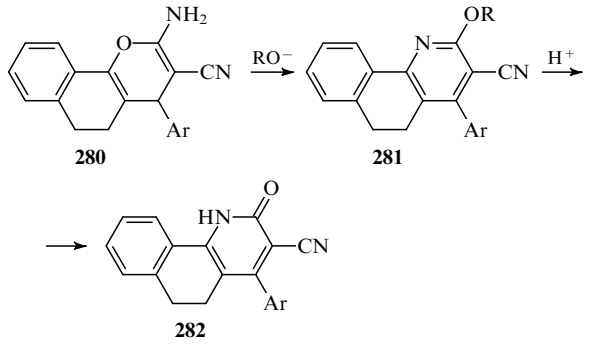


It has been noted[110] that treatment of the 5-ethoxycarbonyl-pyran derivatives **163** with hydrazine hydrate results in their recyclisation to 1-amino-1,4-dihydropyridines **279**.

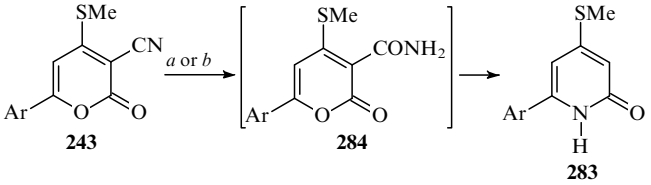


Treatment of 2-aminopyrans with nucleophilic reagents, for example, alkoxides, may lead to opening of the pyran ring followed by cyclisation to pyridine with participation of the

amino-group nitrogen. This provides a route from fused pyrans **280** to pyridine derivatives **281**,[178] which are converted into pyridones **282** in acid media.[179]

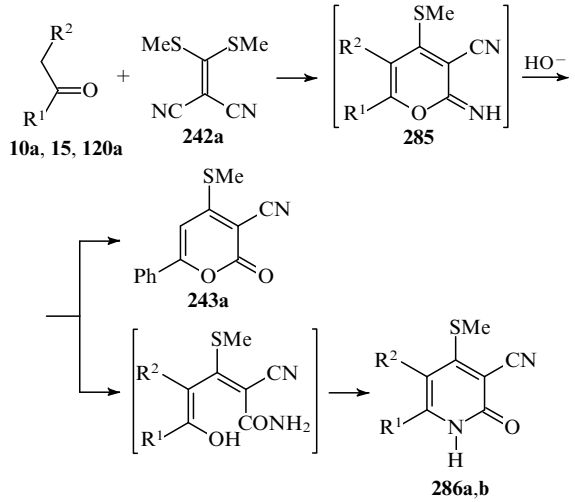


The pyrans **243** are capable of recyclising to pyridones **283** in the $CH_3COOH-HBr$ system [pathway (*a*)]. Apparently, this process begins with the hydrolysis of the cyano group to an amide group with the intermediate formation of pyran **284**. The yields of the pyridones **283** are 24% – 32%. It should be noted that the yields of the pyridones **283** in the alkaline recyclisation of compounds **284** obtained preliminarily by treating the nitrile **243** with polyphosphoric acid (PPA) [pathway (*b*)] are considerably higher (66% – 81%).[160]



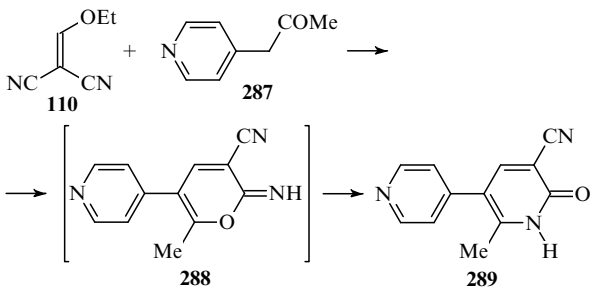
(*a*) CH_3CO_2H/HBr; (*b*) 1. PPA, 2. NaOH.

The reactions of acetone, cyclohexanone, or acetophenone with the dithioacetal **242a** involve intermediate formation of pyrans **285**.[160] However, whereas in the case of acetophenone, the imino group in the intermediate is hydrolysed, and this yields the pyran **243a**, in the case of acetone and cyclohexanone, the iminopyrans **285** undergo nucleophilic opening of the ring followed by transformation into the pyridones **286a**,**b**.

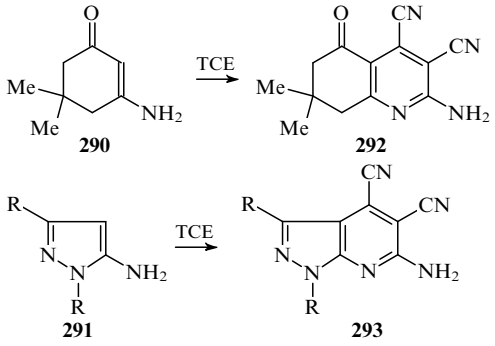


R^1 = Me, R^2 = H (**10a**, **286a**); R^1 — R^2 = $(CH_2)_4$ (**15**, **286b**); R^1 = Ph, R^2 = H (**120a**, **243a**).

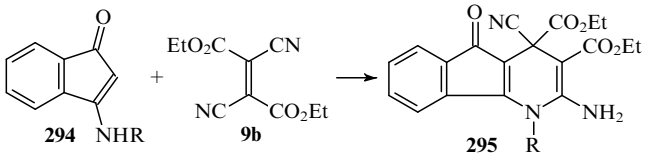
The reaction between the compounds **287** and **110** occurs in a similar way and involves the formation and recyclisation of the pyran **288**. This procedure is used to prepare the cardiotonic preparation milrinone **289**.[180]



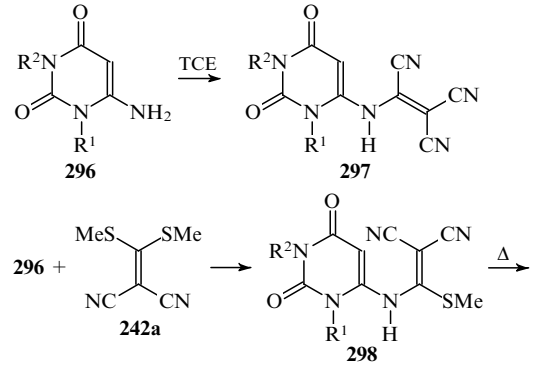
The nucleophilic nitrogen atom needed to close a pyridine ring can also be provided by enamines, prepared from mono- and dicarbonyl compounds. It is known that enamines add to an activated double bond more readily than the corresponding ketones.[181] The interaction of enamines **290** and **291** with TCE **9a** occurs as substitution of the cyano group and subsequent cyclisation of the intermediate products to fused pyridines **292**[84] and **293**.[89]

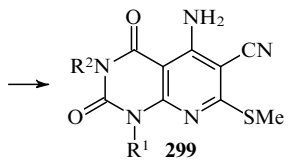


The dicyanofumarate **9b** reacts regioselectively with enamines **294**, prepared from indanethione, giving rise to *N*-substituted fused 1,4-dihydropyridines **295**.[182]



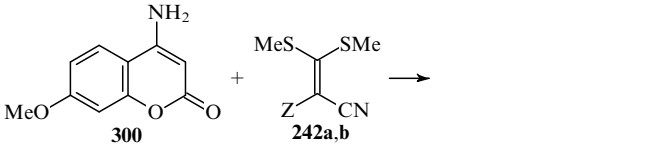
The reactions of some cyclic enamines with unsaturated nitriles containing a nucleofugal group follow a different pathway. In these cases, the activated C=C bond of the nitrile undergoes nucleophilic attack by the enamine nitrogen atom. In some cases, acyclic substitution products have been isolated. Subsequently they can cyclise forming fused pyridines. Thus aminouracils **296** react with TCE or the nitriles **242a** to give the corresponding substitution products **297**[89] and **298**.[183] On heating in diphenyl ether, the latter cyclise to pyridopyrimidines **299**.[183]



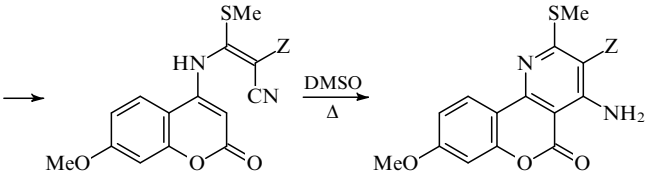


299

The reaction of 4-aminocoumarin **300** with the nitiles **242a**,**b** occurs in a similar way.[184] The cyclisation of the substitution products **301a**,**b** to fused compounds **302a**,**b** occurs upon heating in DMSO. The enamine **290** prepared from dimedone reacts with isomeric benzoylacrylonitrile **303** to give tetrahydroquinoline **304**.[185] In the case of *trans*-**303**, the reaction is conducted by refluxing in toluene, whereas for the *cis*-isomer, it is carried out in acetic acid.

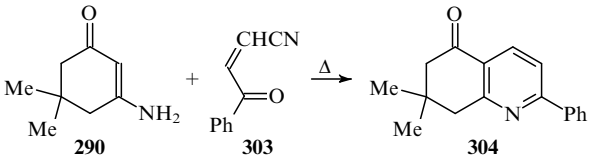


300 **242a**,**b**



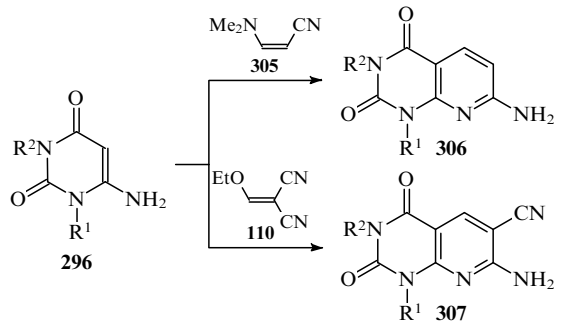
301a,**b** **302a**,**b**

Z = CN (**a**), CO_2Et (**b**).



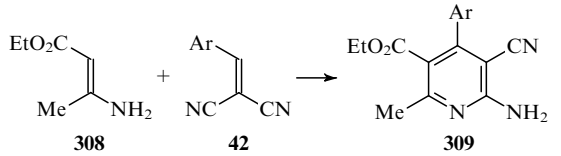
290 **303** **304**

The unsaturated nitriles **305** and **110** contain groups that can be easily replaced by nucleophiles. The reaction of these compounds with the substituted 6-aminouracil derivatives **296** occurs as the substitution of the dimethylamino or ethoxy group by the heterocycle followed by cyclisation to fused pyridines **306** [186] and **307**,[187] respectively. Compounds of the type **306** are of interest as potential dihydrofolate reductase inhibitors.[186]

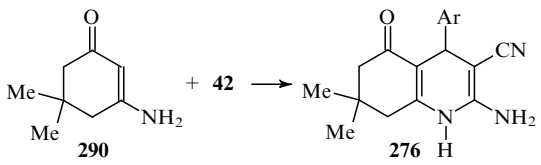


305 **296** **110** **306** **307**

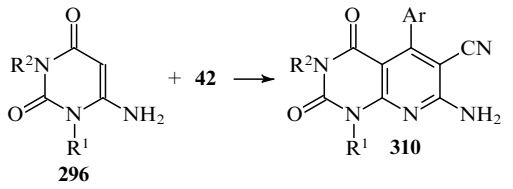
The arylidenemalononitriles **42** undergo Michael reactions with the enamines **308** and **290** derived from acetoacetate and dimedone, and also with the compounds **296**; the reaction is followed by cyclisation to pyridines **309**,[188] 1,4,5,6,7,8-hexahydroquinolines **276**,[132] and substituted pyrido[2,3-*d*]pyrimidines **310**.[189]



308 **42** **309**

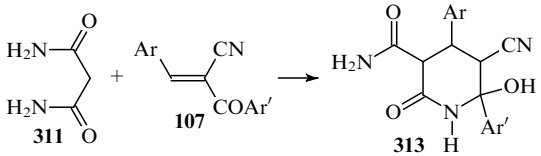


290 **276**

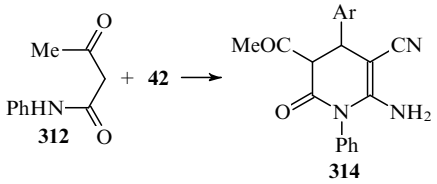


296 **310**

Methods for the synthesis of pyridines based on amines are widely used. In this case, the nitrogen atom of the amide group of one of the reactants participates in the formation of a pyridine ring. This method permits the synthesis of 2(1*H*)-pyridone derivatives. An amide group can be contained both in the carbonyl and the nitrile component. The former type of reaction is represented by the addition of malonodiamide **311** or acetoacetanilide **312** to the unsaturated nitriles **107** and **42**. The intramolecular cyclisation of the intermediate adducts affords hydrogenated pyridones **313** [190] and **314**.[191]

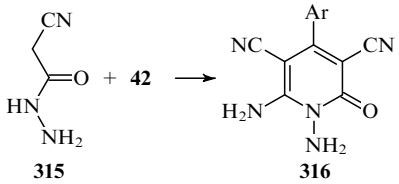


311 **107** **313**



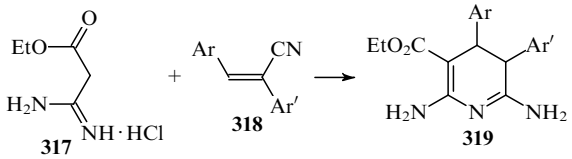
312 **314**

It has been shown [192] that the reaction of cyanoacetylhydrazine **315** with the arylidenemalononitriles **42** gives rise to 1-amino-2(1*H*)-pyridones **316**.



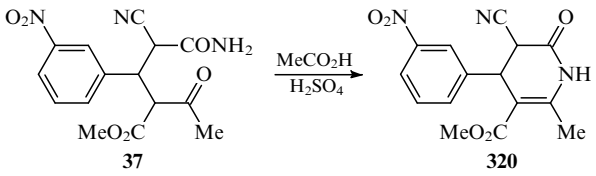
315 **316**

Amidine **317** reacts with nitriles **318** similarly to amides, giving rise to hydrogenated 2,6-diaminopyridines **319**, which possess diuretic and cardiotonic activities.[193]

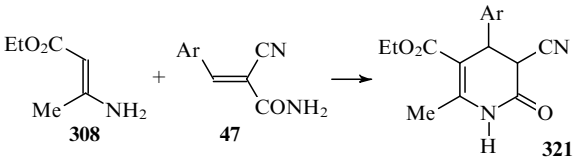


317 **318** **319**

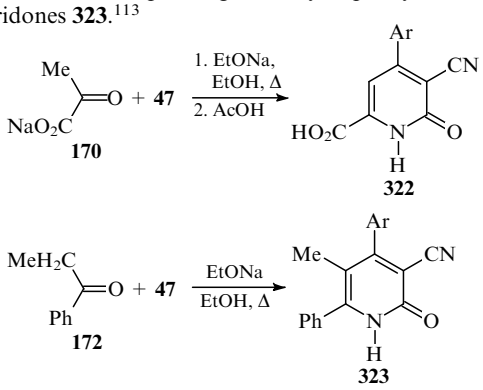
The second type of reactions proceeds in the case of unsaturated nitriles containing an amide group. It was mentioned in Section III that the addition of methyl acetoacetate **35** or oxindole **46** to arylidenecyanoacetamides yields stable Michael adducts. In some cases, they can be subsequently cyclised. Thus the adduct **37** was converted into 3,4-dihydro-2(1*H*)-pyridone **320** in 95% yield by treatment with sulfuric acid in acetic acid.[22]



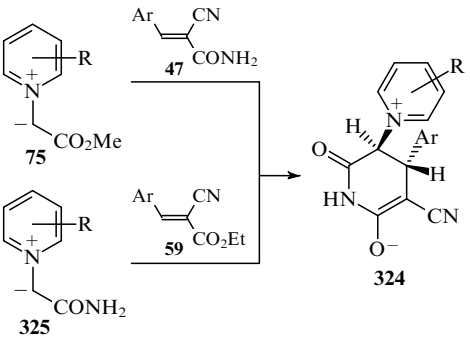
Similar *cis*-3,4-dihydro-2-pyridones **321** were synthesised by the reaction of the amides **47** with the enamine **308**.[189]



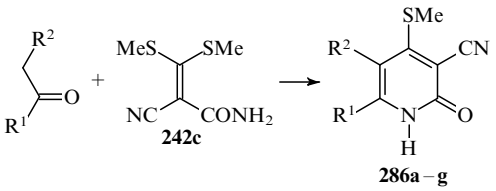
Arylidenecyanoacetamides **47** are transformed into acids **322** upon interaction with sodium pyruvate **170**. This reaction is completed when the reactants have been refluxed in ethanol in the presence of sodium ethoxide for 3 h.[112] The reaction of the amides **47** with propiophenone **172** under similar conditions affords the corresponding 5-methyl-6-phenyl-substituted 2(1*H*)-pyridones **323**.[113]



The pyridinium ylides **75** react with arylidenecyanoacetamides **47** yielding the betaine pyridiniumolates **324**.[194] The same products are formed when the arylidenecyanoacetates **59** are made to react with ylides **325** containing an amide group.[194–196] In all cases, only *trans*-isomers of the betaines **324** were isolated.



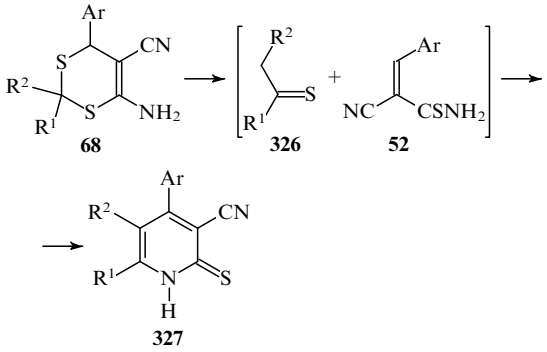
The amidonitriles **242c** react with a broad range of carbonyl and 1,3-dicarbonyl compounds in the DMSO–KOH system at room temperature. The reaction occurs as the nucleophilic vinylic substitution of the mehylthio group followed by cyclisation to 2(1*H*)-pyridones **286a–g**.[160]



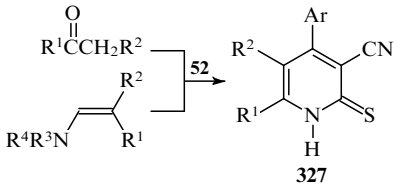
R^1 = Me, R^2 = H (**a**); R^1 — R^2 = $(CH_2)_4$ (**b**); R^1 = Ar, R^2 = H (**c**); R^1 = Ph: R^2 = Me (**d**), CO_2Et (**e**); R^1 = Me: R^2 = Ac (**f**), CO_2Et (**g**).

The reactions of arylidenecyanothioacetamides with carbonyl compounds afford the corresponding pyridine-2(1*H*)-thiones, methods for the synthesis of which (as well as their oxygen and selenium analogues) have been described in a review.[166] Here we consider the characteristic features of this reaction in more detail. The interest in this reaction was aroused after the discovery of recyclisation of 2,2-dialkyl-4-amino-6-aryl-5-cyano-1,3-dithiacyclohex-4-enes **68** to 4-aryl-3-cyano-2(1*H*)-pyridinethiones.[45, 197, 198]

Previously, it was known that 1,3-dithianes, analogous to the compounds **68**, undergo thermal decomposition giving rise to thioketones and ylidene derivatives of cyanothioacetamides.[199] In the molecules of the dithianes **68**, there occurs intramolecular conformationally rigid conjugation, as has been established by X-ray diffraction analysis for the compound with Ar = Ph, R^1–R^2 = $(CH_2)_5$.[200] Therefore, heat treatment of **68** induces cleavage of the ring at the weakest C–S bonds. The products **52** and **326** thus formed undergo the Michael reaction followed by cyclisation to give 4-aryl-3-cyano-2(1*H*)-pyridinethiones **327**.



Study of the regularities of recyclisation made it possible to offer a convenient method for the synthesis of substituted pyridinethiones **327**.[46, 200, 201] This method consists in interaction of arylidenecyanothioacetamides **52** with a broad range of carbonyl compounds such as aliphatic ketones,[35, 46, 201, 202] substituted acetophenones,[202, 203] and cyclic ketones,[35, 46, 200, 201] and also enamines. Due to the high reactivity of enamines, it is better to use them in this reaction.

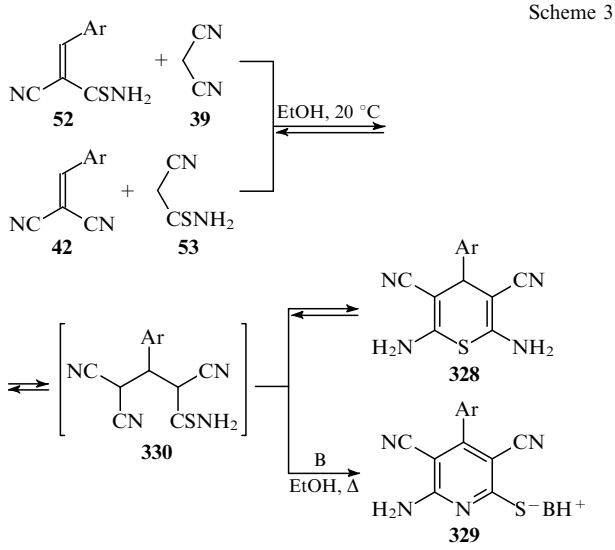


Later, the pyridinethiones **327** were also obtained by the reaction of the arylidene derivatives **52** with acetone and acetophenone on refluxing in ethanol.[204] The fused pyridinethiones **327** in which R^1–R^2 are polymethylene chains were prepared by the reaction of arylmethylenecyanothioacetamides **52** with cyclic ketones in boiling dioxane.[205–207] In addition, the interaction of the 2-thienyl- and 2-furyl-derivatives **52** with cyclic ketones resulted in the synthesis of 4-hetaryl-substituted fused pyridinethiones of the type **327**.[208]

Arylidenecyanothioacetamides **52** react with malononitrile **39** to give 6-amino-4-aryl-3,5-dicyano-4*H*-thiopyrans **328** (Scheme 3). The same compounds can be prepared by coupling of arylidenemalononitriles **42** with cyanothioacetamide **53**.[209] This reaction is reversible, the thiopyrans **328** being formed at room temperature.

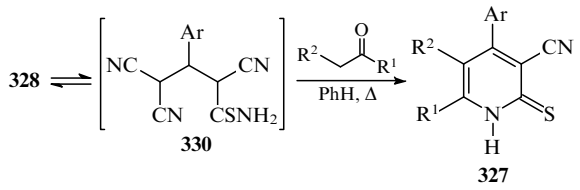
When the compounds **328** are refluxed in ethanol in the presence of bases, they recyclise to give pyridinethiolates **329**.[209, 210] The same products **329** are also formed when the initial reactants **42** and **53** or **52** and **39** are refluxed in ethanol in the presence of bases. Presumably the intermediate Michael

Scheme 3



adduct **330** cyclises under mild conditions to the thiopyran **328**, while in the presence of bases, intermolecular interaction of thioamide and nitrile groups occurs, resulting in irreversible formation of pyridinethiolates **329** (see Scheme 3). A similar recyclisation has been found for selenium analogues of **328** and **329**.[211–213]

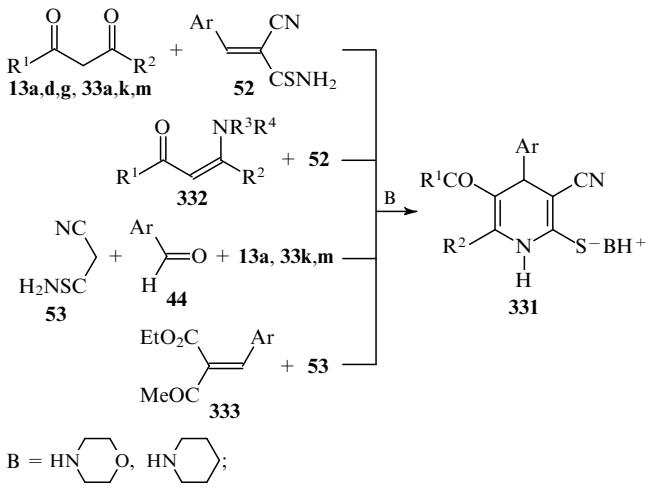
Refluxing the thiapyrans **328** in benzene with various ketones (acetone, acetophenone, cyclohexanone, cyclopentanone) affords the pyridinethiones **327** in 64%–85% yields.[214] Apparently, since both the thiopyrans **328** and the intermediate Michael adducts **330** are thermodynamically unstable, under the reaction conditions, the ring in the thiopyrans **328** is cleaved and the adduct **330** undergoes reversible decomposition to give the initial compounds **52** and **39**. When a carbonyl compound is added, its addition to the nitrile **52** becomes the predominant process, because it results in the irreversible formation of the pyridinethione **327**, which is assumed[214] to be thermodynamically the most stable compound in this system.



The overall process can be represented as exchange by the methylene components with elimination of malononitrile and incorporation of the ketone carbon skeleton in its place.[214] Thus, the interaction of ketones with the thiopyrans **328** occurs similarly to their interaction with arylidenecyanothioacetamides **52**.

The reaction of arylidenecyanothioacetamides **52** with acyclic 1,3-dicarbonyl compounds such as acetylacetone **13a**[202,215,216] or ethyl acetoacetate **33a**[202,217,218] follows a somewhat different pathway. The electron-withdrawing carbonyl group at the 5-position stabilises the intermediate dihydropyridine owing to conjugation with the π-system of the pyridine ring.[219] In the presence of organic bases, such as piperidine, morpholine, *etc.*, substituted 3-cyano-1,4-dihydropyridine-2-thiolates **331** have been obtained. The same products are formed when the corresponding enamines **332** are introduced in the reactions with the nitriles **52**[202,215,217,220] and also in the multicomponent condensation of ther aromatic aldehydes **44**, cyanothioacetamide **53**, and a dicarbonyl compound in the presence of excess piperidine (Scheme 4).[221–223]

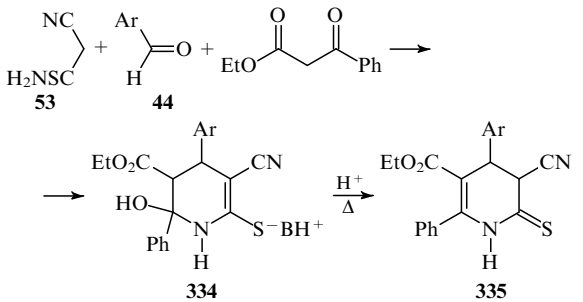
Scheme 4



The pyridinethiolates **331** have also been obtained by reactions of unsaturated dicarbonyl compounds **333** and cyanothioacetamide **53**.[217,224]

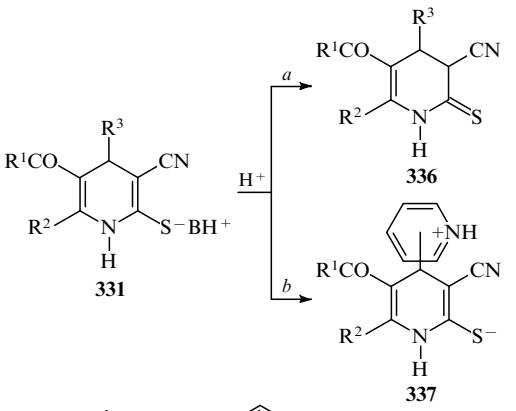
In the case of non-symmetrical dicarbonyl compounds such as benzoylacetone **13d** or 3-benzoyl-1,1,1-trifluoroacetone **13g**, the reaction occurs regioselectively and gives benzoylated pyridinethiolates **331** (R^1 = Ph).[218] The enamines **332** derived from non-symmetrical diketones **13d**,**g** react in a similar way.[218] 2-Furylidene-[218] and 3- and 4-pyridylidenecyanothioacetamides[35,218,225] as well as mixtures of the corresponding aldehydes **44** and the thioamide **53**[35,218] also react with the dicarbonyl compounds **13a** and **33k**,**m** to give the corresponding derivatives of 4-hetaryl-1,4-dihydropyridine-2-thiolates **331** (see Scheme 4).

When the aryl substituent contains an electron-withdrawing substituent[222] or when the reaction is carried out with ethyl benzoylacetate,[223] it is possible to isolate 6-hydroxy-substituted pyridinethiolates **334**, which are dehydrated on heating in an acid medium giving rise to compounds **335**.[222,223]



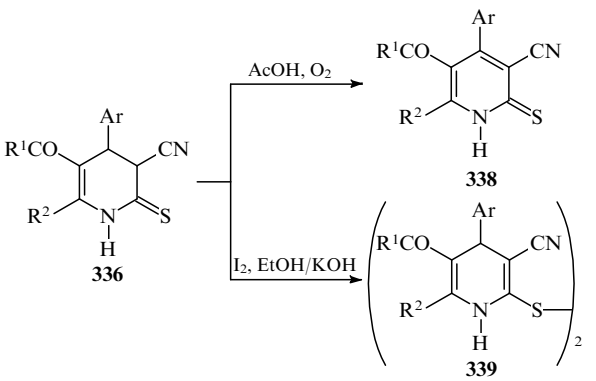
The structure of the pyridinethiolates **331** was studied by X-ray diffraction analysis.[226] The dihydropyridine ring in morpholinium 5-acetyl-3-cyano-6-methyl-4-(2-nitrophenyl)-1,4-dihydro-2-pyridinethiolate was found to exist in a flattened-boat conformation. The negative charge is mostly localised on the sulfur atom. The latter accounts for the high regioselectivity of alkylation reactions of the thiolates **331**. They react with haloalkanes or dimethyl sulfate exclusively at the sulfur atom yielding the corresponding 2-alkylthio-derivatives.[35,202,218,223,225,227,228]

Protonation of 4-aryl(furyl)-substituted derivatives **331** affords 3,4-dihydro-2(1*H*)-pyridinethiones **336**.[202,215–218,220–223,228] Upon acidification, the 4-(3- and 4-pyridyl)pyridine-thiolates **331** are converted into the corresponding betaines **337**.[35,218,225,227]

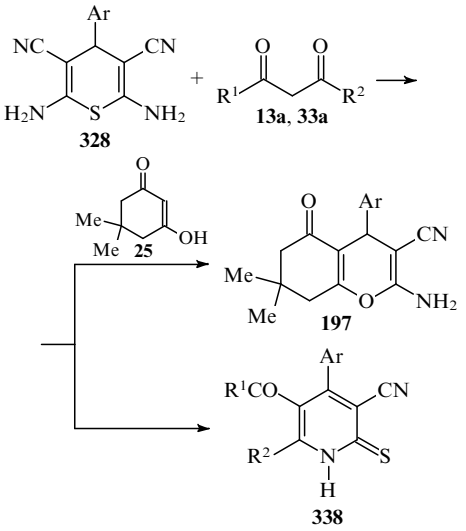


(*a*) R^3 = Ar, O; (*b*) R^2 = N.

Since 3,4-dihydropyridines are markedly less stable than their 1,4-dihydro-analogues,[219] it should be expected that they would be readily dehydrogenated. In fact, on storing at room temperature or on heating in ethanol or acetic acid, the thiones **336** are dehydrogenated to give pyridinethiones **338**, disulfides of 1,4-dihydropyridine-2-thiols **339**, or mixtures of these products, depending on the reaction conditions and the structures of the initial compounds.[35, 202, 215, 217, 218, 223]

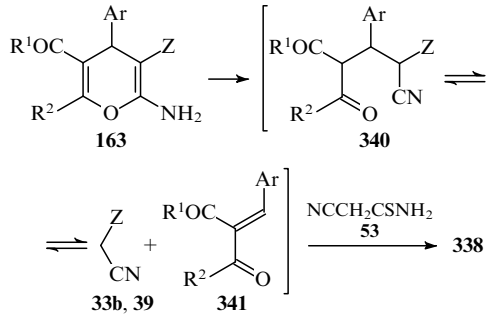


The pyridinethiones **338** were synthesised by interaction of the thiopyrans **328** with the acyclic dicarbonyl compounds **13a** and **33a**.[214] The addition of dimedone **25** to the system causes exchange by methylene components accompanied by elimination of cyanothioacetamide, which results in the formation of the fused pyrans **197**.[214]



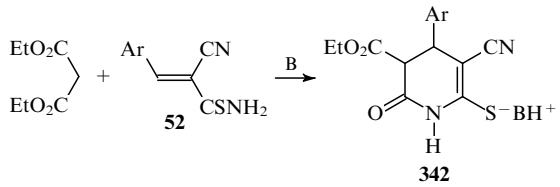
R^1 = R^2 = Me (**13a**); R^1 = OEt, R^2 = Me (**33a**); Z = CN (**39**), CO_2Et (**33b**).

The non-fused 4-hetaryl-substituted pyrans **163** recyclise on treatment with cyanothioacetamide to give the pyridines **338**.[99] The formation of a pyran ring is reversible; this ring can open on treatment with nucleophiles. The acyclic intermediate **340** thus formed undergoes retro-decomposition [10, 60] to the initial components **33b** (or **39**) and **341**. The addition of cyanothioacetamide **53**, introduced in the reaction medium, to unsaturated ketone **341** shifts the equilibrium towards the stable thione **338**. Synthesis of the pyridines **338** by direct interaction of arylidenecyanothioacetamides **52** with the dicarbonyl compounds **13a** and **33a** has been reported.[229] The reaction requires refluxing in ethanol for 3 h in the presence of a catalytic amount of piperidine.



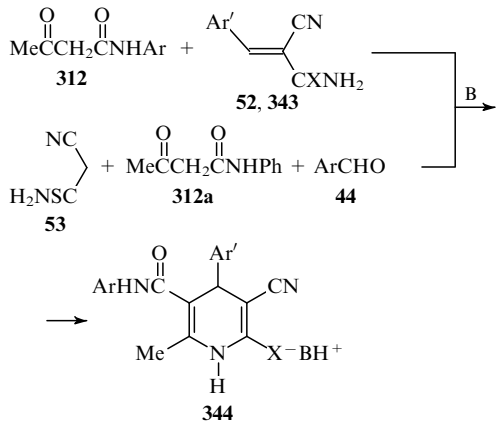
R^1 = R^2 = Me (**13a**); R^1 = OEt, R^2 = Me (**33a**); Z = CN (**39**), CO_2Et (**33b**).

The reaction of ethyl malonate with *ortho*-substituted arylidenecyanothioacetamides results in the corresponding 2(1*H*)-oxo-3,4-dihydropyridine-6-thiolates **342**.[230]



Ar = 2-ClC_6H_4, 2-IC_6H_4, 2-$NO_2C_6H_4$; B = O N–Me.

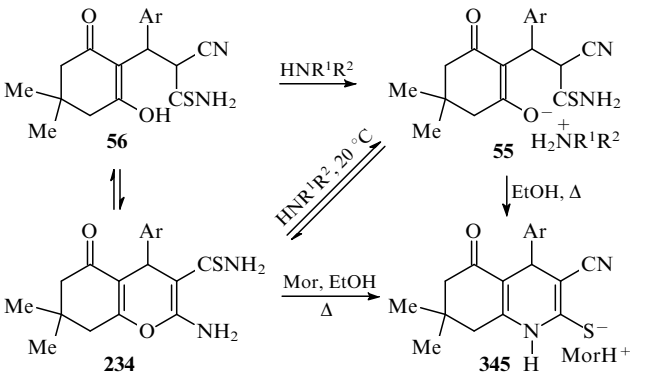
Acetoacetanilides **312** react with the aryl(hetaryl)idenecyanothioacetamides **52** or with arylidenecyanoselenoacetamides **343**, synthesised recently, to give the corresponding 1,4-dihydropyridine-2-thiolates and -selenolates **344**.[231] A method for preparing the thiolates **344** (X = S) from the aldehydes **44**, cyanothioacetamide **53**, and *N*-acetoacetylaniline **312a** has been developed.[232]



X = S (**52**), Se (**343**).

The Michael adducts **56**, derived from dimedone and arylidenecyanothioacetamides, or their salts can cyclise to either the pyran derivatives **234** (see Section III) or substituted quinolines

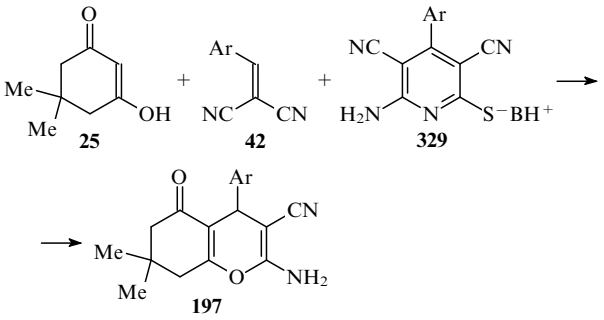
Scheme 5



345, depending on the reaction conditions.[36, 158] The interconversion of the adducts **56**, the salts **55**, and the pyran derivatives **234** are presented in Scheme 5. The Michael adduct salts **55**, produced from arylidenethioacetamides and cyclic 1,3-dicarbonyl compounds in ethanol at room temperature, cyclise on heating giving rise to quinolinethiolates **345**. Refluxing of the adducts **56** in benzene gives rise to the 3-thiocarbamoyl-4*H*-pyrans **234**, which are also converted into the quinolinethiolates **345** on treatment with morpholine followed by refluxing of the reaction mixture. However, if the pyrans **234** are treated with secondary amines at room temperature, it is possible to isolate the intermediates **55**.[36, 157, 158] Thus, recyclisation of the pyrans **234** to quinoline-2-thiolates **345** occurs *via* a stage of formation of the acyclic salts **55**, the formation of the pyrans **234** from the compounds **56** being a reversible process.

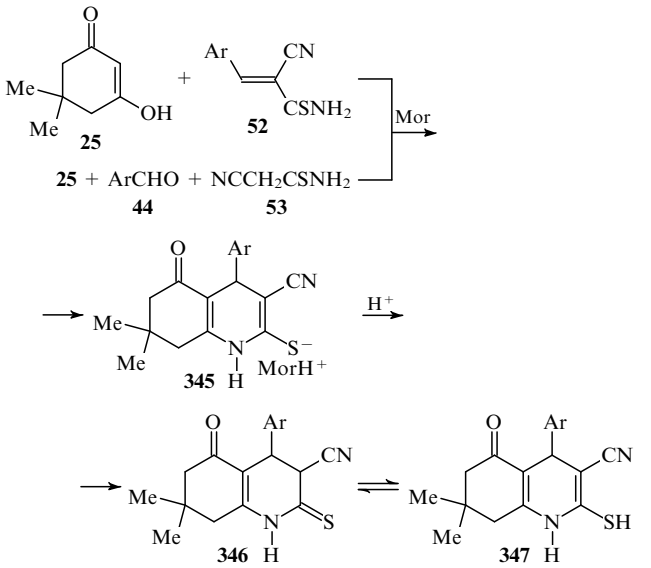
The interaction of the compounds **56** with morpholine in ethanol followed by refluxing of the salts **55** formed *in situ* was also found to yield quinolinethiolates **345**.[34, 36, 158] The cyclisation to the quinolines **345** should be realised for the *threo*-isomers of the intermediates **55** represented by the projection **73** (Section III).

Yet another recyclisation route of 3-thiocarbamoyl-4*H*-pyrans **234** is their transformation into 3-cyano-4*H*-pyrans **197** on refluxing in benzene in the presence of malononitrile and triethylamine.[158] The compounds **197** are also formed when dimedone **25** reacts with arylidenemalononitriles **42**[131] or the thiopyrans **329**.[214]



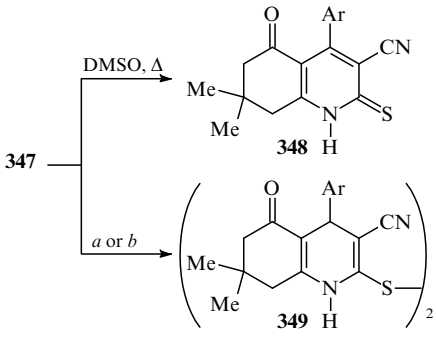
As was shown in Section VI, opening of the 4*H*-pyran ring under the action of secondary amines is also typical of analogous 4-hydroxycoumarin derivatives **236** and thus, it is a common feature of 3-thiocarbamoyl-derivatives of pyrans.

Convenient preparative methods for the synthesis of the quinolinethiolates **345** have been developed consisting of the interaction of dimedone **25** with arylidenethioacetamides **52** or directly with the aromatic aldehydes **44** and cyanothioacetamide **53**.[233] On treatment with acids, the thiolates **345** are converted into compounds existing as thiones **346** in the solid state and entirely passing into the tautomeric thiol form **347** in solution (DMSO, trifluoroacetic acid, or acetone).[36, 233]



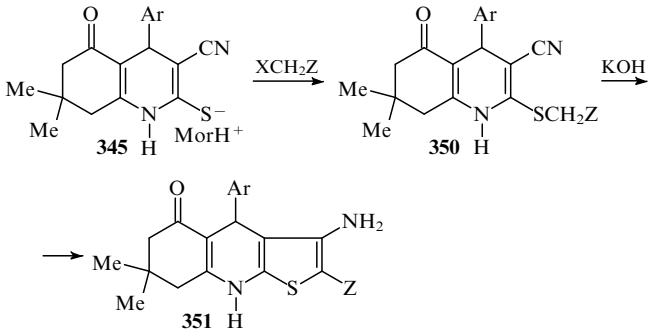
It should be noted that all the thiols **347** formed exist as mixtures of two stereoisomers, although the initial thiolates **345** contain only one isomer.

The quinolinethiones **346** are more stable to dehydrogenation than their non-fused analogues **335**. The regioselective dehydrogenation of the compounds **346** and **347** to give 3,4-dehydro-derivatives **348** was accomplished by heating them in DMSO at 80–100 °C.[233] Oxidation of **346** and **347** by atmospheric oxygen or by nitrobenzene results in the formation of a mixture of dehydrogenated quinolinethiones **348** and disulfides **349**. The latter have been obtained in preparative yields by treating the compounds **347** by iodine in an alkaline alcoholic solution.[233]



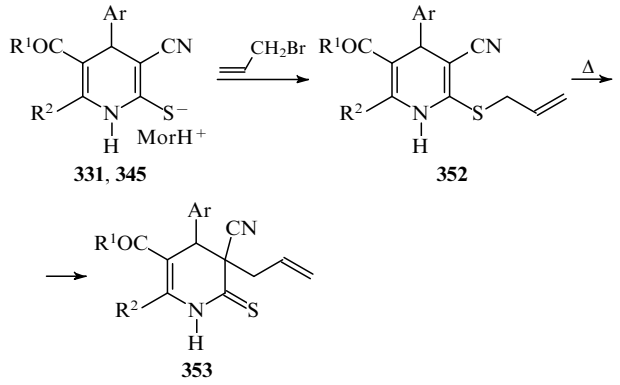
(*a*) I_2, KOH, EtOH; (*b*) O_2, $PhNO_2$.

The interaction of quinolinethiolates **345** with alkyl halides occurs regioselectively giving 2-alkylthio-derivatives of quinolines **350**; when these products contain electron-withdrawing substituents, they cyclise in the presence of excess base to 4,5,6,7,8,9-hexahydrothieno[2,3-*b*]quinolines **351**.[34, 35, 158, 234]



X = Cl, Br; Z = COPh, CN, CO_2Et.

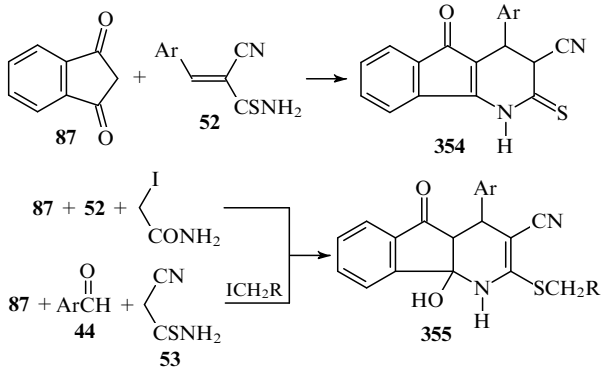
The reactions of 1,4-dihydropyridine-2-thiolates **331** and hexahydroquinolinethiolates **345** with allyl bromide involve the sulfur atom, like reactions with other alkyl halides. However, the 2-allylthio-1,4-dihydropyridine derivatives **352** thus formed undergo regioselective [3 + 3]-sigmatropic rearrangement on heating without a solvent or in a DMSO or ethanol solution giving rise to substituted 3-allyl-3-cyano-1,2,3,4-tetrahydropyridine-2-thiones **353** in high yields.[235]



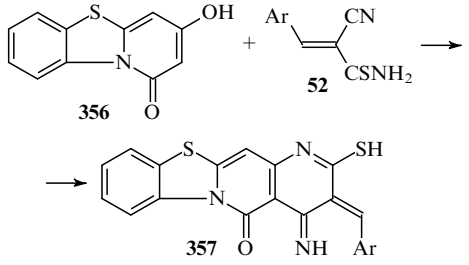
R^1 = Me, EtO; R^2 = Me (**337**); $R^1 - R^2 = CH_2C(Me)_2CH_2$ (**345**).

The structures of the initial compounds and the products were studied and proved by IR and ^1H and ^{13}C NMR spectroscopy [236, 237] and also by X-ray diffraction analysis.[238] A thermal rearrangement of this type is also typical of substituted 2-allylseleno-3-cyano-1,4-dihydropyridines;[237, 238] apparently this is a common property of compounds of the 2-allylthio(seleno)-1,4-dihydropyridine series.

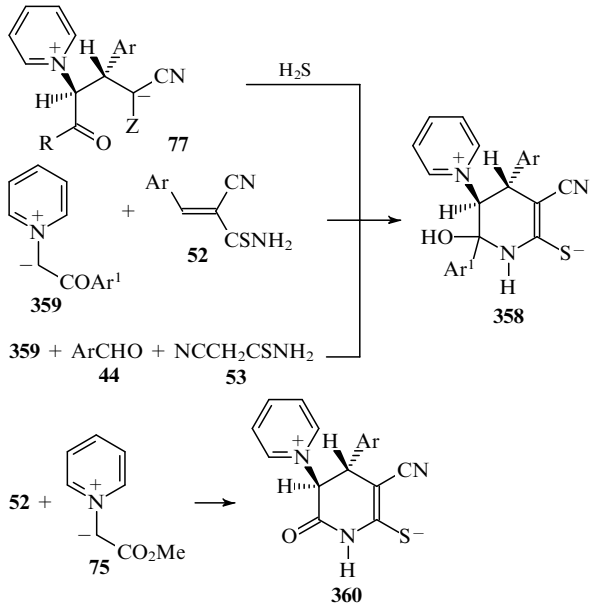
The reactions of arylidenecyanothioacetamides **52** with cyclic 1,3-dicarbonyl compounds have also been studied in relation to indane-1,3-dione **87**. It was found that this reaction affords fused 3,4-dihydropyridine-2-thiones **354**.[239] Three-component condensation of cyanothioacetamide **53**, the aldehydes **44**, and the indanedione **87** and the subsequent treatment with iodoalkanes give rise to fused 2-alkylthio-9*b*-hydroxy-1,4-dihydroindano-[1,2-*b*]pyridines **355**.[239, 240] Similar products are formed from the compounds **52** and **87** in the presence of iodoacetamide.[239]



Pyridobenzothiazole **356** reacts with the arylidenecyanothioacetamides **52** on refluxing in ethanol or pyridine. The structure **357** has been assigned to the reaction product.[241]

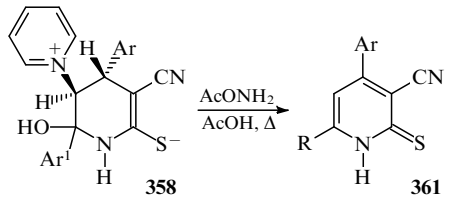


As has been mentioned in Section III, pyridinium ylides react with unsaturated nitriles giving the betaines **77**, which cyclise on treatment with hydrogen sulfide to the corresponding pyridinethiolates **358** with retention of the *trans*-pseudoaxial arrangement of the C(3)H and C(4)H protons.[54] The same thiolates have been obtained by reaction of pyridinium ylides **359** with arylidenecyanothioacetamides **52** or by a three-component reaction of the ylides **359** with the aldehydes 44 and the thioamide **53**.[54, 242] The ylide **75** and the compounds **52** form betaines **360**.[194, 196]



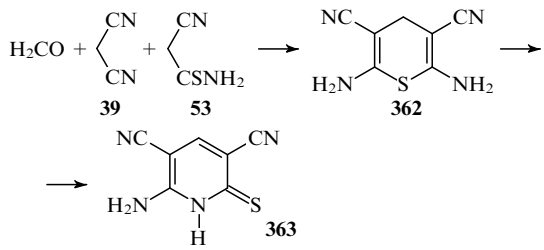
Some stereochemical aspects of the synthesis of pyridine betaines have been surveyed in a review;[9] the atropo- and the stereo-selectivity of formation of these compounds have been discussed.[243] Nucleophilic reactions of pyridinium ylides have been considered in greater detail in another review.[56]

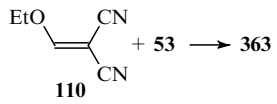
On heating in acetic acid with ammonium acetate, all the hydrogenated pyridinethiolates **358** eliminate pyridine yielding the corresponding pyridinethiones **361**.[54, 242, 244, 245]



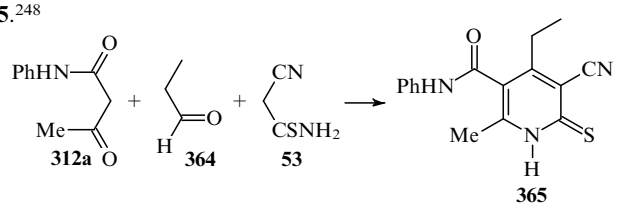
Based on the interaction of the pyridinium ylide **359** (Ar′ = 3-pyridyl) with 3-pyridylmethylenecyanothioacetamide, a method for the synthesis of the tobacco alkaloid nicotelline and its analogues has been developed.[246]

Pyridinethiones having no substituents at the 4-position can be synthesised using reactions with formaldehyde. Thus three-component condensation of formaldehyde, malononitrile **39**, and cyanothioacetamide **53** gives [159] 2(1*H*)-pyridinethione **363**, which is produced *via* a stage of recyclisation of 4*H*-thiopyran **362**. The compound **363** has been obtained previously as the product of interaction of cyanothioacetamide **53** with ethoxymethylidenemalononitrile **110**.[247]

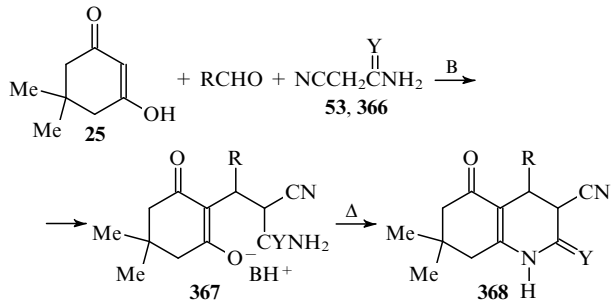




Three-component condensation of aliphatic aldehydes with carbonyl compounds and cyanothio(seleno)acetamides opened up way to 4-alkyl-substituted 2(1*H*)-pyridinethions and -selenones, which had been difficult to synthesise before. The reaction of the anilide of acetoacetic acid **312a** with propionaldehyde **364** and cyanothioacetamide **53** yields 4-ethyl-substituted pyridine **365**.[248]

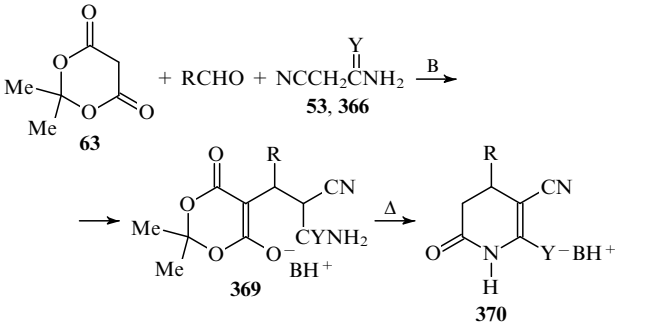


Dimedone **25** reacts with aliphatic aldehydes and the cyanoamides **53** or **366** to give compounds **367** similar to the aryl derivatives **55** described previously. The compounds **367** can be regarded as adducts of dimedone and alkylidenecyanothio(seleno)acetamides, which are apparently formed *in situ* in this reaction. When the temperature is increased, the compounds **367** cyclise to 4-alkyl-substituted hexahydro-2(1*H*)-quinolinethiones(-selenones) **368**.[249]



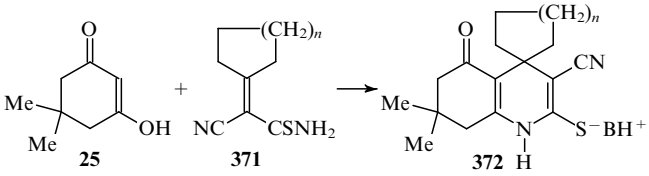
Y = S (**53**), Se (**366**).

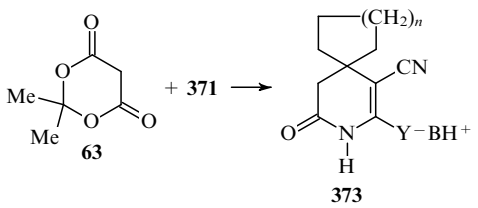
Under these conditions, Meldrum's acid **63** forms analogous salts **369**; at higher temperatures, they cyclise with destruction of the 1,3-dioxane ring, being thus converted into hydrogenated pyridones **370**.[249]



Y = S (**53**), Se (**366**).

The use of compounds **371**, resulting from condensation of cyclic ketones with cyanothioacetamide, in the reactions with the dicarbonyl compounds **25** and **63** permitted the synthesis of spiro-derivatives of hydrogenated quinolines **372** and pyridones **373**, which are of interest from the stereochemical viewpoint.[249]





Analysis of the published data indicates that reactions of carbonyl compounds with α,β- unsaturated nitriles is a quite promising field of research. Studies along this line make it possible to synthesise a large number of diverse organic compounds possessing useful practical properties and also make a substantial contribution to the development of theoretical problems of organic chemistry.

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