Russian Chemical Reviews **67** (11) 923 – 940 (1998) © 1998 Russian Academy of Sciences and Turpion Ltd

UDC 547.233; 7

Synthesis and properties of β,β-bisfunctionalised ketene *N*,*N*-acetals

V A Makarov, V G Granik

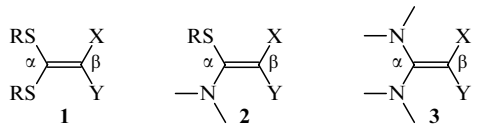
Contents

I.	Introduction	923
II.	Synthesis of disubstituted ketene *N*,*N*-acetals	923
III.	Properties of ketene *N*,*N*-acetals	930
IV.	Conclusion	938

Abstract. Data on the synthesis of β,β-disubstituted ketene *N*,*N*-acetals as well as their physicochemical properties and reactions with electrophilic and nucleophilic reagents are generalised. Special attention is paid to the synthesis of various heterocyclic compounds based on these compounds. The bibliography includes 182 references.

I. Introduction

Ketene *S*,*S*-, *S*,*N*- and *N*,*N*-acetals† **1**–**3** draw the chemists' attention due to their high reactivity and the prospects of their broad and versatile synthetic utilisation, in particular, for the synthesis of heterocyclic compounds.



Compounds **1** have been considered in comprehensive reviews.[1–4] These reviews cover the properties and transformations of *N*,*S*-acetals **2** to a considerably smaller extent. Ketene *N*,*N*-acetals **3** have been discussed there rather incompletely.

The results of the use of ketene *N*,*N*-acetals for the synthesis of heterocyclic compounds are generalised in the review;[5] however, it mostly discusses monosubstituted ketene *N*,*N*-acetals **3** (Y = H). On the other hand, a considerable number of studies have been devoted to the synthesis and transformations of disubstituted ketenes **3** in which X and Y are functional, mostly electron-acceptor substituents. The present review considers the methods for the synthesis of ketene *N*,*N*-acetals, their physicochemical and chemical properties and prospects of their use in the synthesis of various heterocyclic systems.

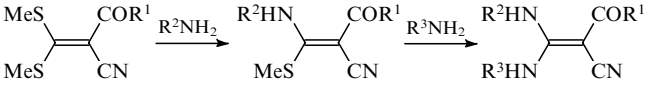
V A Makarov, V G Granik Russian Research Centre 'Research Institute of Organic Intermediaries and Dyes', ul. Bol'shaya Sadovaya 1/4, 103787 Moscow, Russian Federation.
Fax (7-095) 254 12 00. Tel. (7-095) 254 97 24 (V A Makarov), (7-095) 254 94 65 (V G Granik)

Received 13 October 1997
Uspekhi Khimii **67** (11) 1013 – 1031 (1998); translated by S S Veselyi

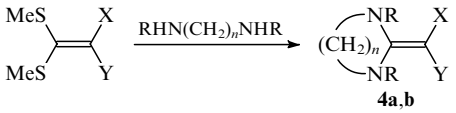
II. Synthesis of disubstituted ketene *N*,*N*-acetals

1. Synthesis based on ketene *S*,*S*- and *N*,*S*-acetals and ketene dihalides

The majority of publications concerning the synthesis of ketene *N*,*N*-acetals **3** deal with the reactions of substituted ketene *S*,*S*- (**1**) or *N*,*S*-acetals (**2**) with amines.[6–39] It is well known that the alkyl(aryl, hetaryl)thio group (SR) is a 'good leaving group', and its replacement by an amine-containing fragment is usually not problematic. However, replacement of one alkylthio group in ketene *S*,*S*-acetals **1** by the amino group results in a considerable decrease in the reactivity of the other SR-substituent due to the strong electron-donor effect of the amino group. Thus, it is possible to obtain asymmetrical *N*,*N*-acetals **3** in several stages from *N*,*S*-acetals **2**. A typical example of such a sequential synthesis of ketene *N*,*N*-acetals is presented in Ref. 29.



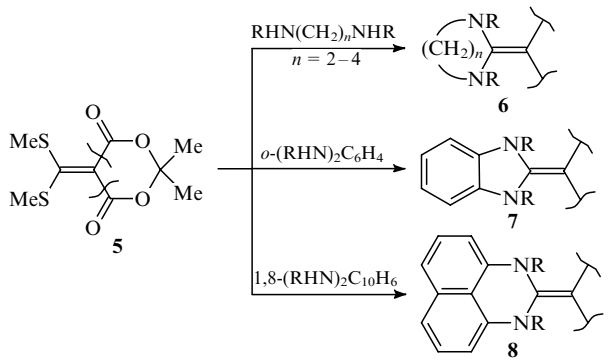
In some cases, ketene *S*,*S*-acetals were made to react with ethylenediamines.[8, 10, 12, 13, 17, 23, 24, 28, 30, 33–36, 39] This resulted in 2-methyleneimidazoline derivatives **4a**.[10] If substituted propane-1,3-diamines are used instead of ethylenediamine derivatives,[12, 28, 33] hydrogenated pyrimidine derivatives **4b** are formed.



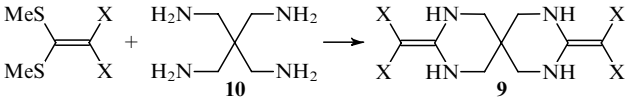
X = COR′, CO_2R', CN, Ar; Y = COR′, CO_2R', CN; n = 2 (**a**), 3 (**b**).

Reactions of cyclic ketene *S*,*S*-acetal **5** with various diamines, including *o*-phenylenediamine derivatives (see also Refs 14, 17, 19, 24, 30, and 34) and 1,8-diaminonaphthalene, have been studied.[28] Is was found that the rate of formation of cyclic systems **6**–**8** depends on the nature of the diamine. The reaction of ketene *S*,*S*-acetal **5** with butane-1,4-diamine derivatives (n = 4) or aromatic amines occurs much more slowly than that with ethane(-propane)diamines (n = 2, 3).

† Other names for these compounds, such as ketene aminals, highly polarised or 'push-pull' enamines, and enediamines are also widely used in the literature.

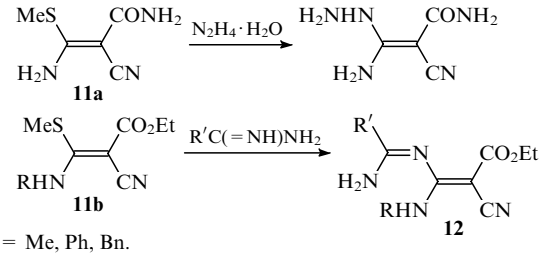


The reaction of *S*,*S*-acetals **1** or *S*,*N*-acetals **2** with various compounds containing the unsubstituted amino group opens up no less wide prospects for the synthesis of diverse derivatives of ketene *N*,*N*-acetals. For example, spiro compounds **9** incorporating two enediamine fragments have been synthesised from ketene *S*,*S*-acetals and the tetramine **10**.[40]



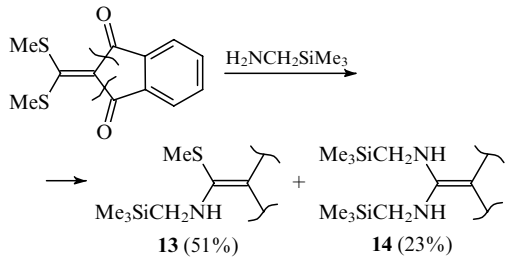
X = CN, CO_2Me.

The reaction of *S*,*N*-acetal **11a** with hydrazine afforded 3-amino-2-cyano-3-hydrazinoacrylamide.[22] Reactions of substituted acetals **11b** with various amidines and guanidines result in the corresponding 'push-pull' enamidines **12**.[20,21]

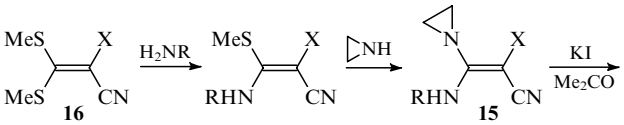


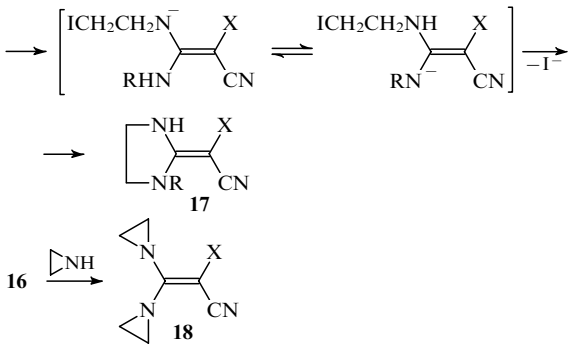
R = Me, Ph, Bn.

2-Bis(methylthio)methylenindane-1,3-dione reacts with trimethylsilylmethylamine on refluxing in methanol to give a mixture of mono- and disubstituted products **13** and **14**.[32]



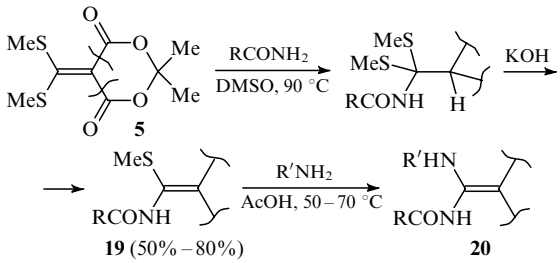
Monoaziridino-R-amino derivatives of ketene *N*,*N*-acetals **15** are formed upon successive introduction of, first, monosubstituted amines and then ethyleneimine in the reaction with ketene *S*,*S*-acetals **16**. The action of the iodide ion on compounds **15** results in ketene acetals of the imidazolidine series **17**.[18] Direct reaction of ethyleneimine with compounds **16** gives bisaziridino derivatives of ketene *N*,*N*-acetals **18**.[18]



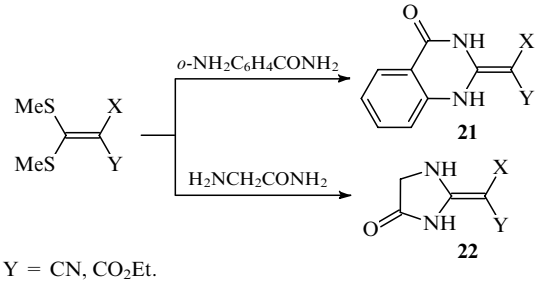


X = ArCO, HetCO.

Ketene *S*,*S*-acetals **5** can react even with such weakly basic compounds as carboxamides. This reaction gives *N*-acyl derivatives of ketene *S*,*N*-acetals **19** as the final products. The latter readily give *N*-acylketene *N*,*N*-acetals **20** on treatment with primary amines.[29]

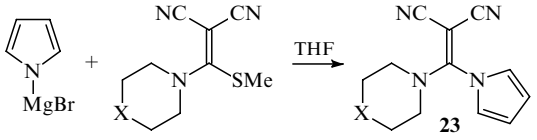


Reaction of ketene *S*,*S*-acetals with anthranylamide[37] or glycinamide[16] results in the corresponding pyrimidinone (**21**) or imidazolidone (**22**) derivatives.



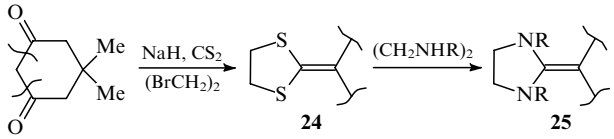
X, Y = CN, CO_2Et.

The reaction of ketene *N*,*S*-acetals with pyrrolyl-1-magnesium bromide readily gives ketene *N*,*N*-acetals **23** containing the pyrrole ring as one of the amine moieties.[31]



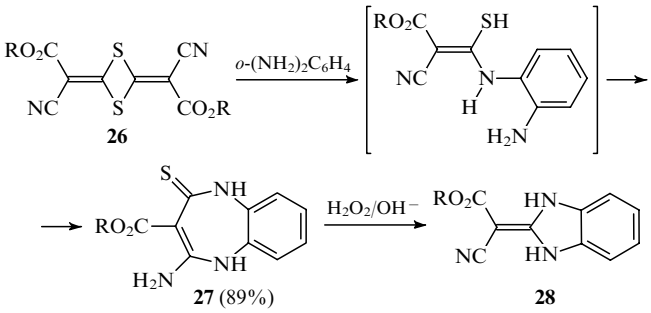
X = CH_2, O.

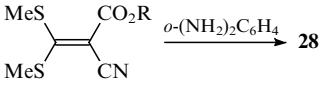
It should be noted that ketene *S*,*S*-acetals in which the sulfur atoms are incorporated in the cyclic systems can also be converted to ketene *N*,*N*-acetals. For example, 1,3-dithiolane **24** reacts with *N*,*N*′-substituted ethylenediamines to give imidazolidine derivatives **25**.[8]



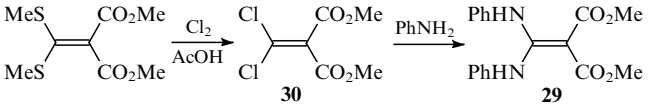
R = Ar, ArAlk.

The reaction of substituted 1,3-dithietanes **26** with *o*-phenylenediamine results in benzodiazepine derivatives **27**, which are oxidised in alkaline medium to give ketene *N*,*N*-acetals of the benzoimidazole series **28**. These compounds have also been obtained by independent synthesis from alkyl 2,2-bismethylthiomethylenecyanoacetate and *o*-phenylenediamine.[19]





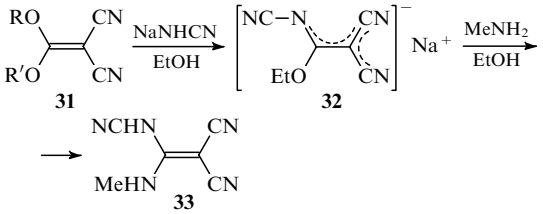
Chlorination of ketene *S*,*S*-acetals in acetic acid readily gives ketene dichlorides, which represent convenient starting compounds for subsequent synthesis of ketene *N*,*N*-acetals. For example, acetal **29** was obtained by the reaction of the appropriate dichloride **30** with aniline.[41]



Similar reactions are also known for other ketene dichlorides, *viz*., 2-dichloromethyleneindane-1,3-dione[42] and 2-dichloromethylene-4,5-dichlorocyclopent-4-ene-1,3-dione,[43] as well as for some ketene dibromides[44] and ketene diiodides.[45]

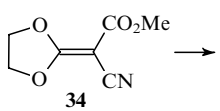
2. Synthesis based on ketene *O*,*O*- and *O*,*N*-acetals and related compounds

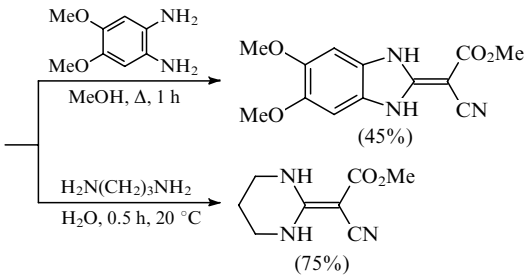
Ketene *O*,*O*-acetals and related compounds are promising starting reagents for the synthesis of ketene *N*,*N*-acetals. For example, bisalkoxymethylenemalonodinitriles **31** react with sodium cyanamide under mild conditions with formation of the sodium salt **32**, which gives *N*-cyanoketene *N*,*N*-acetal **33** on heating with methylamine.[46] Dimethoxymethylenemalonodinitrile **31** (R = R′ = Me) reacts similarly with ammonia and ethylenediamine.[47]



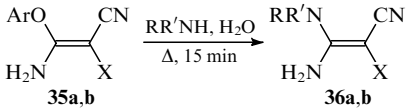
R = R′ = Et; R, R′ = $(CH_2)_2$.

The reaction of the 1,3-dioxolane derivative **34** with various diamines results in cyclic ketene *N*,*N*-acetals, while the reaction of compound **34** with aromatic diamines requires more drastic conditions than that with aliphatic ones.[48]





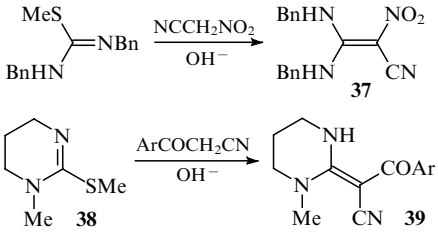
Amino(aryloxy)methylenemalonodinitrile (**35a**) and ethyl amino(aryloxy)methylenecyanoacetate (**35b**) react with amines to give the corresponding enediamine derivatives **36a**,**b**.[49]



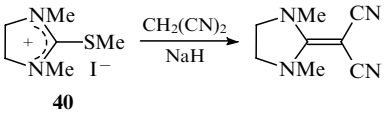
X = CN (**a**), CO_2Et (**b**).

3. Synthesis based on thiourea derivatives

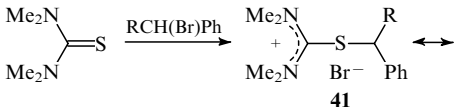
It is well known that ketene *S*,*S*- and *S*,*N*-acetals react with amines rather smoothly, since the alkylthio group is a 'good leaving group' (see Section 1). Yet another group of reactions based on the replacement of the RS group, *viz*., the reactions of compounds containing the reactive methylene group with *S*-alkylisothioureas, also result in the corresponding 'push-pull' enediamines. For instance, treatment of *N*,*N*′-dibenzyl-*S*-methylisothiourea with nitroacetonitrile in alkaline medium gave a small yield (~20%) of β-nitro-β-cyanoenediamine **37**.[50] Cyclic thiourea derivatives react similarly.[51–57] For example, the reaction of compound **38** with aroylacetonitriles results in cyclic acetals **39**.

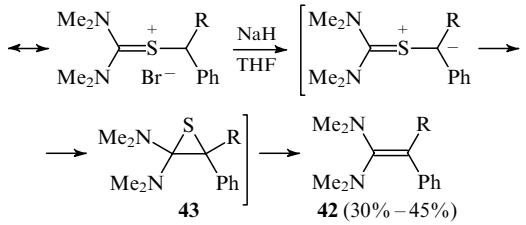


Isothiouronium salts also react with compounds containing the reactive methylene group in the presence of sodium hydride.[58] For example, the reaction of salt **40** with malonodinitrile results in the corresponding symmetric enediamine.



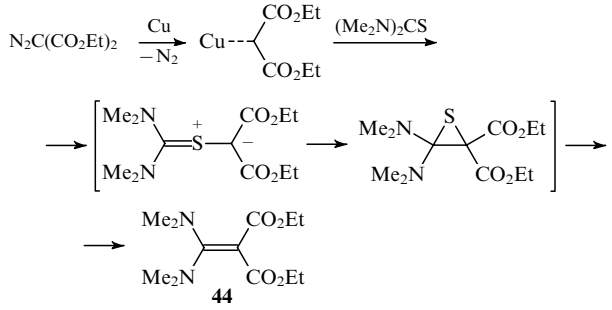
Not only *S*-methyl derivatives of isothiouronium salts, but also compounds with more complex *S*-substituents can serve as starting compounds in the synthesis of ketene *N*,*N*-acetals.[59] Treatment of salts **41** containing an electron-acceptor group at the sulfur atom with sodium hydride in tetrahydrofuran gives enediamines **42** in moderate yields. It is believed[59] that this reaction gives intermediate ylides, which then undergo cyclisation to thiiranes **43**. Elimination of the sulfur atom from the thiirane ring results in compounds **42**.



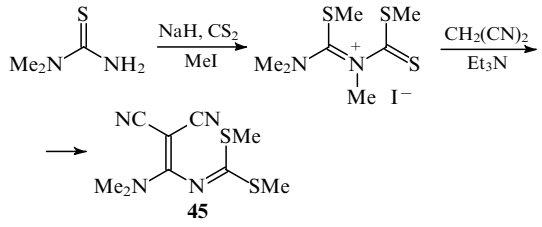


R = CO_2R', Bz.

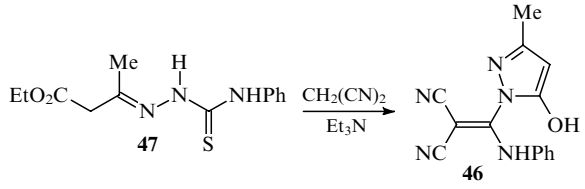
In the same study,[59] a method is proposed for the synthesis of ketene *N*,*N*-acetal **44** with the use of diethyl diazomalonate and tetramethylthiourea as the starting compounds.



An interesting method for the synthesis of enediamine **45** is described in Ref 60.



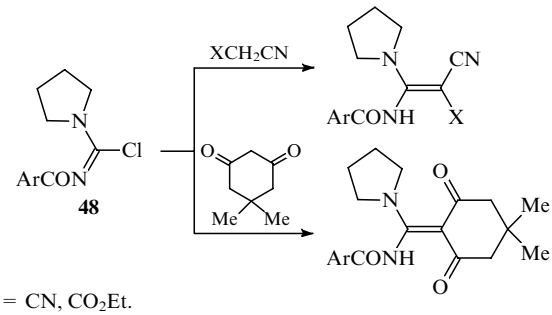
It was reported[61] that ketene *N*,*N*-acetals can also be obtained from thiourea derivatives without preliminary S-alkylation. For example, enediamine **46** is obtained by condensation of compound **47** with malonodinitrile.



It is evident from the scheme shown above that the formation of the enamine moiety is accompanied by the pyrazole ring closure.

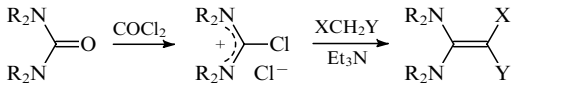
4. Synthesis based on 'activated' amides and ureas

It is known that 'activated amides', *i.e.*, amide acetals, imidates, imidoyl chlorides and related compounds, are rather promising starting reagents for the formation of various enamine systems. Enediamines, including highly polarised ones, are obtained by the condensation of 'activated amides' with compounds having a reactive methylene group.[62–64] For example, imidoyl chloride **48** reacts readily with such compounds as ethyl cyanoacetate, malonodinitrile and dimedone in dimethyl sulfoxide in the presence of sodium hydride to give substituted ketene *N*,*N*-acetals.[65]



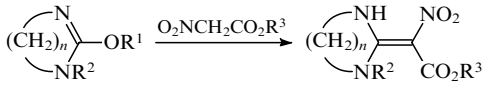
X = CN, CO_2Et.

Chloroamidines **49** obtained by the action of phosgene on tetraalkylurea are converted to 'push-pull' enamines **50a–c** in the reaction with ethyl malonate and ethyl cyanoacetate or malonodinitrile.[66]

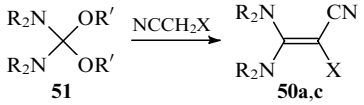


X = Y = CN (**a**), CO_2Et (**b**); X = CN, Y = CO_2Et (**c**).

Derivatives of cyclic ureas, particularly imidates, also react readily with compounds that incorporate a reactive methylene unit.[67]

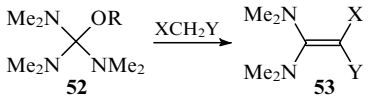


The urea acetals **51** can undergo condensation with ethyl cyanoacetate or malonodinitrile to afford ketene *N*,*N*-acetals **50a**,**c**.[68, 69]

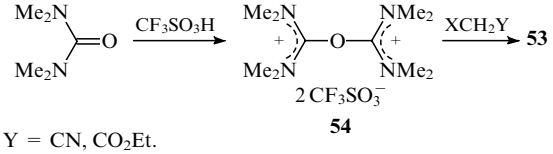


X = CN, CO_2Et.

Orthoamidoesters **52** also enter into similar reactions to give aminals **53**.[70, 71] It should be noted that compounds **52** are much more reactive than urea acetals **51**.

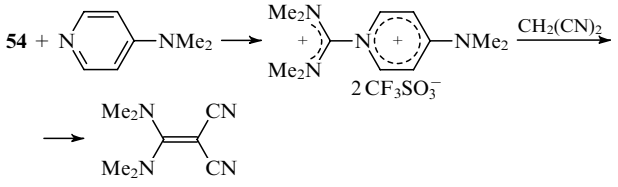


The bisamidinium salt **54** obtained by the reaction of an urea derivative with trifluoromethanesulfonic acid was also used for the synthesis of 'push-pull' enediamines **53**.[72]

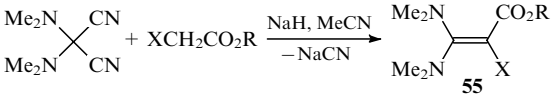


X, Y = CN, CO_2Et.

A modified procedure has been reported,[73] in which salt **54** was initially treated with 4-dimethylaminopyridine, and its condensation with malonodinitrile was carried out only thereafter.



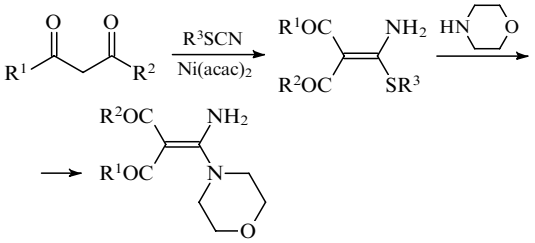
Bis(dialkylamino)malononitriles, like urea acetals, can undergo condensation with compounds containing the reactive methylene unit. For example, the reaction of bis(dimethyl-amino)malonodinitrile with alkyl malonate or acetoacetate in the presence of sodium hydride in acetonitrile gives enediamines **55**.[74]



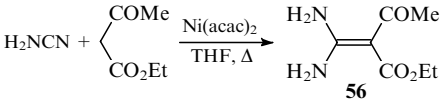
X = CO_2R', COMe.

5. Synthesis based on various *S*-, *N*- and *C*-cyano derivatives

A number of studies deal with the synthesis of enediamines under consideration by addition of the cyano group to the reactive methylene unit. For example, the reaction of organic thiocyanates with β-diketones in the presence of nickel acetylacetonate gives ketene *S*,*N*-acetals, which can react with amines (in particular with morpholine) to afford ketene *N*,*N*-acetals in high yields.[75]

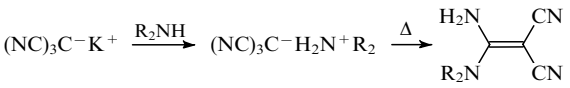


Cyanamide and its derivatives react in a similar way.[76–80] For example, the reaction of cyanamide with ethyl acetoacetate in the presence of nickel acetylacetonate results in the aminal **56**.

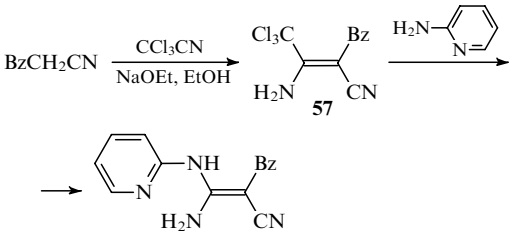


Cyanamide reacts similarly with β-dicarbonyl compounds in the presence of $SnCl_4$.[81]

Another way for the synthesis of ketene *N*,*N*-acetals is based on the reaction of tricyanomethane (cyanoform) and related compounds with amines.[82,83]

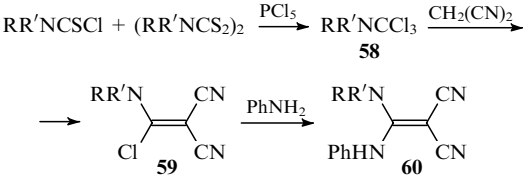


Trichloroacetonitrile proved to be a convenient starting reagent in the synthesis of the target enamines. Its condensation with CH_2-acids initially gives (α-trichloromethyl)enamines, in which the CCl_3 group is readily replaced by the amino group with the formation of enediamines.[84–86] The reaction of trichloro-acetonitrile with benzoylacetonitrile followed by the reaction of the resulting compound **57** with 2-aminopyridine can be presented as an example.[86]

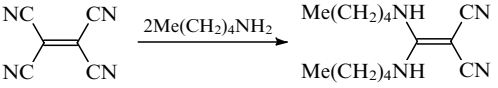


Similar replacement of the CCl_3 and CF_3 groups in enamines by the amino groups with the formation vicinal ethylenediamine derivatives has been reported.[87,88]

Reactions of trichloromethyldialkylamines **58** with compounds containing reactive methylene groups also result in ketene *N*,*N*-acetals.[89] For example, compounds **58** react with malonodi-nitrile to give chloroenamines **59**. The latter react with aniline to afford enediamines **60**.

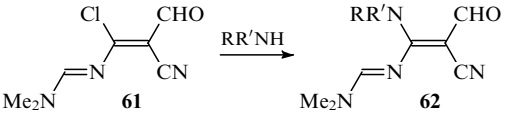


Finally, the reaction of tetracyanoethylene with primary amines (*e.g.*, pentylamine) readily yields symmetrical enedi-amines. Secondary amines can also be used in this reaction.[90,91]



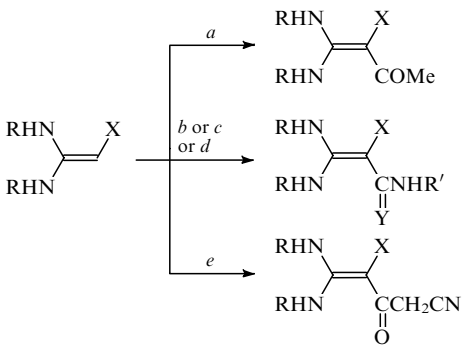
6. Synthesis based on enamine derivatives

α-Chloroenamines [92] and α-chloroenamidines [93] react with amines to give ketene *N*,*N*-acetals. For example, the reaction of chlor-oenamidine **61** with a secondary amine results in the product **62**.[93]



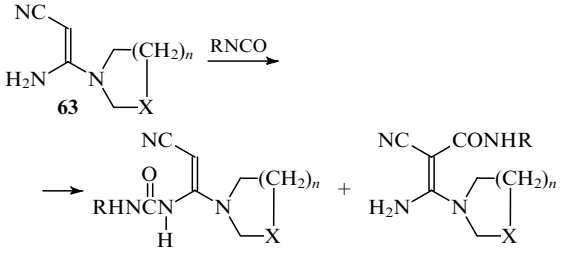
A wide range of β,β-disubstituted ketene *N*,*N*-acetals have been synthesised by C-acylation of β-monosubstituted α,α-diami-noethylenes.[94–99] Cyanoacetic acid in the presence of Ac_2O,[94] acetic anhydride,[95] isocyanates, isothiocyanates,[96,97] and benzoyl-isothiocyanate were used as acylating agents.[98,99]

Scheme 1



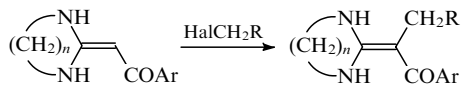
(*a*) Ac_2O, R–R = $(CH_2)_2$, X = CO_2Et;
(*b*) R′NCY, R′ = Bz, R–R = $(CH_2)_3$, X = CSAr, Y = S;
(*c*) R′NCY, R′ = Bz, X = NO_2, Y = S;
(*d*) R′NCY, R′ = Ph, X = CN, Y = O, S;
(*e*) $NCCH_2CO_2H$, Ac_2O, X = NO_2.

It has been shown [97] that acylation of enamines **63** with isocyanates occurs not only at the β-carbon atom but also at the amino group.



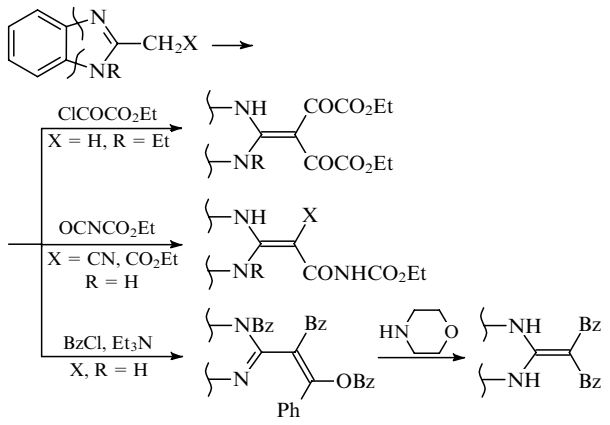
X = CH_2, *n* = 1, 2; X = O, *n* = 2.

β-Alkylation of β-monosubstituted ketene aminals with com-pounds containing reactive halogen has also been reported.[100]

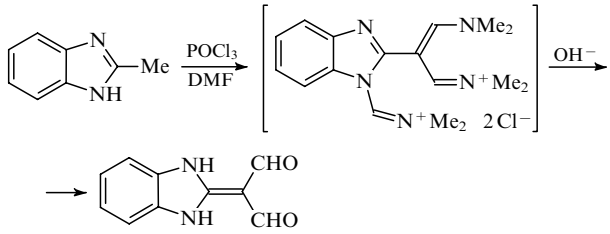


R = CO_2Et, Ph; Hal = Cl, Br.

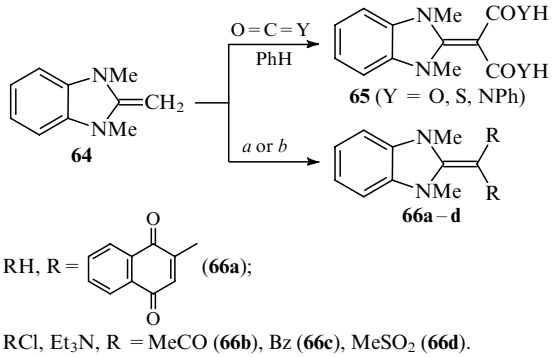
A series of ketene aminals have been synthesised by acylation of derivatives of 2-methylimidazoline,[101] 2-alkylbenzoimidazoles [102–104] and 2-methyltetrahydropyrimidines.[105] Examples of such syntheses based on 2-alkylbenzoimidazoles are shown in the scheme below.



2-Methylbenzoimidazole also undergoes bisformylation according to Vilsmeier in the presence of phosphorus oxychloride.[106]



The reaction of 1,3-dimethyl-2-methylenebenzoimidazoline (**64**) with compounds of general formula O=C=Y, where Y = O, S, NPh,[107] or with 1,4-naphthoquinone[108] results in ketene *N*,*N*-acetals **65** or **66a**, respectively. Acylation of compound **64** with acyl halides or related halogen-containing compounds in triethylamine gives the enediamines **66b–d**.[108]

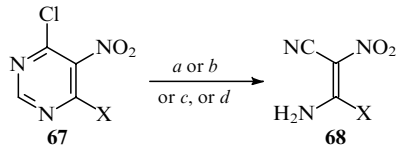


(*a*) RH, R = (**66a**);

(*b*) RCl, Et_3N, R = MeCO (**66b**), Bz (**66c**), $MeSO_2$ (**66d**).

7. Synthesis based on pyrimidine derivatives

One of the most peculiar preparative methods for the synthesis of 'push-pull' enamines is that starting from pyrimidines with a strong electron-acceptor substituent at position 5 of the pyrimidine ring. In 1967, it was found [109] that the action of organic or mineral acids on such pyrimidines results in easy opening of their ring. For example, the reaction of substituted pyrimidine **67** with acetic, chloroacetic, trifluoroacetic or hydrochloric acids results in the opening of the pyrimidine ring and formation of the enediamine **68**.

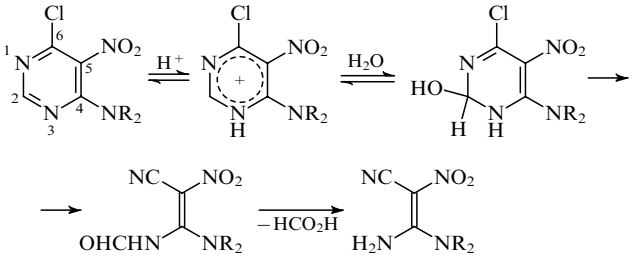


X = NMe_2, ; (*a*) AcOH; (*b*) $ClCH_2CO_2H$; (*c*) CF_3CO_2H; (*d*) HCl.

It was established [109] that if X is a tertiary amino group, the yields of enediamines **68** range from 50% to 95%. If X is a secondary amino group, the yields of compounds **68** are much lower. For example, if X = NHMe, the yield of the product is 18%, and if X = NH_2, it becomes impossible to obtain the corresponding enamine at all. In the latter case, the halogen at the pyrimidine ring is replaced by the hydroxy group.

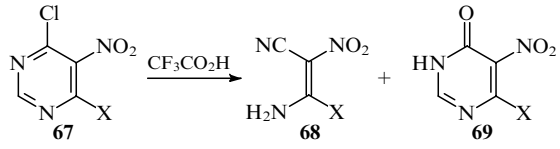
The following mechanism of the pyrimidine ring opening has been proposed (Scheme 2).[110] First, the nitrogen atom of the starting pyrimidine is protonated. The resulting pyrimidinium cation adds a molecule of water at position 2. Then elimination of the substituent from position 6 occurs with simultaneous opening of the pyrimidine ring at N(1)–C(2) bond. Subsequent *N*-deformylation of the resulting nitrile finally results in the enamine.

Scheme 2



The effect of the extent of substitution of the amino group in 4-amino-6-chloro-5-nitropyrimidines on the processes that occur on their heating in acetic or trifluoroacetic acids has been studied in detail.[111] This confirmed the conclusions [109] that ketene aminals **68** are formed in good yields if a tertiary amino group is present at position 4.

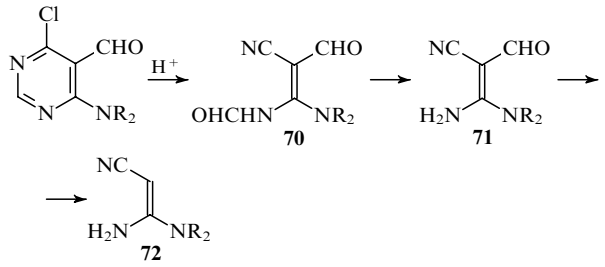
The action of trifluoroacetic acid on pyrimidine derivatives containing a primary or secondary amino group at position 4 was monitored by ^1H NMR spectroscopy.[112]



X	NHMe	NHEt	$NHPr^i$	$NHBu^t$	NH_2
Yield of compound **68** (%)	47	20	21	25	30
Yield of compound **69** (%)	53	80	79	75	70

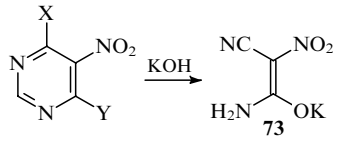
The formation of 'push-pull' enamines of the type **68** is also observed upon ring opening of 5-formyl-, 5-cyano- and 5-carboxypyrimidines.[112,113] However, compounds of this type tend to form pyrimidones **69** to a greater extent than nitropyrimidines.

The mechanism of the pyrimidine ring opening shown in Scheme 2 has been confirmed.[112] The authors managed to isolate and identify the *N*-formyl derivative **70**. It was also found that prolonged heating of 5-formylpyrimidines in an acidic medium results in compounds **70**, then 3,3-diamino-2-formylacrylonitrile derivatives **71** are formed, and finally their C-deformylation occurs to give cyanoenediamines **72**.[112]



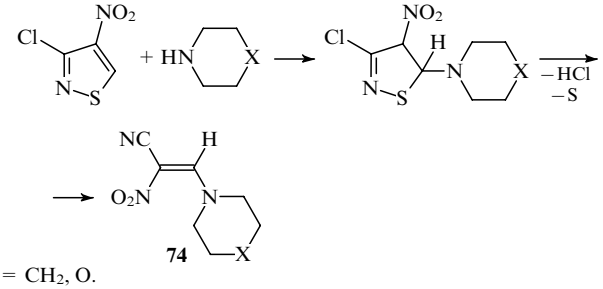
It was shown[114] that treatment of 4-amino-6-chloro-5-formylpyrimidines with an alkali also results in ketene *N*,*N*-acetals.

It is of note that heating of 4-chloro- or 4-methoxy-5-nitro-6-X-pyrimidines in an alkaline medium made it possible to obtain potassium cyanonitroacetamide **73**.[115]



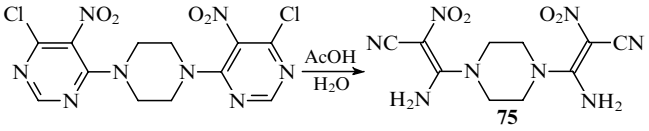
X = SC(S)NEt$_2$, Y = OMe; X = Y = Cl.

Ring opening of 4,6-dichloro-5-nitropyrimidine can be achieved on heating with secondary amines. However, treatment of chloronitroisothiazole with piperidine or morpholine gives β-cyano-β-nitroenamines **74** rather than enediamines.[116]

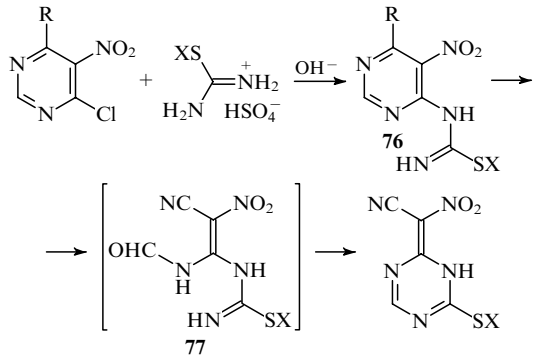


X = CH$_2$, O.

The bisketene aminal **75** was obtained according to the following scheme:[117]



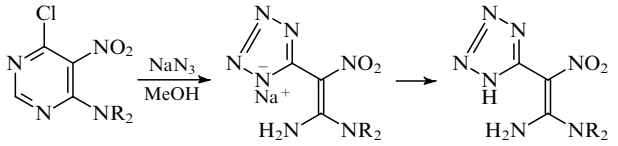
The reaction of 4-chloro-5-nitro-6-R-pyrimidines with *S*-alkyl(aryl)isothiouronium salts on heating in an alkaline medium results in substituted pyrimidines **76**. Subsequently, the products **76** were converted to 'push-pull' enamines **77**, which then underwent cyclisation into substituted *sym*-triazines.[118]



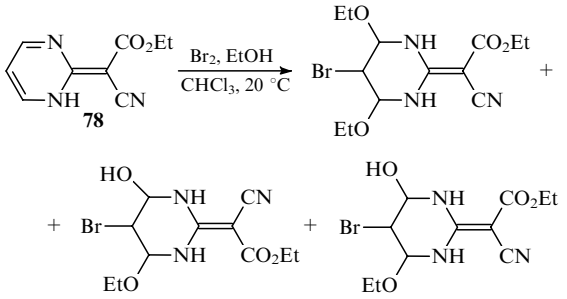
R = Cl, OMe; X = Alk, Ar.

It has recently been shown[119] that 4-arylamino-6-chloro-5-nitropyrimidines are transformed to enediamines **68** on boiling in dilute HCl to give considerable amounts of the corresponding 4-arylamino-5-nitropyrimidin-6-ones **69**.

A peculiar method for the synthesis of nitroenediamines containing a tetrazole moiety at the β-position is based on the reaction of 4-amino-6-chloro-5-nitropyrimidine derivatives with sodium azide.[120]

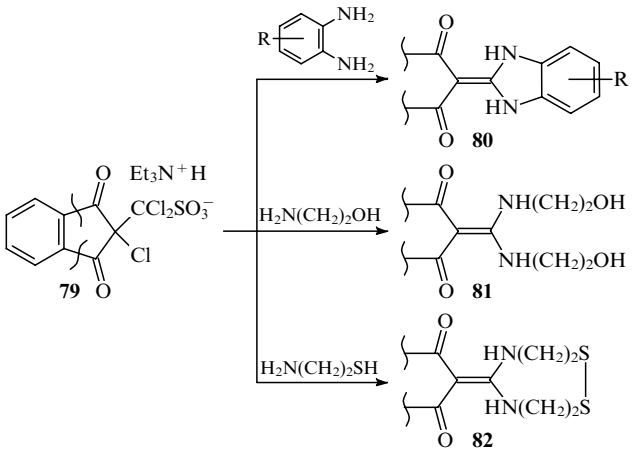


Bromination of methylenedihydropyrimidine **78** gives a mixture of cyclic enamines.[121]

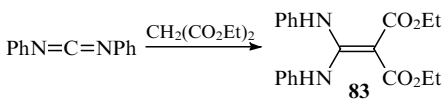


8. Miscellaneous methods for the synthesis of ketene aminals

The reaction of triethylammonium (2-chloro-1,3-dioxoindan-2-yl)dichloromethanesulfonate (**79**) with various amines results in ketene *N*,*N*-acetals **80**–**82**.[122]

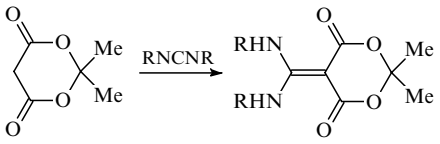


In certain studies, carbodiimides have been used for the synthesis of ketene aminals. This reaction was first described in 1899 with the synthesis of enediamine **83** from *N*,*N*′-diphenylcarbodiimide and diethyl malonate as an example.[123]

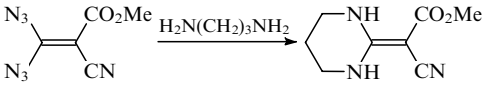


Compound **83** can also be obtained by the reaction of *N*,*N*′-diphenylthiourea with sodium diethyl malonate.[124]

Dicyclohexylcarbodiimide and other carbodiimides react with Meldrum's acid to give the corresponding enediamines.[125, 126]

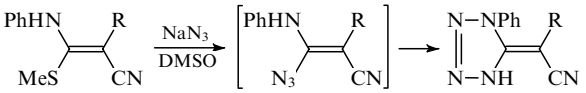


Vinyl azides have also been used as the starting compounds in the synthesis of ketene *N*,*N*-acetals.[127,128] For example, the reaction of vinyl diazide **84** with diaminopropane gave a small yield of cyclic product **85**.



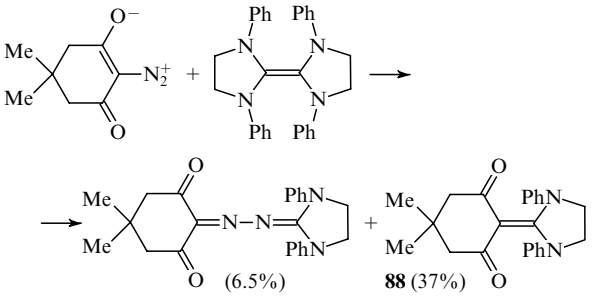
84 **85** (14%)

The reaction of ketene *N*,*S*-acetals with sodium azide probably gives vinyl azides **86** as intermediates, which are then converted into heterocyclic ketene aminals **87**.[129]



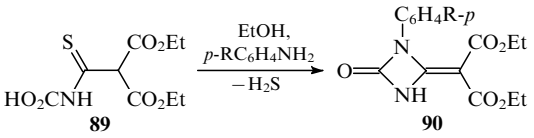
86 **87**

The reaction of 2-diazo-1,3-diketones with tetraaminoethylene derivatives results mainly in enediamino diketones **88**.[130]



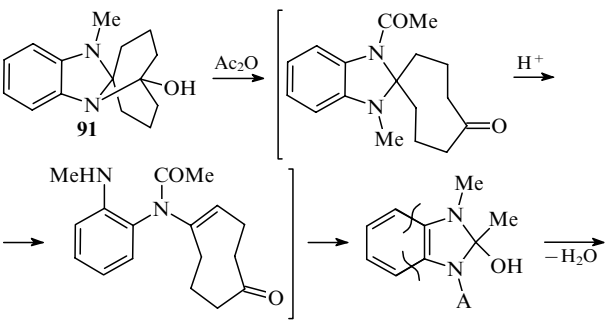
(6.5%) **88** (37%)

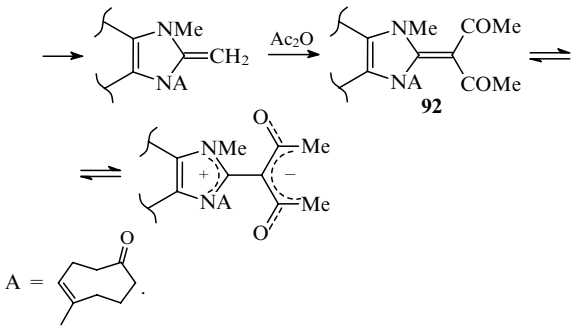
The synthesis of four-membered heterocyclic compounds, *viz*., diazetidine derivatives incorporating the enediamine moiety, has been reported.[131] For example, condensation of *N*-(thioacyl)-carbamic acid derivative **89** with *para*-substituted anilines yields cyclic products **90**.



89 **90**

Heating of 1-hydroxy-5-methyl-1,2,3,4,4*a*,5-hexahydro-1,4*a*-propanopyrido[1,2-*a*]benzoimidazole (**91**) with acetic anhydride in toluene results eventually in ketene aminal of the benzoimidazole series **92**.[132] This process is believed[132] to occur according to the following scheme:

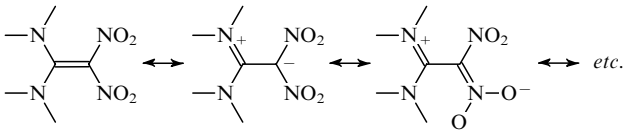




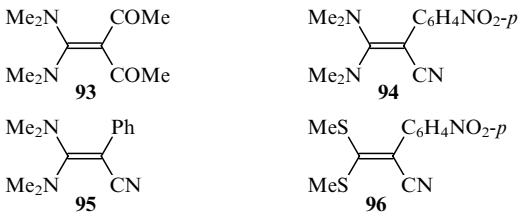
III. Properties of ketene *N*,*N*-acetals

1. Physicochemical parameters

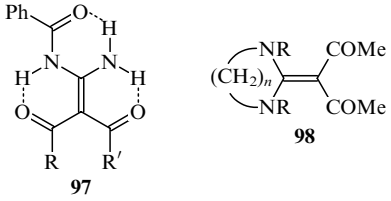
The major characteristics of ketene *N*,*N*-acetals is the direct polar conjugation of two α-amino groups with β,β-electron-acceptor substituents. Naturally, this conjugation affects the spectral and other physicochemical properties of ketene *N*,*N*-acetals. For example, according to X-ray diffraction data, abrupt elongation of the C=C bond in β,β-dinitroenediamines is observed, while the N–C bonds are much shortened. This can be rationalised as the superposition of the following resonance structures:



The lengths of the C=C bonds in β,β-dinitroenediamines lie within 1.451–1.474 Å, those of the N–C bonds lie within 1.315–1.316 Å and those of the C–NO_2 bonds lie within 1.399–1.494 Å.[45] It is known[133] that the barrier to *cis*–*trans*-isomerisation in β,β-diacyl *N*,*N*-acetals **93** ('rotation' around the carbon–carbon double bond) is extremely low and is $\Delta G^{\#} < 8$ kcal mol^{-1} (to compare with enamines, see Refs 134–136).



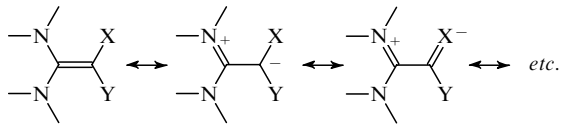
If weaker electron-acceptor substituents are present in the molecule (for example, in compounds **94** and **95**), the rotation barrier increases to 15 and 21 kcal mol^{-1}, respectively.[10] The same trend is observed if the electron-donor effect of the α-substituents decreases. For example, for ketene *S*,*S*-acetal **96**, $\Delta G^{\#} > 25$ kcal mol^{-1}. It is essential that in the cases where the formation of intramolecular hydrogen bonds in diacyl ketene aminals is possible, *cis*–*trans*-isomerisation is slowed down considerably. For example, the ^{1}H NMR spectrum of compound **97** (in $CDCl_3$) contains a double set of signals corresponding to the *E*- and *Z*-isomers, whereas one series of signals is observed in a solvent that favours the scission of intramolecular hydrogen bonds (DMSO-d_6).[8,77,78]



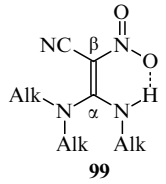
97 **98**

In cyclic enediamines **98**, the rotation barriers are also very low and are ~12–13 kcal mol^{-1} (see Refs 137, 138). It is of note that replacement of the C=O group in the β-substituent by the C=S group increases the $\Delta G^{\#}$ to ~30 kcal mol^{-1}. This effect is related to the stabilisation of the ground state and destabilisation of the transition state.[139]

IR spectra of 'push-pull' enediamines containing the carbonyl group are their important characteristics, the absorption bands of the CO groups are observed in the region below 1650 cm^{-1}. This indicates strong conjugation of the carbonyl groups with the electron-donor, substituted α-amino groups.[59, 77, 126, 140, 141] ^{13}C NMR spectra of this type of compounds are also rather characteristic.[28, 78, 142] For example, the signal for the C_β atom in *N*-benzoylenediamino diketones **97** is in the region δ ~87–100 ppm, while the signal for the C_α atom is at δ ~161–163 ppm. These chemical shifts indicate that the electron pairs of the nitrogen atoms participate in the 'enamine conjugation'.

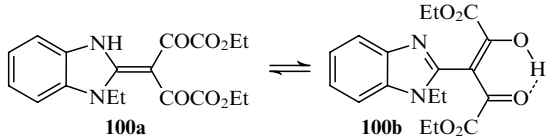


A detailed study of ^{1}H and ^{13}C NMR spectra carried out for nitrocyanoenediamines **99**[143] showed that the stereochemistry of these compounds is determined by the possibility of formation of intramolecular hydrogen bonds between the amino group and the nitro group.



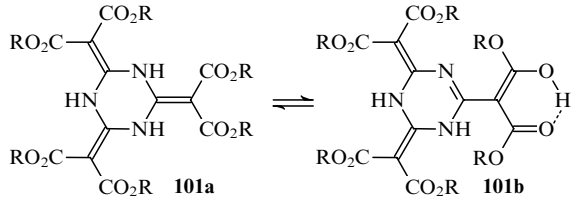
99

^{13}C NMR spectra of compounds **99** are also characterised by an upfield shift of signals for the C_β atom (δ ~90–103 ppm), while the signals for the C_α atoms are in the region δ 157–170 ppm. Specific conformation features of cyclic 'push-pull' ethylenes with sterically hindered electron-donor and electron-acceptor groups were studied.[144, 145] It was shown that the electron-donor and electron-acceptor fragments in these compounds are turned relative to the central carbon–carbon double bond. The tautomerism in ketene aminals and related compounds was studied.[102, 146, 147] It was shown that compound **100** exists predominantly in the tautomeric form **100a**.



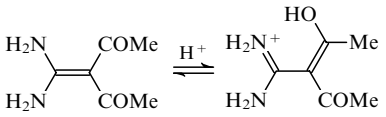
100a **100b**

The position of tautomeric equilibrium depends on the solvent. For example, the equilibrium **101a** ⇄ **101b** in $CHCl_3$, dioxane, methanol and water is shifted towards the enamine **101a**, whereas in DMSO and DMF it is shifted towards the enol **101b**. In acetonitrile, a mixture of tautomers **101a**,**b** is formed.[146]

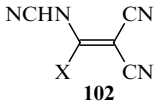


101a **101b**

It was shown[79] that diacyl ketene aminals represent bases and are protonated on the oxygen atom.



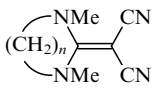
However, if the amino group has a strong electron-acceptor substituent, these compounds are strong organic acids. For example, the ionisation constants (pK_a) of *N*-cyano-β,β-dicyanoketene aminals **102** in water are ~2.6–2.8, *i.e.*, they are even stronger acids than formic acid (pK_a 3.75)



102

X	NH_2	NHMe	NMe_2
pK_a	2.83	2.70	2.63

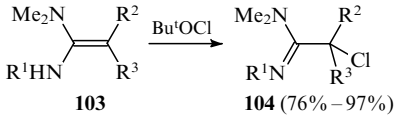
Finally, the pronounced effect of direct polar conjugation in 'push-pull' enamines is also characterised by their high dipole moments.[58] For example, the dipole moments of imidazoline or pyrimidine derivatives of ketene *N*,*N*-acetals are ~8 D, while it is only 6.5 D for such a strongly polarised compound as *N*-phenylsydnone.[148]



n	2	3
μ (benzene), D	7.93	8.02

2. Reactions of β,β-disubstituted ketene *N*,*N*-acetals with electrophilic and nucleophilic reagents

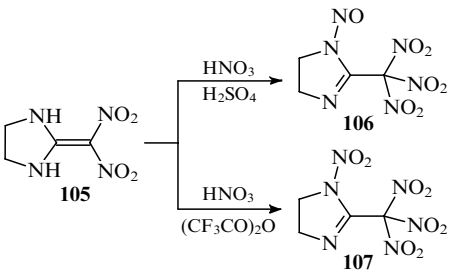
The presence of two α,α-amino groups in ketene aminals increases the nucleophilicity of the C_β-position considerably, and hence increases the possibility of attack on this position by electrophilic reagents. For example, it is known[149] that the reaction of ketene aminals **103** with *tert*-butyl hypochlorite smoothly gives the corresponding chloroamidines **104** in high yields despite the presence of two substituents at the C_β-atom.



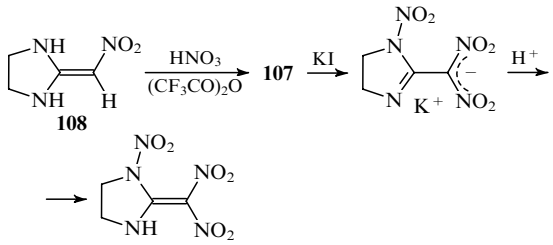
103 **104** (76%–97%)

R^1 = Ph, Me, Pr^i; R^2, R^3 = CN, CO_2Et.

Nitration of 'push-pull' enediamines under various conditions has been studied.[150] It was found that the use of a mixture of nitric and sulfuric acids resulted in C_β-nitration and *N*-nitrosation, while in a mixture of HNO_3 and trifluoroacetic anhydride, C_β- and *N*-nitration occurred. In the latter case, the order of nitration steps on the C_β and N atoms has not been determined. Nitration of the ketene aminal **105** under various conditions results in products **106** and **107**.[150] It is essential that compound **107** is also formed upon nitration of β-monosubstituted 'push-pull' enediamine **108** with an HNO_3–trifluoroacetic anhydride mixture.

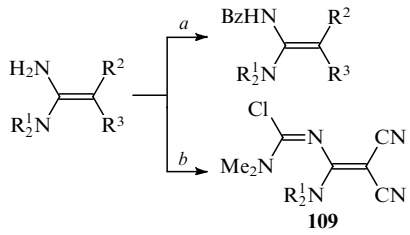


105 **106** **107**



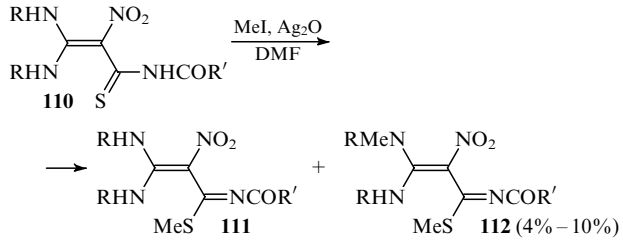
A method for reductive elimination of one NO_2 group from the C_β atom in compound **107** upon treatment with potassium iodide has been described.[151]

The reaction of β,β-disubstituted ketene *N*,*N*-acetals with acyl halides results in *N*-acylation products.[88] If dimethyltrichloromethylamine is used as the acylating reagent, the reaction occurs at the nitrogen atom to give the derivative **109** containing the chloroformamidine moiety.

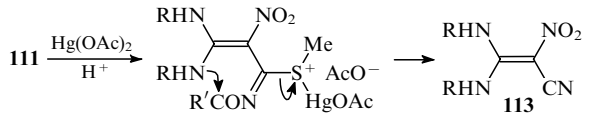


(*a*) BzCl, R^1 = H, R^2, R^3 = CN, CO_2R^4;
(*b*) CCl_3NMe_2, R^1 = Me, R^2 = R^3 = CN.

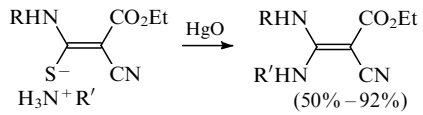
Alkylation of ketene aminals is an important reaction that characterises enamines and deserves separate discussion. For example, the alkylation of thioamides **110** with methyl iodide occurs mostly on the sulfur atom. In addition to *S*-methyl derivatives **111**, *N*,*S*-dimethyl derivatives **112** are formed.[152]



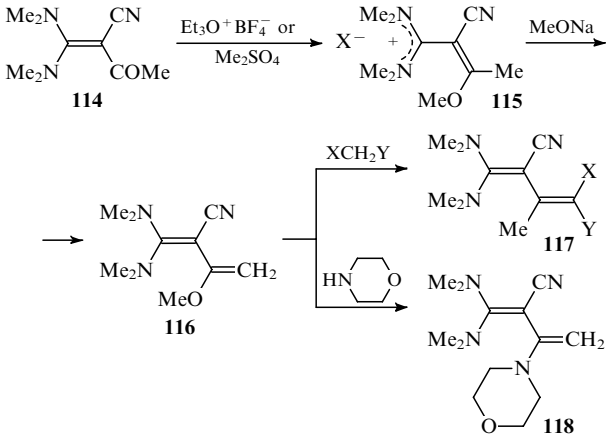
Oxidation of aminals **111** with mercuric acetate in acidic medium results in enediamines **113**.[152]



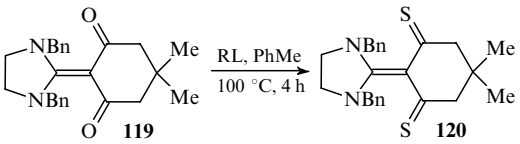
It should be noted that the oxidation of the ammonium salts of cyano(ethoxycarbonyl)thiocarbamoylmethanes with mercury(II) oxide readily gives ketene aminals.[153]

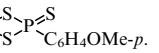


Enediamino ketone **114** undergoes alkylation with triethyloxonium tetrafluoroborate or dimethyl sulfate on the oxygen atom to give the corresponding complex **115**, which, in turn, can react with alkoxide anions to produce alkoxydienediamine **116**. Compound **116** is a convenient starting reagent for the synthesis of various dienamines, *e.g.*, dienediamine **117** or dienetriamine **118**.[70]

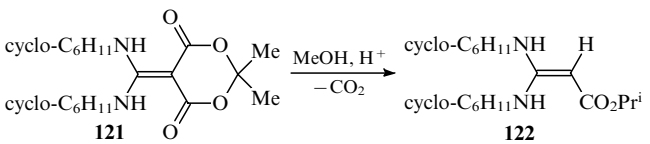


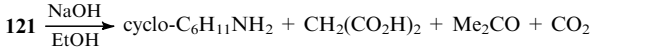
Yet another reaction of ketene aminals with electrophilic reagents worthy of note is that of enediamino diketones with the Lawesson reagent (LR). For example, enediamino diketone **119** can be converted to the corresponding enediamino dithione **120**.[8]



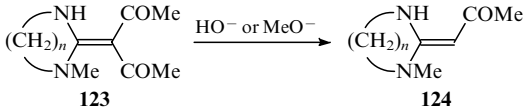
LR = 

A series of reactions of ketene aminals with nucleophilic reagents has been described.[125] For example, acid hydrolysis of a Meldrum's acid derivative **121** resulting in the β-monosubstituted derivative **122** is worth mentioning. The same authors described degradation of compound **121** upon treatment with ethanolic alkali.

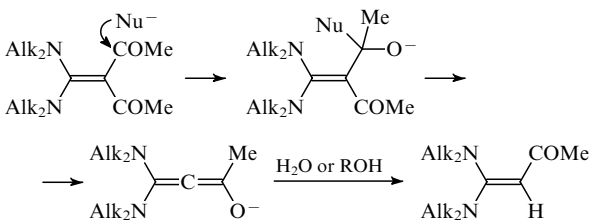




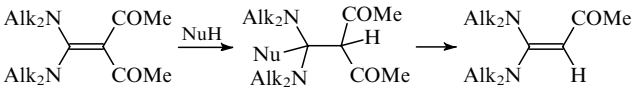
Monodeacylation of enediamino diketones has been described.[12] For example, the action of the hydroxy or methoxide anion on diketones **123** results in ketones **124**.



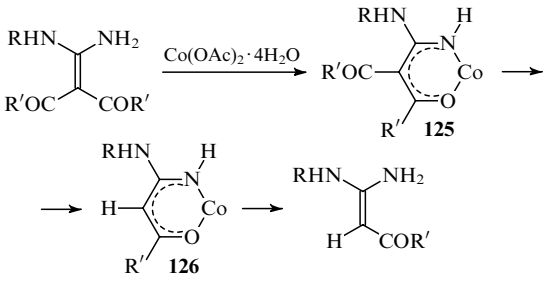
A possible version of the mechanism of this process includes the addition of the nucleophile at the carbonyl group.[12]



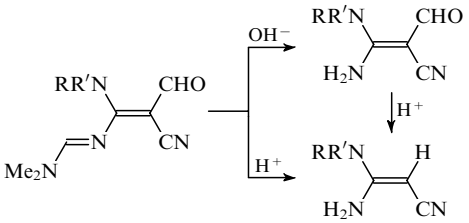
A version involving the attack of the nucleophile on the α-position may not be ruled out, either.



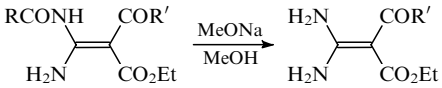
Recently,[154] an important method for C-deacylation of enediamino diketones upon treatment with cobalt acetate with intermediate formation of chelate complexes **125** and **126** has been suggested.



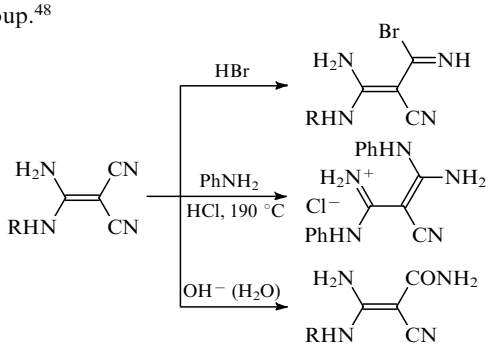
Elimination of the β-formyl group in acidic medium has been described[93] for ketene aminals incorporating the formamidine moiety.



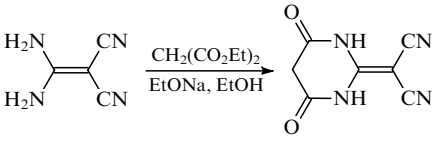
N-Acylketene *N*,*N*-acetals readily undergo N-deacylation on treatment with sodium methoxide in methanol.[80]



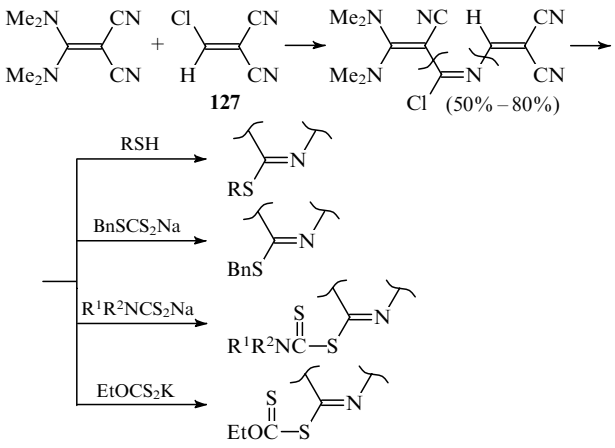
The transformation of β-substituents in 'push-pull' enamines under the action of nucleophilic reagents has been reported.[47,48,92] For example, treatment with hydrobromic acid gives bromoimines,[92] and heating with aniline hydrochloride results in salts of ketene aminals. Treatment with alkali converts the cyano group in 'push-pull' enamines into the carbamoyl group.[48]



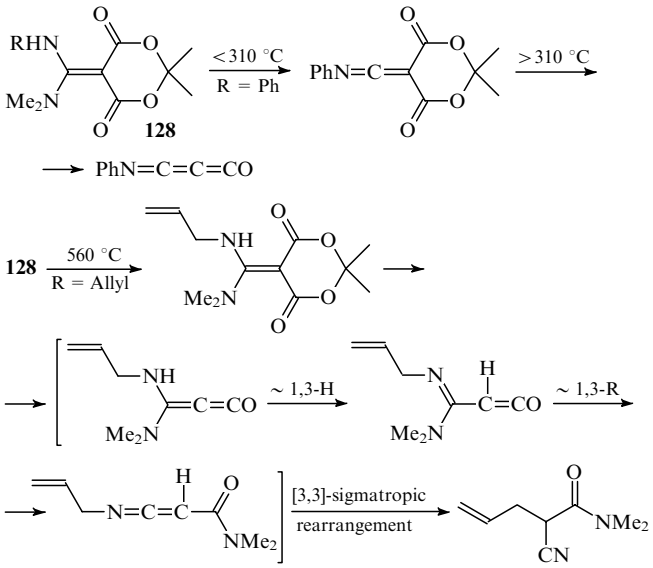
If a ketene aminal contains two unsubstituted amino groups, it can react with diethyl malonate to give a cyclic diacylketene aminal.[47]



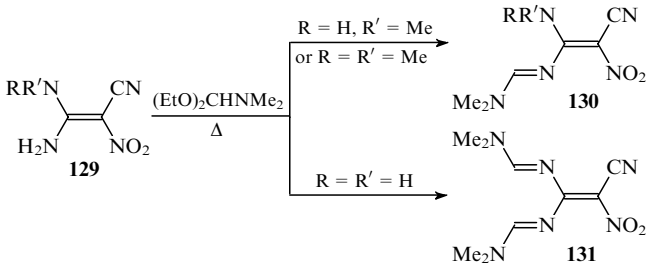
Diverse transformations of the cyano group in dicyanodiaminoethylene **127** have been discovered in a study of its reaction with chloromethylenemalononitrile.[155]



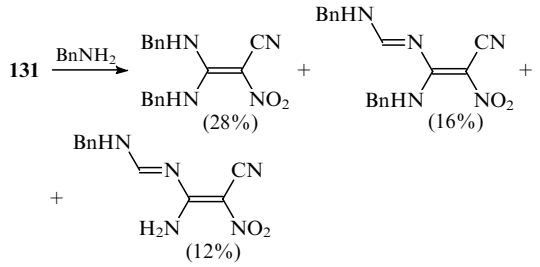
In addition, one should note such a reaction involving ketene *N*,*N*-acetals as thermolysis of compounds **128** based on Meldrum's acid.[9,25] The result of this process depends on the reaction temperature and the nature of the *N*-substituent.



It has been found recently[119] that the 'push-pull' enamines **129** with at least one nonsubstituted amino group readily react with amidoacetals to give the corresponding amidines **130** and **131** and the reaction rate depends on the extent of substitution of the other amino group (NH_2 > NHMe > NMe_2).

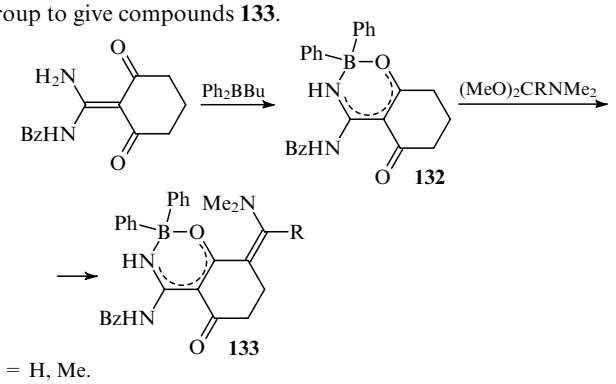


Transamination was studied using enamidine **131** as an example. It is known[156] that enamidines undergo transamination more readily than the corresponding enamines. However, it was found that compound **131** reacts in a non-standard way due to the additional α-amino-containing fragment, and replacement of enamidine fragments is accompanied by the reaction on the *meso*-carbon atom of the amidine group.[119]



A very important property of ketene *N*,*N*-acetals is their ability to form chelate complexes with metals[115,157–160] and boron compounds.[161–166] This enabled the development of a new direction of heterocyclic synthesis that opens a route to diverse azaheterocyclic compounds (see below). We consider here only some of the unusual properties of chelate complexes, which provide the possibility to perform processes non-characteristic of the starting ligands.

It is known[167,168] that enamines incorporating a primary amino group react with amide and lactam acetals primarily on the NH_2 group. If boron chelates are used, an opportunity appears to perform reactions on the active methylene group without involving the amino group. For example, it has been shown[161–162,165] that the chelate **132** reacts with dimethylformamide and dimethylacetamide acetals selectively on the CH_2 group to give compounds **133**.

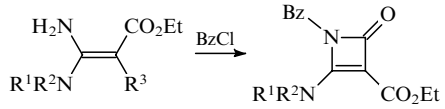


R = H, Me.

3. Synthesis of heterocyclic compounds based on ketene *N*,*N*-acetals

a. Four-membered heterocycles

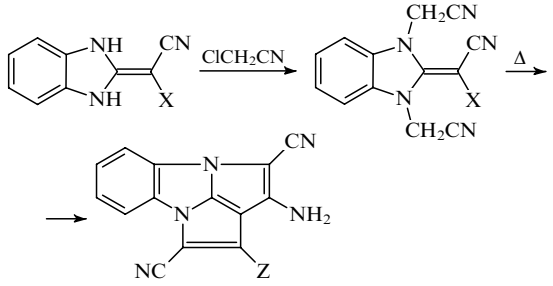
Benzoylation of ketene aminals results in azetine derivatives.[88]



The formation of diazetidine derivatives[131] has been discussed above (see Section II.8).

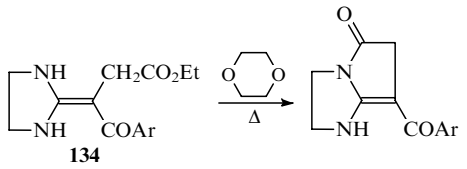
b. Five-membered heterocycles

The closure of pyrrole rings according to the Thorpe–Ziegler and/or Dieckmann reaction starting from ketene *N*,*N*-acetals of the benzoimidazole series has been described.[14]



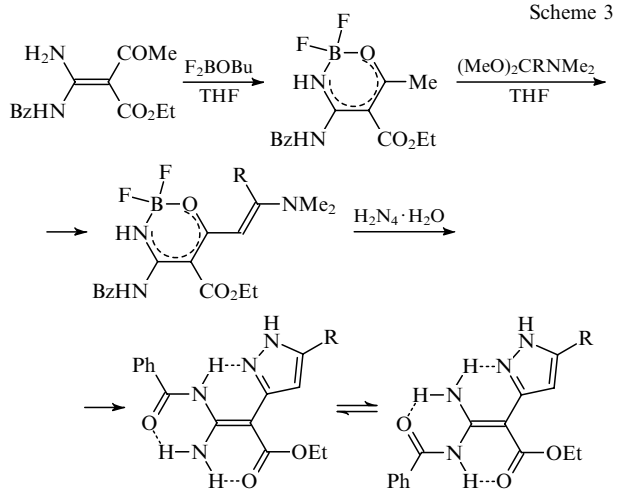
X = CN, CO_2Et; Z = NH_2, OH.

The pyrrole ring could also be obtained by cyclisation of aminals **134** on refluxing in dioxane.[100]

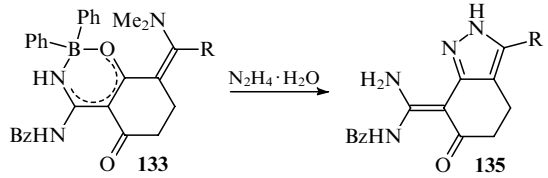


Synthesis of pyrazole derivatives occupies an important place in the chemistry of 'push-pull' enamines. For example, the strategy of chelate synthesis considered above was also found to be very efficient for the synthesis of various substituted pyrazole-containing systems.[162,165] An example of this kind of synthesis is shown in the Scheme 3.

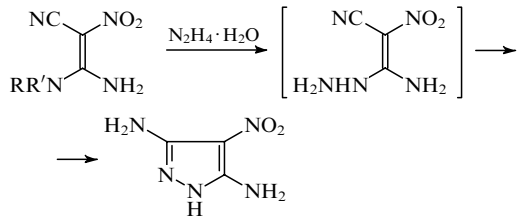
Scheme 3



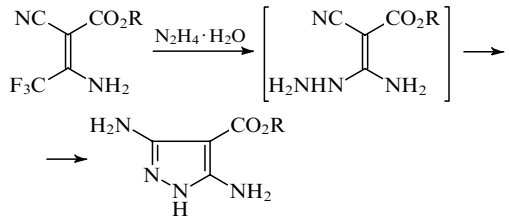
Similar synthesis of indazole derivatives **135** from the chelate **133** and hydrazine hydrate has been described.[165]



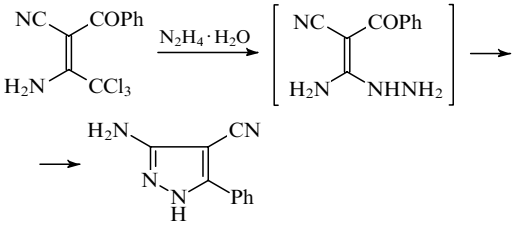
A wide range of substituted pyrazoles have been obtained by transamination of the dialkylamino group in ketene aminals with hydrazine hydrate followed by cyclisation on the cyano group.[50,84,113,143,169,170] For example, 3,5-diamino-4-pyrazole has been obtained this way.



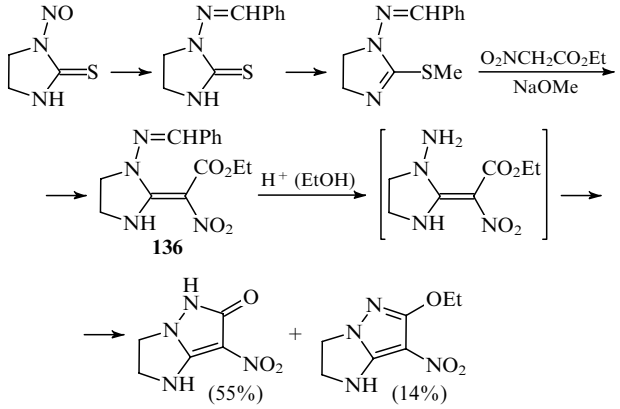
Similarly, the hydrazino group can replace the good leaving group, *viz*., $CHal_3$.[87] For example, this method was used to obtain alkyl 3,5-diaminopyrazole-4-carboxylates.



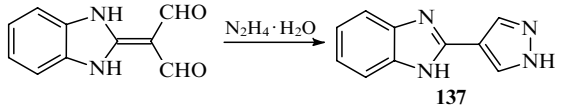
Cyclisation can involve not only cyano groups but also other functional groups.[85, 86]



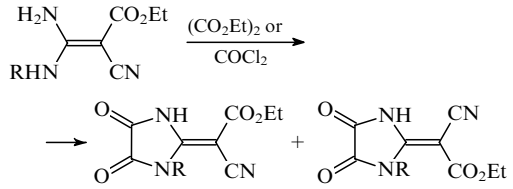
N-Aminoketene aminals obtained in a different way can also be used as starting compounds in the synthesis of fused pyrazoles.[52] An example of such a synthesis based on compound **136** is shown in the scheme:



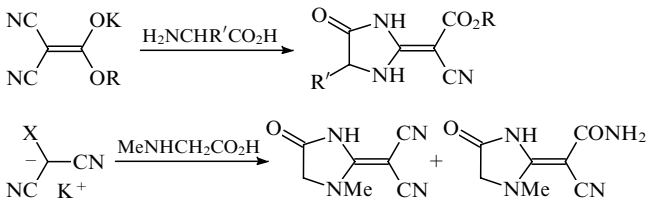
The synthesis of pyrazolylbenzoimidazole **137** is based on the reaction of *gem*-formyl groups of the starting benzoimidazole with hydrazine hydrate.[106]



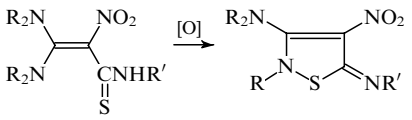
Several studies[171, 172] dealt with the synthesis of imidazole derivatives from 'push-pull' enamines (see also Ref. 18). For example, the reaction of ethyl diaminomethylenecyanoacetate with phosgene or diethyl oxalate results in imidazolidinediones.[171]



Imidazoles are formed from salts of alkyl dicyanoacetate or tricyanomethane and amino acids,[172] ketene aminals being the intermediate products.

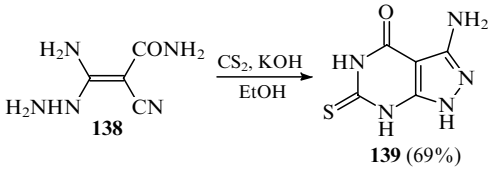


Substituted isothiazoles were synthesised by the oxidation of the appropriate enediaminothioamides.[26, 98]



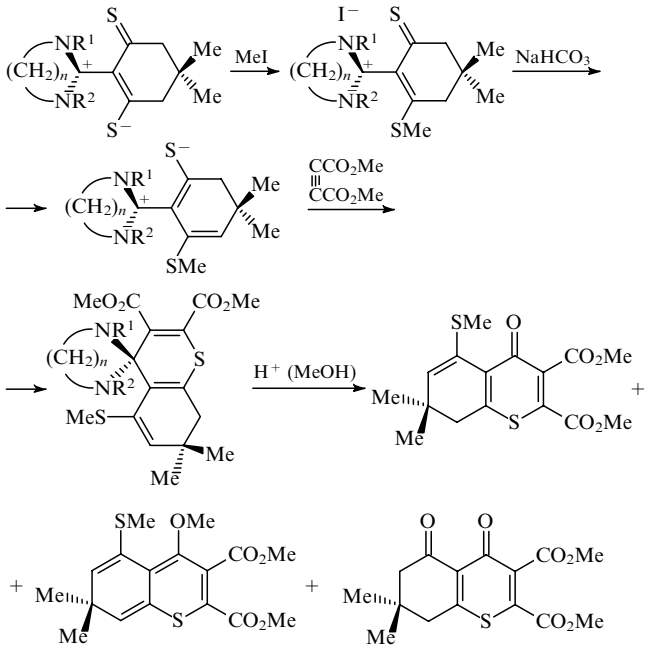
The synthesis of tetrazoles from ketene aminals has already been discussed above (see Section II.8).[129]

Finally, the reaction of hydrazinoenamine **138** with carbon disulfide results in the closure of both the pyrazole and pyrimidine rings to give a purine isoster, *viz*., pyrazolo[3,4-*d*]pyrimidine **139**.[22]

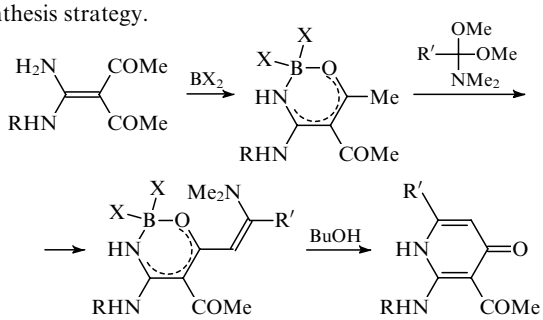


c. Synthesis of six-membered heterocycles

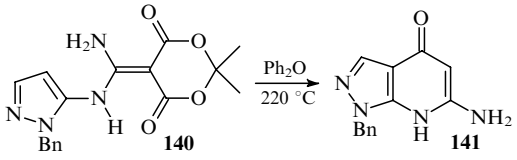
Thiapyran derivatives were obtained according to the following scheme.[145]



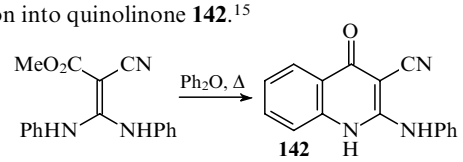
A few studies[166, 173] deal with the synthesis of substituted pyridines based on ketene aminals with the use of the chelate synthesis strategy.



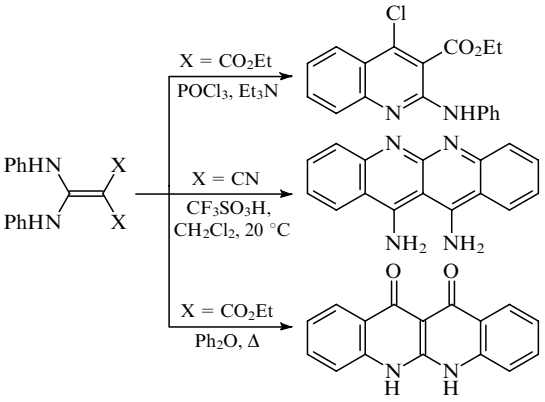
Recyclisation of pyrazolylketene aminal **140** at high temperature results in pyrazolo[3,4-*b*]pyridone **141**.[7]



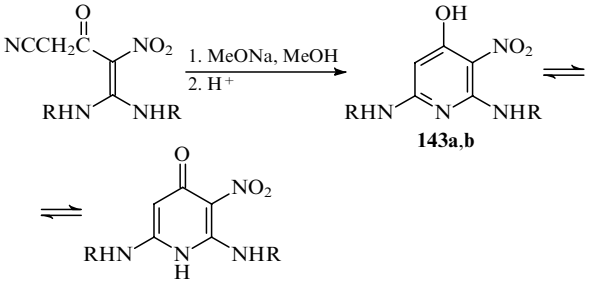
Methyl bisanilinomethylene cyanoacetate undergoes cyclisation into quinolinone **142**.[15]



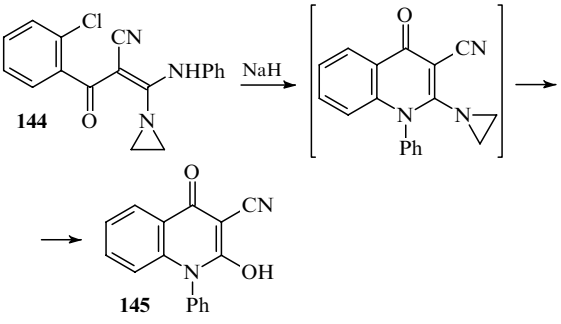
Similar cyclisations have been described in Refs 128 and 140.



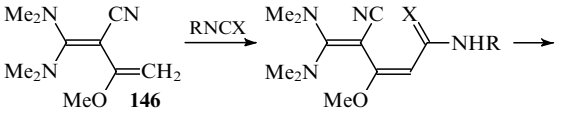
Intramolecular cyclisation of substituted β-cyanoacetyl-β-nitroketene *N*,*N*-acetals results in 4-pyridone derivatives **143a**,**b**.[94] It is of note that the hydroxypyridine tautomeric form predominates for pyridone **143a** (R = H), whereas the pyridone form predominates for pyridone **143b** (R = Me).

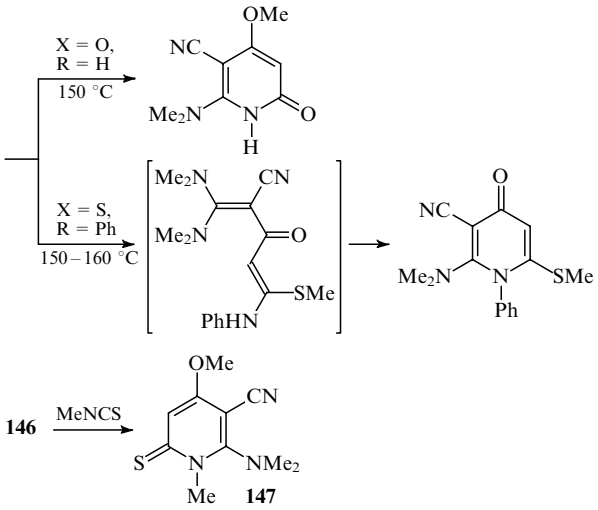


Intramolecular cyclisation of ketene *N*,*N*-acetal **144** upon treatment with sodium hydride to give benzopyridone **145** has been reported.[18]

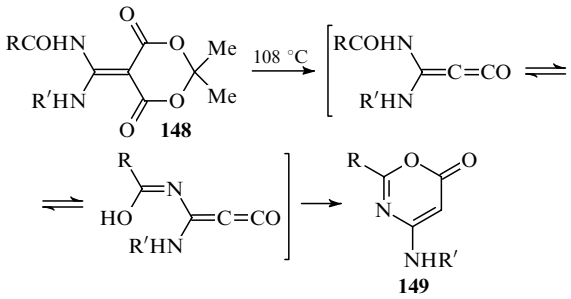


Finally, the synthesis of various pyridones based on alkoxydienediamine vinylogues **146** and **147** should be noted.[70]

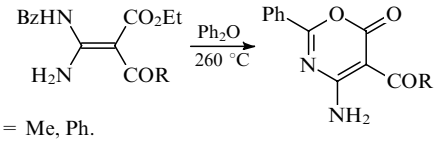




Thermolysis of *N*-acylaminals **148** results in substituted oxazin-6-ones **149**.[29]



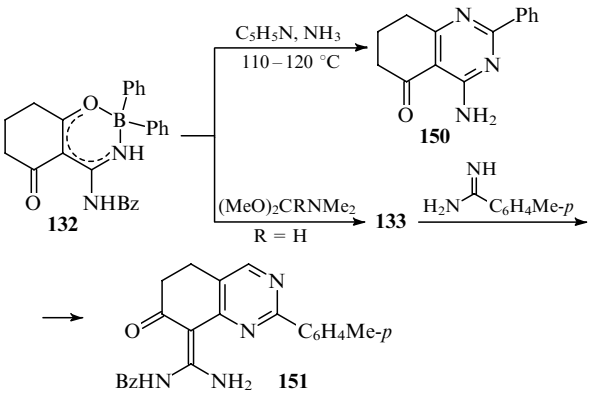
Another method for the synthesis of substituted 1,3-oxazin-6-ones has also been reported.[174]



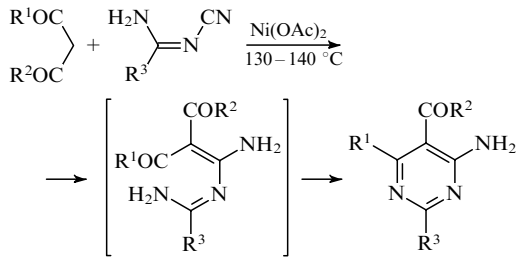
R = Me, Ph.

The majority of studies devoted to the synthesis of heterocyclic compounds from ketene aminals deal with the synthesis of pyrimidine derivatives. In this case, chelate synthesis is also an important approach to their synthesis.

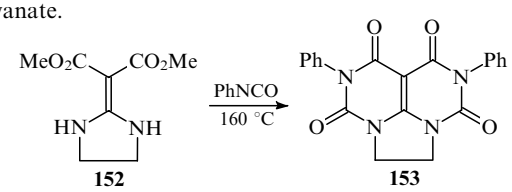
The use of boron chelates **132** has enabled the synthesis of substituted pyrimidines **150** and **151**.[161, 163, 164]



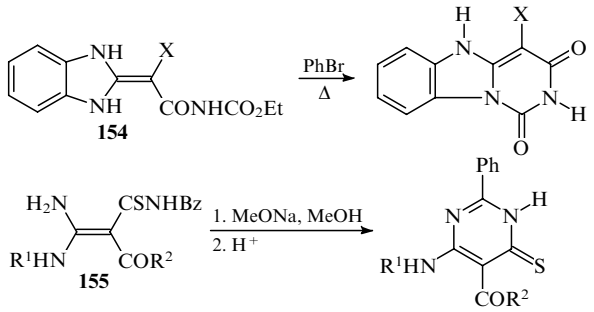
The condensation of β-diketones with *N*-cyanoamidines (R^3 = Me, Ph) or dicyanoguanidine (R^3 = NH_2) in the presence of nickel acetate, which is required for the formation of reactive chelates, occurs through intermediate derivatives of ketene *N*,*N*-acetals with their subsequent cyclisation into substituted 2,4-diaminopyrimidines.[160, 175]



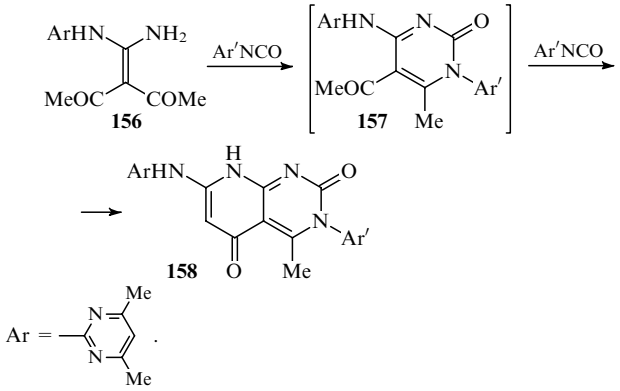
Enediaminodicarbonyl compounds react with isocyanates to give pyrimidines.[176,177] For example, cyclic aminal **152** was converted into pyrimidinone **153** by treatment with phenyl isocyanate.



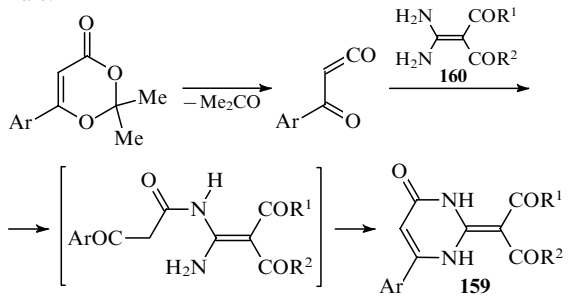
Ketene aminals with the *N*-ethoxycarbonylcarbamoyl substituent[103] (**154**) or with the *N*-benzoylthiocarbamoyl substituent[178] (**155**) at the β-position undergo cyclisation into pyrimidine derivatives on heating or under conditions of basic catalysis.



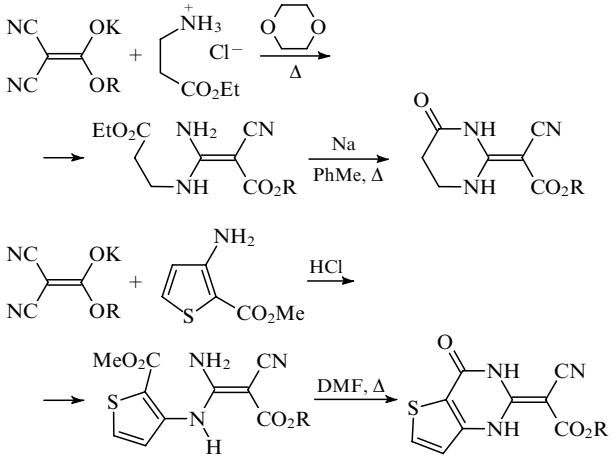
Enediamino diketones **156** react with aryl isocyanates giving intermediate 4-arylamino-5-acetylpyrimidin-2-one derivatives **157**, which are converted into pyrido[2,3-*d*]pyrimidines **158** under the reaction conditions.[179]



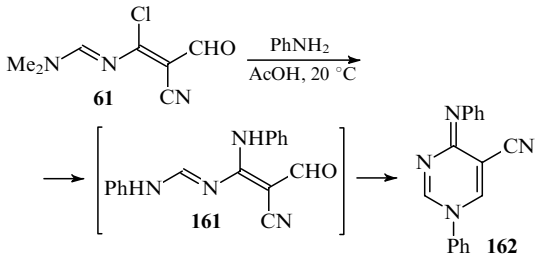
Pyrimidine derivatives **159** have been obtained as products of the reaction of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones with ketene aminals.[180,181]



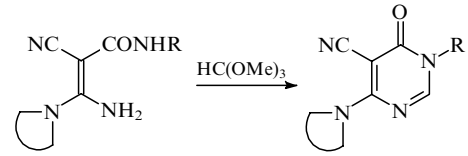
The ethoxycarbonyldicyanomethane salt **160** reacts with methyl 3-aminothiophene-2-carboxylate and amino acid esters to give ketene *N*,*N*-acetals which can undergo cyclisation into pyrimidine and thieno[3,2-*d*]pyrimidine derivatives.[142]



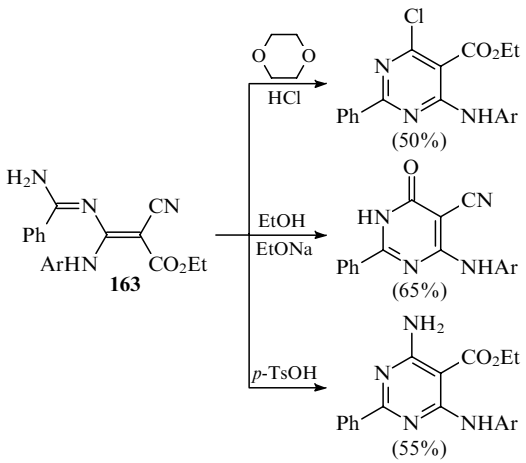
Compound **61** reacts with aniline in acetic acid to give the intermediate ketene aminal **161**, which then undergoes cyclisation into pyrimidinone imine **162**.[93]



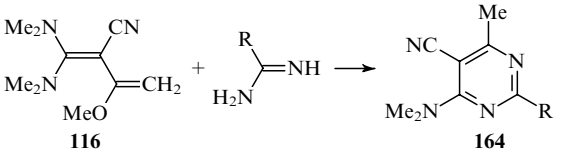
α,α-Diamino-β-carbamoyl-β-cyanoethylene derivatives are transformed on heating with methyl orthoformate to give substituted 4-amino-5-cyanopyrimidin-6-ones.[97]



Cyclisation of 'push-pull' enaminoamidines **163** under various conditions results in moderate yields of 6-amino-2-phenylpyrimidine derivatives.[20]

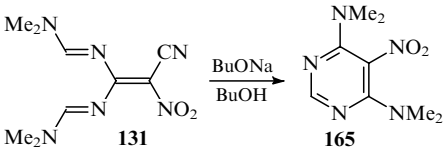


Alkoxydienediamines are also convenient starting compounds for pyrimidine synthesis.[70] For example, diamine **116** reacts with amidines to give substituted pyrimidines **164**.



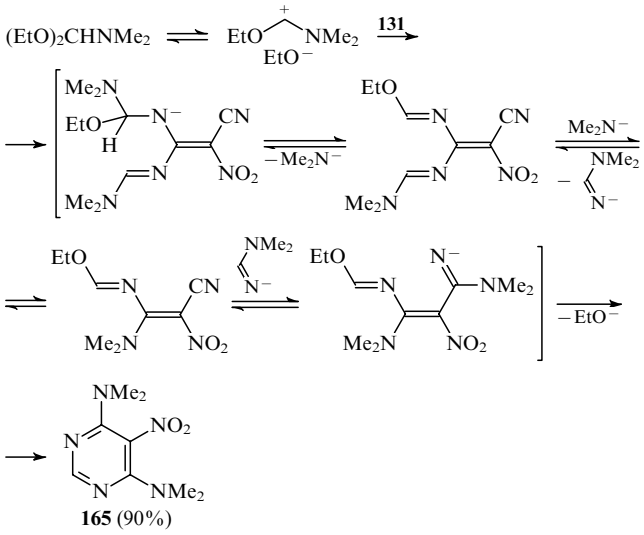
116 **164**

Finally, let us mention an unusual synthesis of 4,6-bis(dimethylamino)-5-nitropyrimidine **165** from diamidine **131**.[182]



131 **165**

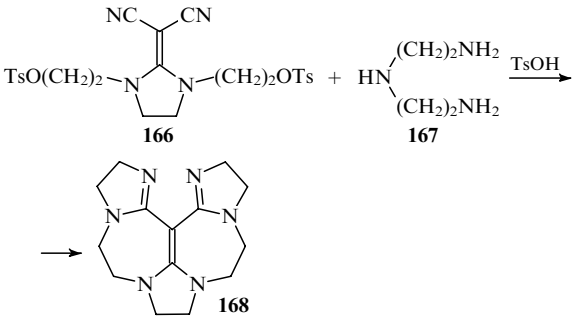
Compound **165** is also formed upon treatment of diamidine **131** with DMF diethyl acetal. The following scheme of this non-trivial transformation was suggested:[182]



165 (90%)

d. Seven-membered heterocycles

Simultaneous closure of five- and seven-membered heterocycles in the reaction of aminal **166** with triamine **167** to give compound **168** has been reported in a study[13] dealing with the synthesis of diazepine derivatives from ketene aminals.



166 **167** **168**

A different approach[19] to the synthesis of benzodiazepines has been considered in Section II.1.

IV. Conclusion

To sum up the data presented in this review, it can be stated that a fruitful direction based on the use of β,β-bifunctionally substituted ketene *N*,*N*-acetals in organic synthesis has been created by now. The preparative availability of these compounds and their high reactivity form considerable prospects for their application in the synthesis of diverse organic and especially heterocyclic systems that are of interest both in theoretical and practical aspects.

The authors are grateful to Dr. Christoph Hoock (BYK GULDEN, Germany) for his help in using the databases.

This review has been written with financial support of the Ministry of Science and Technology of Federal Republic of Germany [the project 'Transform' 01 KX9812 — Bundesministerium für Forschung und Technologie (BMFT)].

References

1. R K Dieter *Tetrahedron* **42** 3029 (1986)
2. H Junjappa, H Ila, C V Asokan *Tetrahedron* **46** 5423 (1990)
3. Y Tominaga, S Kohra, H Honkawa, A Hosomi *Heterocycles* **29** 1409 (1989)
4. H Takahata, T Yamazaki *Heterocycles* **27** 1953 (1988)
5. A V Komkov, Candidate Thesis in Chemical Sciences, Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, 1995
6. R Bazzen, W Schunak *Arch. Pharm.* **315** 680 (1982)
7. Y S Sanghvi, S B Larson, R K Robins, G R Revankar *J. Chem. Soc., Perkin Trans. 1* 2943 (1990)
8. J Sandstrom, K Stenvall, N Sen, K Venkatesan *J. Chem. Soc., Perkin Trans 2* 1939 (1985)
9. T Mosandi, C O Roppe, R Flammang *J. Chem. Soc., Chem. Commun.* 1571 (1992)
10. E Ericsson, J Sandstrom, J Wennerbeck *Acta Chem. Scand.* **24** 3102 (1970)
11. R Gompper, W Topfl *Chem. Ber.* **95** 2871 (1962)
12. H-T Wang, X-J Wang, Z-T Huang *Chem. Ber.* **123** 2141 (1990)
13. R Schwesinger, M Missfeldt, K Peters, H G Schnering *Angew. Chem.* **99** 1210 (1987)
14. A K El-Shafei, A M Soliman, A A R Sultan, A M M El-Saghier *Gazz. Chim. Ital.* **125** 115 (1989)
15. Y Tominaga, T Michioka, K Moriyama, A Hosomi *J. Heterocycl. Chem.* **27** 1217 (1990)
16. Y Kuwayama, S Kataoka *Yakugaku Zasshi* **85** 387 (1965); *Chem. Abstr.* **63** 8342 (1965)
17. S Sasho, H Obase, S Ichikawa, T Kitazawa, H Nonaka, R Yoshizaki, A Ishii, K Shuto *J. Med. Chem.* **36** 572 (1993)
18. W-D Rudorf *Tetrahedron* **36** 1791 (1980)
19. K Peseke *Tetrahedron* **32** 483 (1976)
20. C J Shishoo, M B Devani, V S Bhadti, S Ananthan, G V Ullas *Tetrahedron Lett.* **25** 1291 (1984)
21. C J Shishoo, M B Devani, V S Bhadti, S Ananthan, G V Ullas *J. Chem. Res. (M)* 3882 (1985)
22. V J Ram, N Hague, A Shoeb *J. Prakt. Chem.* **334** 190 (1992)
23. W-D Rudorf, M Augustin *J. Prakt. Chem.* **319** 545 (1977)
24. M Augustin, Ch Groth, H Kristen, K Peseke, Ch Wiechmann *J. Prakt. Chem.* **321** 205 (1979)
25. A B Cheikh, J Chuche, N Manisse, J C Pommelet, K-P Netsch, P Lorencak, C Wentrup *J. Org. Chem.* **56** 970 (1991)
26. US P. 4 075 001; *Chem. Abstr.* **88** 170 135 (1978)
27. BRD P. 2 423 813; *Chem. Abstr.* **82** 170 943 (1975)
28. Z-T Huang, X Shi *Synth. Commun.* **20** 1321 (1990)
29. X Huang, B Chen, G Wu, H Chen *Synth. Commun.* **21** 1213 (1991)
30. Z-T Huang, M-X Wang *Synthesis* 1273 (1992)
31. K Hartke, S Radau *Liebigs Ann. Chem.* 2110 (1974)
32. Y Tominaga, S Takada, S Kohra *Heterocycles* **40** 105 (1995)
33. X-J Wang, Z-T Huang *Acta Chim. Sinica* **47** 890 (1989); *Chem. Abstr.* **112** 198 216 (1990)
34. M Augustin, S Bielka *Z. Chem.* **20** 96 (1980)
35. M-X Wang, J-M Lvanjo, Z-T Huang *J. Chem. Res. (M)* 1001 (1994)
36. E Ericsson *J. Mol. Struct.* **24** 373 (1975)
37. Y Cheng, H-X Wang, W-X Gan, Z-T Huang *Synth. Commun.* **26** 475 (1996)
38. T Mosandl, S Stadtmueller, H W Wang, C Wentrup *J. Phys. Chem.* **98** 1080 (1994)
39. W-D Rudorf, J Koeditz, N Nenze, A Teraskian *Phosphorus Sulfur Silicon Relat. Elem.* **107** 87 (1995)
40. C-Y Yu, L B Wang, Z-T Huang *Synth. Commun.* **26** 2297 (1996)
41. R Gompper, R Kunz *Chem. Ber.* **99** 2900 (1966)
42. W Hanefeld, D Kluck *Arch. Pharm.* **315** 68 (1982)

43. L N Chernova, V D Simonov, Yu N Alyamkin, Z M Minnulin *Zh. Org. Khim.* **15** 512 (1979) [a]
44. N V Nguyen, K Baum *Tetrahedron Lett.* **33** 2949 (1992)
45. K Baum, S S Bigelow, N V Nguyen, T A Archibald, R Gilardi, J L George *J. Org. Chem.* **57** 235 (1992)
46. E Allenstein, R Fuchs *Chem. Ber.* **101** 1232 (1968)
47. W Middleton, V A Engelhardt *J. Am. Chem. Soc.* **80** 2788 (1958)
48. R Neidlein, D Kikely, W Kramer *J. Heterocycl. Chem.* **26** 1335 (1989)
49. D Martin, K-H Schwarz, S Rackow, P Reich, E Grundemann *Chem. Ber.* **99** 2302 (1966)
50. M I Kanishchev, N V Korneeva, S A Shevelev *Izv. Akad. Nauk SSSR, Ser. Khim.* 2342 (1986) [b]
51. S Rajappa, M P Nair, B G Advani, R Sreenivasan *J. Chem. Soc., Perkin Trans 1* 3161 (1981)
52. K Pilgram *J. Heterocycl. Chem.* **17** 1413 (1980)
53. Z-T Huang, L-H Tzai *Chem. Ber.* **119** 2208 (1968)
54. US P. 4 053 619; *Chem. Abstr.* **88** 37 798 (1978)
55. US P. 405 2411; *Chem. Abstr.* **88** 22 902 (1978)
56. L B Wang, C-Y Yu, Z-T Huang *Synth. Commun.* **25** 1353 (1995)
57. M A F Shoraf, E-E H M Eral H A A Hummonda *Phosphorus Sulfur Relat. Elem.* **92** 19 (1994)
58. E Ericsson, T Marnung, J Sandstrom, I Wennerbeck *Acta Chem. Scand.* **28** 1109 (1974)
59. S Mitamura, M Takaku, H Nozaki *Bull. Chem. Soc. Jpn.* **47** 3152 (1974)
60. M Yokoyama, K Arai, T Imamoto *J. Chem. Soc., Perkin Trans 1* 1059 (1982)
61. R M Mohareb, H Z Shoms, Y M Elkoly *Phosphorus Sulfur Relat. Elem.* **72** 93 (1992)
62. R G Gluschkov, V G Granik *Adv. Heterocycl. Chem.* **12** 185 (1970)
63. V G Granik *Usp. Khim.* **53** 651 (1984) [*Russ. Chem. Rev.* **53** 383 (1984)]
64. V G Granik *Khim. Geterotsikl. Soedin.* 762 (1992) [c]
65. W Ried, H-E Erle *Liebigs Ann. Chem.* 201 (1982)
66. H Bredereck, K Bredereck *Chem. Ber.* **94** 2278 (1961)
67. BRD P. 2 624 530; *Chem. Abstr.* **86** 189 967 (1977)
68. H Meerwein, W Florian, N Schon, G Stopp *Liebigs Ann. Chem.* **641** 1 (1961)
69. W Kantlehner, H Jaus, L Kienitz, H Bredereck *Liebigs Ann. Chem.* 2096 (1979)
70. W Kantlehner, I C Ivanov, W W Mergen, H Bredereck *Liebigs Ann. Chem.* 372 (1980)
71. W Kantlehner, W W Mergen *Synthesis* 343 (1979)
72. G Maas, B Feith *Synth. Commun.* **14** 1073 (1984)
73. B Feith, H M Weber, G Maas *Chem. Ber.* **119** 3276 (1986)
74. W Kantlehner, U Greiner *Liebigs Ann. Chem.* 965 (1990)
75. V A Dorokhov, M F Gordeev, E M Shashkova, A V Komkov, V S Bogdanov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2600 (1991) [b]
76. V A Dorokhov, M F Gordeev, V S Bogdanov, A L Leister, V V Semenov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2660 (1990) [b]
77. V A Dorokhov, M F Gordeev, Z K Dem'yanets, M N Bochkareva, V S Bogdanov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1806 (1989) [b]
78. V A Dorokhov, M F Gordeev, Z K Dem'yanets, V S Bogdanov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1683 (1987) [b]
79. V A Dorokhov, M F Gordeev, V S Bogdanov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1431 (1988) [b]
80. V A Dorokhov, Z K Dem'yanets *Izv. Akad. Nauk, Ser. Khim.* 419 (1993) [b]
81. A C Veronese, V Gandolji *J. Chem. Res. (M)* 1837 (1988)
82. S Trofimenko, E L Little, H F Mower *J. Org. Chem.* **27** 433 (1962)
83. J A Elvidge, P N Judson, A Pezeival, R Shah *J. Chem. Soc., Perkin Trans 1* 1741 (1983)
84. M Coennen, J Faust, C Ringel, R Mayer *J. Prakt. Chem.* **27** 239 (1965)
85. B B Gavrilenko, S I Miller *J. Org. Chem.* **40** 2720 (1975)
86. M H Elnagdi, S M Fahmy, E A A Hafez, M R H Elmoghayar, S A R Amer *J. Heterocycl. Chem.* **16** 1109 (1979)
87. N D Bodnarchuk, B B Gavrilenko, V V Momot *Zh. Org. Khim.* **9** 36 (1973) [a]
88. N D Bodnarchuk, A A Yatsishin *Zh. Org. Khim.* **13** 954 (1977) [a]
89. V P Kukhar', V I Pasternak, G V Pesotskaya *Zh. Org. Khim.* **9** 39 (1973) [a]
90. F Lautenschlaeger, M Myhre, F Hopton, J Wilson *J. Heterocycl. Chem.* **8** 241 (1971)
91. Y Masaki, T Miuro, M Ochiai *Bull. Chem. Soc. Jpn.* **69** 195 (1996)
92. E Allenstein *Chem. Ber.* **96** 3230 (1963)
93. K Klemm, W Prüsse, L Baron, E Daltrozzo *Chem. Ber.* **114** 2001 (1981)
94. H Mertens, R Troschutz *Arch. Pharm.* **319** 947 (1986)
95. T Yamazaki, K Matoba, T Imai, R N Castle *J. Heterocycl. Chem.* **16** 517 (1979)
96. T Sasaki, A Kojima *J. Chem. Soc., C* 476 (1970)
97. M T Cocco, C Congiu, A Maccioni, V Onnis *J. Heterocycl. Chem.* **31** 329 (1994)
98. S Rajappa, B G Advani, R Sreenivasan *Tetrahedron* **33** 1057 (1977)
99. S Rajappa, M D Nair, R Sreenivasan, B G Advani *Tetrahedron* **38** 1673 (1982)
100. Z-T Huang, Z-R Liu *Chem. Ber.* **122** 95 (1988)
101. G Dannhardt, S Laufer, K Ziereis *Arch. Pharm.* **321** 429 (1988)
102. J D Albiright, R G Shepherd *J. Heterocycl. Chem.* **10** 899 (1973)
103. E-S A H Badawey, S M Rida, F S G Soliman, T Kappe *J. Heterocycl. Chem.* **26** 405 (1989)
104. I V Zhvinchuk, M O Lozinskii, A V Vypiralenko *Zh. Org. Khim.* **30** 909 (1994) [a]
105. M D Nair, S Rajappa, J A Desai *Indian J. Chem.* **21B** 1 (1982)
106. H A Naik, V Purnaprajna, S Seshadri *Indian J. Chem.* **15B** 338 (1977)
107. J Bourson *Bull. Soc. Chim. Fr.* 2373 (1973)
108. J Bourson *Bull. Soc. Chim. Fr.* 525 (1974)
109. J Clark, J Gelling, G Neath *J. Chem. Soc., Chem. Commun.* 859 (1967)
110. J Clark, M Curphey, J W Southon *J. Chem. Soc., Perkin Trans 1* 1611 (1974)
111. J Clark, J Gelling, J W Southon, M S Morton *J. Chem. Soc., Perkin Trans 1* 494 (1970)
112. J Clark, B Parvizi, J W Southon *J. Chem. Soc., Perkin Trans 1* 125 (1976)
113. J Clark, B Parvizi, R Colman *J. Chem. Soc., Perkin Trans 1* 1004 (1976)
114. D St C Black, N E Rothinie *Aust. J. Chem.* **36** 2413 (1983)
115. V A Makarov, A L Sedov, M P Nemeryuk, N P Solov'eva, O S Anisimova, T S Safonova *Khim. Geterotsikl. Soedin.* 1420 (1994) [c]
116. M Winn *J. Org. Chem.* **40** 955 (1975)
117. V A Makarov, A L Sedov, M P Nemeryuk, N P Solov'eva, O S Anisimova, T S Safonova *Khim. Geterotsikl. Soedin.* 208 (1995) [c]
118. M P Nemeryuk, A L Sedov, V A Makarov, N P Solov'eva, T S Safonova *Khim. Geterotsikl. Soedin.* 999 (1991) [c]
119. V A Makarov, A L Sedov, O S Anisimova, V G Granik *Khim. Geterotsikl. Soedin.* 811 (1996) [c]
120. V A Makarov, A L Sedov, M P Nemeryuk, N P Solov'eva, T S Safonova *Khim. Geterotsikl. Soedin.* 976 (1994) [c]
121. I V Oleinik, O A Zagulyaev, O A Grigor'eva, V M Mamaev *Khim. Geterotsikl. Soedin.* 1110 (1991) [c]
122. W Hanefeld, B Spangenberg *Arch. Pharm.* **321** 253 (1988)
123. W Traube, A Eyme *Ber. Dtsch. Chem. Ges.* **32** 3176 (1899)
124. V E Tishchenko, N V Koshkin *Zh. Org. Khim.* **4** 1021 (1934) [a]
125. A Stephen *Monatsh. Chem.* **97** 695 (1966)
126. M Augustin, E Gunther *Z. Chem.* **30** 169 (1990)
127. R W Saalfrank, H Wirth *Chem. Ber.* **122** 969 (1989)
128. S Shi, F Wude *J. Org. Chem.* **53** 5379 (1988)
129. R W Saalfrank, R Harbig, O Struck, E M Peters, K Peters, H G von Schering *Z. Naturforsh. B, Chem. Sci.* **51** 399 (1996)
130. M Regitz, A Liedhegener, D Stadler *Liebigs Ann. Chem.* **713** 101 (1968)
131. T N Ghosh, D Das-Gupta *J. Indian Chem. Soc.* 41 (1942)
132. E Malamidou-Xenikaki *J. Chem. Soc., Perkin Trans 1* 2523 (1996)
133. J Sandstrom *Top. Stereochem.* **14** 83 (1983)
134. J Shvo, H Shanan-Atidi *J. Am. Chem. Soc.* **91** 6683 (1969)
135. J Shvo, H Shanan-Atidi *J. Am. Chem. Soc.* **91** 6689 (1969)
136. N P Kostyuchenko, V G Granik, A M Zhidkova, R G Glushkov, Yu N Sheinker *Khim. Geterotsikl. Soedin.*1212 (1974) [c]
137. U Sjostrand, J Sandstrom *Tetrahedron* **34** 3305 (1978)
138. G Isaksson, J Sandstrom *Tetrahedron Lett.* **24** 2233 (1967)

139. A Z-Q Khan, R Isaksson, J Sandstrom *J. Chem. Soc., Perkin Trans 2* 491 (1987)
140. R Gompper, R Kunz *Chem. Ber.* **98** 1391 (1965)
141. D A Long, W O George *Spectrochim. Acta* **20** 1799 (1964)
142. R Neidlein, Z Sui *Helv. Chim. Acta* **74** 579 (1991)
143. N P Solov'eva, V A Makarov, V G Granik *Khim. Geterotsikl. Soedin.* 89 (1997) [c]
144. J Sandstrom, U Sjostrand *Tetrahedron* 34 371 (1978)
145. A Z-Q Khan, J Sandstrom *J. Org. Chem.* **56** 1902 (1991)
146. G F Reynolds, A F Saari *J. Heterocycl. Chem.* **12** 295 (1975)
147. G F Reynolds, R Berber, W Boutwell *J. Heterocycl. Chem.* **9** 1009 (1972)
148. A P Katritskii (Ed.) *Fizicheskie Metody v Khimii Geterotsiklicheskikh Soedinenii* (Physical Methods in the Chemistry of Heterocyclic Compounds) (Moscow: Khimiya, 1966)
149. A A Yatsishin, N D Bodnarchuk *Zh. Org. Khim.* **15** 1381 (1979) [a]
150. K Baum, N V Nguyen, R Gilardi, J J Flippen-Anderson, C George *J. Org. Chem.* **57** 3026 (1992)
151. D G Glover, M J Kramer *J. Org. Chem.* **26** 4734 (1961)
152. M J G Trmino, A Linden, H Heimgarther, A M Cabrera *Helv. Chim. Acta* **76** 2817 (1993)
153. K Peseke *Z. Chem.* **15** 146 (1975)
154. V A Dorokhov, M F Gordeev, A V Komkov, V S Bogdanov *Izv. Akad. Nauk SSSR, Ser. Khim.* 401 (1990) [b]
155. W Ried, K Schlpke *Liebigs Ann. Chem.* 389 (1986)
156. V G Granik, V N Dozorova, N B Marchenko, L I Budanova, V A Kuzovkin, R G Glushkov *Khim.-Farmatsevt. Zh.* 1249 (1987)
157. C Schmidt, K Polborn, W Beck *Chem. Ber.* **125** 61 (1992)
158. V A Dorokhov, M F Gordeev, M N Bochkareva, M G Kurella, L G Vorontsova, S V L'vov, O S Chizhov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1134 (1989) [b]
159. V A Dorokhov, M F Gordeev *Izv. Akad. Nauk SSSR, Ser. Khim.* 1211 (1989) [b]
160. V A Dorokhov, M F Gordeev, A V Komkov, V S Bogdanov *Izv. Akad. Nauk SSSR, Ser. Khim.* 159 (1991) [b]
161. V A Dorokhov, M A Prezent *Izv. Akad. Nauk, Ser. Khim.* 888 (1994) [b]
162. V A Dorokhov, M A Prezent, V S Bogdanov *Izv. Akad. Nauk, Ser. Khim.* 2211 (1994) [b]
163. V A Dorokhov, M A Prezent *Izv. Akad. Nauk, Ser. Khim.* 1504 (1993) [b]
164. V A Dorokhov, M A Prezent, V S Bogdanov *Izv. Akad. Nauk, Ser. Khim.* 1638 (1994) [b]
165. V A Dorokhov, M F Gordeev, M A Prezent *Izv. Akad. Nauk SSSR, Ser. Khim.* 525 (1991) [b]
166. V A Dorokhov, A V Komkov, A M Sakharov, V S Bogdanov *Izv. Akad. Nauk, Ser. Khim.* 177 (1996) [b]
167. V G Granik, N B Marchenko, E O Sochneva, T F Vlasova, A B Grigor'ev, M K Polievktov, R G Glushkov *Khim. Geterotsikl. Soedin.* 1506 (1976) [c]
168. V G Granik, Doctoral Thesis in Chemical Sciences, All-Union Research Chemical Pharmacological Institute, Moscow 1978
169. W D Rudorf, M Augustin *J. Prakt. Chem.* **320** 585 (1978)
170. V A Makarov, O S Anisimova, V G Granik *Khim. Geterotsikl. Soedin.* 329 (1997) [c]
171. N D Bodnarchuk, A A Yatsishin *Zh. Org. Khim.* **13** 2432 (1977)
172. R Neidlein, Z Sui *Chem. Ber.* **123** 2203 (1990)
173. V A Dorokhov, M F Gordeev *Izv. Akad. Nauk SSSR, Ser. Khim.* 2874 (1989) [b]
174. V A Dorokhov, V S Bogdanov, M F Gordeev *Izv. Akad. Nauk SSSR, Ser. Khim.* 2874 (1989) [b]
175. V A Dorokhov, M F Gordeev, A V Komkov, V S Bogdanov *Izv. AN SSSR. Ser. khim.* 145 (1990)
176. V A Dorokhov, M F Gordeev, A V Komkov, V S Bogdanov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2593 (1991) [b]
177. H Wamhoff, W Lamers *Synthesis* 111 (1993)
178. V A Dorokhov, A V Komkov, E M Shashkova, V S Bogdanov, M N Bochkareva *Izv. Akad. Nauk, Ser. Khim.* 1932 (1993) [b]
179. M F Gordeev, A V Komkov, V A Dorokhov *Khim. Geterotsikl. Soedin.* 1286 (1990) [c]
180. V L Gein, S G Pitirimova, O V Vinokurova, Yu S Andreichikov, A V Komkov, V S Bogdanov, V A Dorokhov *Izv. Akad. Nauk, Ser. Khim.* 1475 (1994) [b]
181. V L Gein, S G Pitirimova, Yu S Andreichikov, M F Gordeev, V S Bogdanov, V A Dorokhov *Izv. Akad. Nauk, Ser. Khim.* 1225 (1992) [b]
182. V A Makarov, V A Tafeenko, V G Granik *Khim. Geterotsikl. Soedin.* 343 (1997) [c]

[a] —*Russ. J. Org. Chem. (Engl. Transl.)*
[b] — *Russ. Chem. Bull. (Engl. Transl.)*
[c] — *Chem. Heterocycl. Conpd. (Engl. Transl.)*
[d] — *Pharm. Chem. J. (Engl. Transl.)*