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Methods of synthesis of conjugated ω-amino ketones

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Contents

I. Introduction 1021
II. Methods of synthesis of β-aminovinyl ketones, δ-amino dienones and α,α′-bis(3-aminopropenylidene)alkanones 1021
III. Conjugated ω-amino polyenones 1032
IV. Conjugated ω-amino ketones containing a heterocyclic fragment 1034

Abstract. The published data on the synthesis of β-enamino ketones, δ-amino dienones and conjugated ω-amino polyenones of diverse structures are generalised. The bibliography includes 129 references.

I. Introduction

Conjugated ω-amino ketones represent an ample class of organic compounds which attract the attention of a broad circle of organic chemists, biochemists, physicochemists, *etc*. Owing to their high reactivities, these compounds find application in the synthesis of various biologically active heterocyclic systems, natural compounds, dyes and photosensitive materials.

The presence in ω-amino ketones of an electron-donating and an electron-withdrawing group separated by conjugated double bonds imparts to them specific properties and makes them perfect models for the study of fundamental problems, such as the nature of chemical bonds, electron transfer along the conjugation chain, chromaticity, sensitivity to the action of different kinds of energy, tautomerism, *cis* – *trans*-isomerism, *etc*.

The methods employed in the synthesis of β-aminovinyl ketones (AVK) have been generalised in reviews [1,2] and the monograph by Freimanis.[3] Several novel versions of conventional reactions which make it possible to increase the yields of the target products and to simplify the synthetic procedures have been proposed recently. The approaches to regio- and stereospecific synthesis of enamino ketones containing additional functional groups are being developed intensively. The most practicable methods for the synthesis of AVK and those based on unusual chemical conversions are considered in this review. Special attention is given to conjugated ω-amino polyenones prepared with the help of procedures developed in recent years. These compounds include α,α′-bis(ω-aminopolyenyl)alkanones, which contain two polymethine chains linked through a carbonyl group and manifest unusual spectral and luminescent properties.

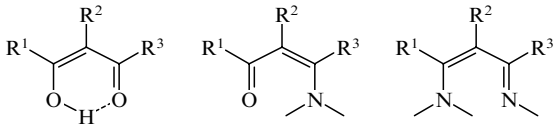
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II. Methods of synthesis of β-aminovinyl ketones, δ-amino dienones and α,α′-bis(3-aminopropenylidene)alkanones

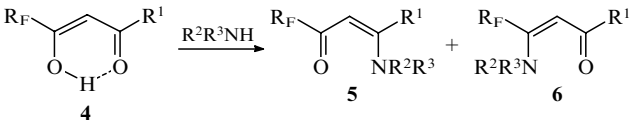
1. Reactions of β-diketones with amines

Condensation of readily accessible β-diketones with ammonia and amines is a traditional approach to the synthesis of β-aminovinyl ketones.[1–8] The starting diketone reacts in both diketo- and keto-enol forms. This reaction is usually carried out by boiling β-diketone – amine mixtures in solvents (*e.g.*, benzene, toluene) which allow removal of the water formed.[4–7] In the reaction of non-symmetrical β-diketones **1** ($R^1 \neq R^3$), one or both regioisomeric AVK **2**, β-aminovinylimine **3** or their mixture can be formed due to the non-equivalence of the electrophilic centres C(1) and C(2).[1,3,6–8]



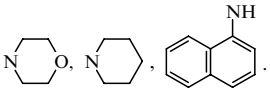
1 **2** **3**

The difference in the reactivities of the electrophilic centres C(1) and C(3) is especially pronounced in the case of non-symmetrical polyfluorinated β-diketones **4** due to the difference in the inductive effects of the substituents R_F and R^1 (Refs 6–8). Polyfluorinated β-diketones **4** react with ammonia and amines at only one of the electrophilic centres to give fluorine-containing AVK **5**.[6–8]



4 **5** **6**

R_F = CF_3, $H(CF_2)_2$, $H(CF_2)_4$; R^1 = Me, Bu^n, Bu^t, Ph, C_6H_4Cl, C_6H_4Br, $C_6H_4NO_2$, C_5H_4Me, C_6H_4OMe; R^2R^3N = NH_2, NHPh, NHMe,

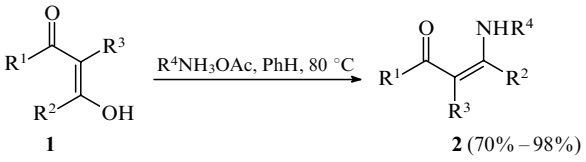


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It is of note that the condensation of arylfluoroalkyl diketones **4** with NH_3, NH_2Me and NH_2Ph affords a mixture of regioisomeric AVK **5** and **6**; the proportion of the isomer **6** with a geminal amino group and the fluoroalkyl residue depends on the length of the fluoroalkyl substituent and the nature of substituents in the amine.[7,8] This reaction is carried out with azeotropic distillation of the water eliminated. In the case of low-boiling amines, this reaction is difficult to perform, since this requires repeated

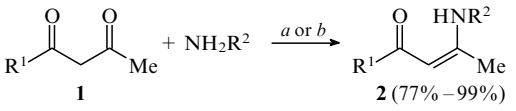
bubbling of the amine into the reaction mixture for the reaction to complete.[4,6,7,9] This reaction is also accompanied by scission of the β-diketones at the C(1)—C(2) bond and by secondary condensations.[1,8] Therefore, modifications of the process [10–14] which exclude the formation of by-products, increase the selectivity and simplify the procedure are of special interest.

Thus, a method for the synthesis of AVK **2** was proposed which includes boiling 1,3-diketones with ammonium acetate or acetates of low-boiling amines in benzene in the presence of AcOH; the water formed is removed by azeotropic distillation.[10]



R^1 = Me, Ph; R^2 = Me; R^3 = H, $CH_2CH=CH_2$; R^2-R^3 = $(CH_2)_3$, $CH_2CH(Me)CH_2$; R^4 = H, Et.

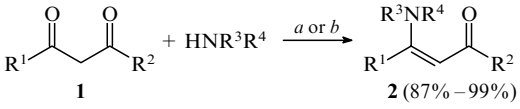
Satisfactory results were obtained in the condensation of methyl diketones with primary amines on inorganic supports.[11,12] Under heterogenous conditions, the reactions proceed with higher selectivities and under milder conditions than the corresponding homogenous reactions.



R^1 = Me, Ph; R^2 = H, Me, Et, Bu^t, Pr^i, Ph, Bn, CH_2CN; (*a*) Al_2O_3; (*b*) montmorillonite K10.

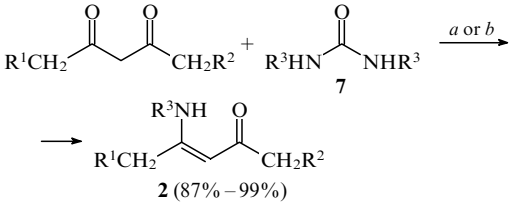
Neutral alumina or montmorillonite K10 can be used as solid supports. The reagents must be completely adsorbed on the support. This procedure is extremely simple as regards its implementation. To isolate enamino ketones **2**, the reaction mixture is diluted with CH_2Cl_2, the solid phase is filtered off, the solvent is removed *in vacuo* and the residue is subjected to distillation. In reactions with acetyl acetone (**1**, R^1 = Me), primary amines can be used as aqueous solutions, which is especially important in the case of low-boiling amines.[12]

If heterogenous reactions are carried out in a microwave (MW) oven,[13,14] the reaction time decreases from 24 h to 1–20 min. Both primary and secondary amines can be introduced into the reaction.[13]



R^1 = R^2 = Ph, R^3-R^4 = $(CH_2)_4$, $(CH_2)_5$; R^1 = Me, R^2 = Ph, OMe; R^3-R^4 = $(CH_2)_4$; (*a*) SiO_2, MW, 1–20 min; (*b*) montmorillonite K10, MW, 1–20 min.

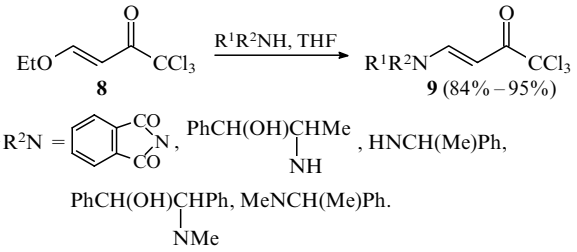
It was shown [13] that primary amines yield acyclic AVK **2** with *Z*-configuration of the α,β-double bond. The use of symmetrical disubstituted ureas **7** [14] instead of amines also results in AVK **2** having a *Z*-configuration of the double bond and stabilised by an intramolecular hydrogen bond.



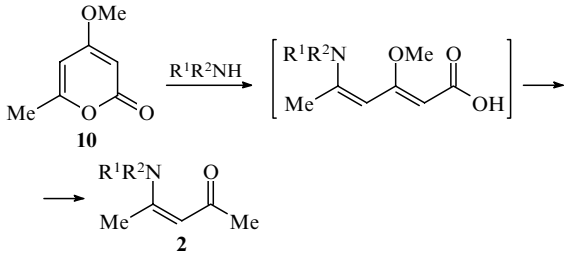
R^1 = R^2 = Me, Ph; R^3 = H, Me, Et, Ph; (*a*) SiO_2, MW, 1–20 min; (*b*) montmorillonite K10, MW, 1–20 min.

2. Reactions of unsaturated alkoxy ketones with amines

The alkoxy group in readily accessible β-alkoxyvinyl ketones **8** [15–18] is exchanged for an amino group upon reactions with ammonia and primary and secondary amines.[3,18–22] This reaction is widely employed in the synthesis of halogen-containing AVK **9**.[18–22] As a rule, the reaction of amines with β-alkoxyvinyl ketones proceeds at room temperature or with gentle heating and results in high yields of AVK **9** even in the case of sterically hindered amines.[15,19–22]



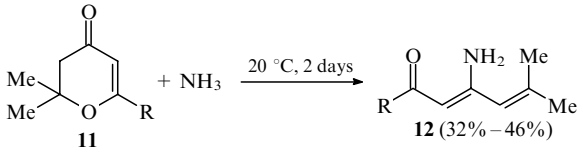
The reactions of alkoxy-substituted 2*H*- and 4*H*-pyrones with amines also belong to this type of transformations.[3,23–25] Thus prolonged boiling of 6-methyl-4-methoxy-2-pyrone **10** with amines in the absence of solvents resulted in the formation of AVK **2**.[24] The details of these experiments have not been reported.



R^1 = H; R^2 = C_7H_{15}; R^1-R^2 = $(CH_2)_4$.

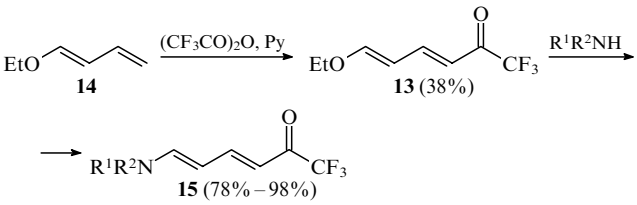
It is believed [24] that AVK **2** are formed as a result of an attack by the amine at position 6 of the pyrone ring with subsequent decarboxylation and hydrolysis of the diacetoacetic acid derivative.

Treatment of dihydropyrones **11** with aqueous or methanolic ammonia gives amino dienones **12**.[25]



R = CF_3, CCl_3.

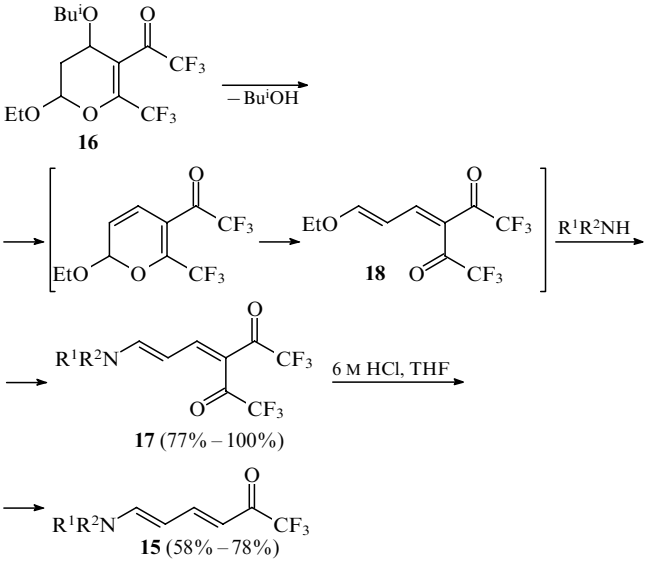
δ-Alkoxy hexadienone **13** obtained by the acylation of 1-ethoxybuta-1,3-diene (**14**) with trifluoroacetic anhydride reacts with amines much like β-alkoxyvinyl ketones.[26] The alkoxy group in the dienone **13** is readily exchanged for an amino group to give δ-amino dienones **15**.



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

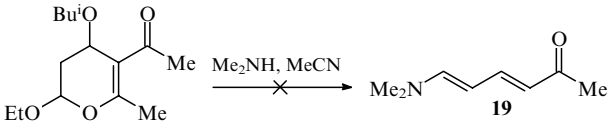
δ-Amino dienones **15** were also prepared [27] from 3,4-dihydro-2*H*-pyran derivative **16**. Compound **16** reacts with various aliphatic and aromatic amines to give substituted diketones **17**. Presumably,[27] the putative mechanism of this reaction involves

ethoxy-substituted dienedione **18** as an intermediate. Acid hydrolysis of diketones **17** with aliphatic substituents at the nitrogen atom results in δ-amino dienones **15**. Diketones **17** with aromatic substituents at the nitrogen atom do not undergo deacetylation under conditions of acid hydrolysis.



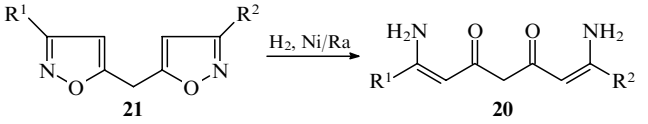
$R^1 = R^2 =$ Me, Et, Bn; R^1 = Me, R^2 = Ph; $R^1 - R^2 = (CH_2)_4$, $(CH_2)_5$.

Non-fluorinated derivatives of 3,4-dihydro-2*H*-pyran do not react with amines. An attempt to apply this approach to the synthesis of 6-dimethylaminohexa-3,5-dien-2-one (**19**) was unsuccessful.[27]



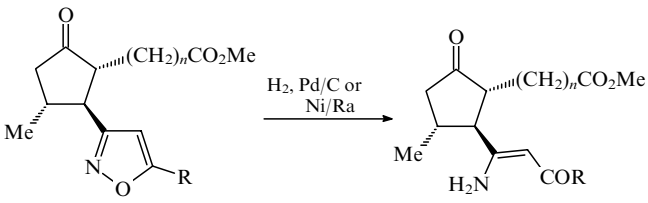
3. Reductive cleavage of isoxazoles

Reductive cleavage of the isoxazole ring under conditions of catalytic hydrogenation is one of the most well-studied and widely employed procedures for the preparation of enamino ketones.[28–31] Diaminodivinyl diketones **20** were obtained by the reduction of the diisoxazolylmethane derivatives **21** in the presence of Raney nickel (Ni/Ra).



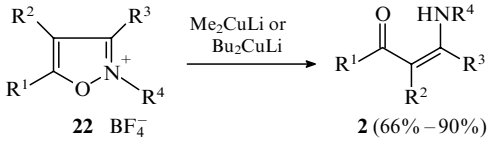
$R^1 = R^2 =$ Me, Ph; R^1 = Ph, R^2 = Me.

Catalytic hydrogenation of isoxazoles affords enamino ketones selectively, other functional groups of the starting compounds are not affected.[31]



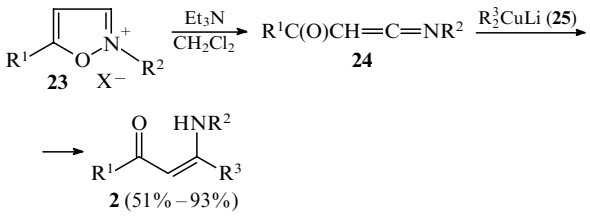
n = 3, 5; R = C_5H_{11}, $CH_2OC_6H_4F$-2.

The enamino ketones **2** were obtained in good yields by reductive cleavage of 3,4,5-substituted isoxazolium salts **22** with lithium dialkyl cuprates generated *in situ* from methyl- or butyllithium and copper iodide.[32] This reaction proceeds very quickly and under very mild conditions (−20 °C, 15 min) and affords enamino ketones **2** with different (including functional) substituents in the α-position.[32]



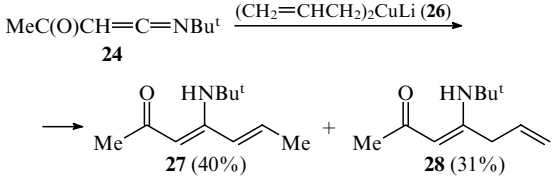
$R^1 = R^3 = R^4$ = Me, Ph; R^2 = H, Br, Cl, COPh, COMe, CO_2Et, CN, NO_2.

More readily accessible 5-substituted isoxazolium salts **23** do not react with lithium cuprates. In this case, preliminary treatment with triethylamine resulting in oxo ketene imines **24** is required. The reactions of the latter with organocuprates **25** afford AVK **2**, simultaneously a substituent is introduced into the β-position of the AVK formed.[33]



X = ClO_4, BF_4; R^1 = Me, Ph; R^2 = Bu^t, Et; R^3 = Me, Bu^n, Bu^t, Ph.

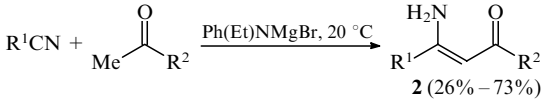
The reaction of oxo ketene imine **24** (R^1 = Me, R^2 = Bu^t) with lithium diallyl cuprate (**26**) leads to the isomerisation of the allyl group into the propenyl group to yield a mixture of enamino ketones **27** and **28** containing conjugated and isolated double bonds.



4. Condensation of acid nitriles with methyl ketones

Until recently, information concerning the synthesis of AVK by condensation of nitriles with ketones was scarce.[3,34] A method for the synthesis of enamino ketones containing a primary amino group from nitriles and methyl ketones has been developed in the last few years where (phenyl)ethylaminomagnesium bromide is used as a condensing reagent. This procedure affords enamino ketones of various structures, which are difficult to prepare by other methods.[35,36]

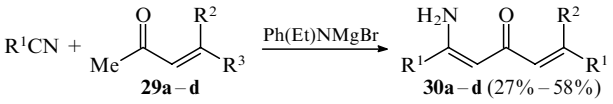
The yields of enamino ketones depend on the nature of substituents in the starting compounds. The best results were obtained in the reaction of trichloroacetonitrile with aryl(hetaryl) methyl ketones and *tert*-alkyl methyl ketones with acid nitriles containing electron-withdrawing aromatic substituents.[36]



R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
Ph	Bu^t	48	$PhOCH_2$	Bu^t	48
4-$MeOC_6H_4$	Bu^t	26	CCl_3	Bu^t	58
4-BrC_6H_4	Bu^t	80		Pr^i	34
				Ph	73
	Bu^t	60			71
Bn	Bu^t	54			

The presence of a double bond [37] or a functional group [38–46] in the molecule of a methyl ketone does not prevent the reaction with nitriles, the cyano group of which is activated by a polyhalogenoalkyl substituent, which makes it possible to synthesise enamino ketones containing several functional groups.

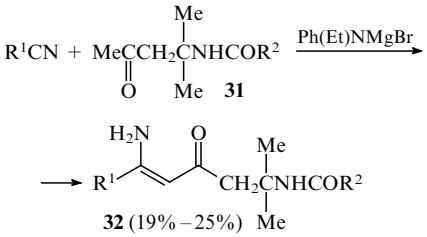
Thus the reaction of trichloro- and trifluoroacetonitriles with α,β-unsaturated ketones **29a–d** results in β-aminodivinyl ketones **30a–d**.[37]



29a–d **30a–d** (27%–58%)

R^1 = CCl_3, CF_3; R^2 = R^3 = Me (**a**); R^2 = H: R^3 = Ph (**b**), 4-$MeOC_6H_4$ (**c**),  (**d**).

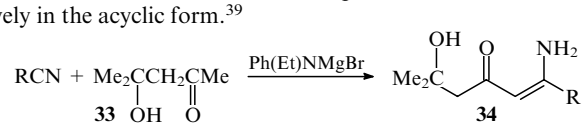
The condensation of β-acylaminoalkyl methyl ketones **31** with halogenoacetonitriles gives AVK **32**.[38] This is the first example of the involvement of β-acylaminoalkyl methyl ketones as a methylene component in aldol-type reactions.



31 **32** (19%–25%)

R^1 = CCl_3, CF_3; R^2 = Me, Ph.

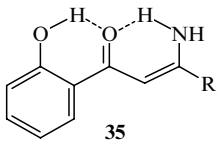
The reaction of trichloro- and trifluoroacetonitrile with the so-called diacetone alcohol **33** proceeds as nucleophilic addition to the nitrile group and yields β-aminovinyl β′-hydroxyalkyl ketones **34**; the latter are stable compounds, which occur exclusively in the acyclic form.[39]



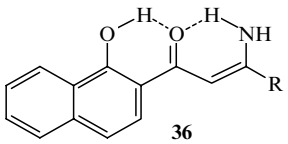
33 **34**

R = CCl_3, CF_3.

The condensation of trichloro- or trifluoroacetonitrile with 2-hydroxyacetophenone [39] and 2-acetyl-1-naphthol [40] gives the corresponding hydroxy enamino ketones **35** and **36**, which occur as *Z*-isomers with a coplanar *s-cis*-configuration stabilised by intramolecular hydrogen bonds.



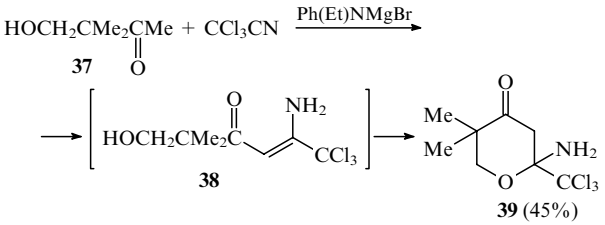
35



36

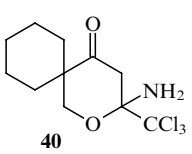
R = CCl_3, CF_3.

On going to sterically hindered β-hydroxyalkyl methyl ketones, the structures of the reaction products depend on the nature of the halogen in the halogenoacetonitrile.[41,42] Thus the reaction of trichloroacetonitrile with 4-hydroxy-3,3-dimethylbutan-2-one (**37**) is not stopped in the formation of an open form of the hydroxy enamino ketone **38**; its spontaneous cyclisation yields tetrahydropyranone **39**.[41]

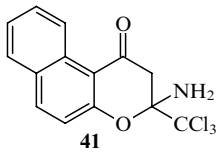


37 **38** **39** (45%)

The condensation of trichloroacetonitrile with 1-acetyl-1-hydroxymethylcyclohexane [41] and 1-acetyl-2-naphthol [40] proceeds similarly to give the cyclic products **40** and **41**. Acyclic forms were absent in both cases.

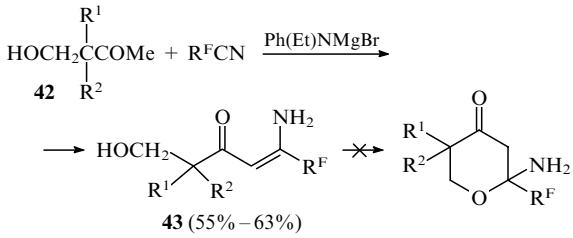


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41

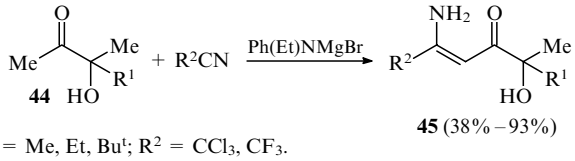
The reactions of polyfluorocarboxylic acid nitriles with sterically hindered β-hydroxyalkyl ketones **42** under the same conditions afford hydroxy enamino ketones **43** as the final products; the latter are stable on storage and do not cyclise spontaneously into tetrahydropyrones.[42]



42 **43** (55%–63%)

R^1 = R^2 = Me, R^1–R^2 = $(CH_2)_5$; R^F = CF_3, $(CF_2)_2H$.

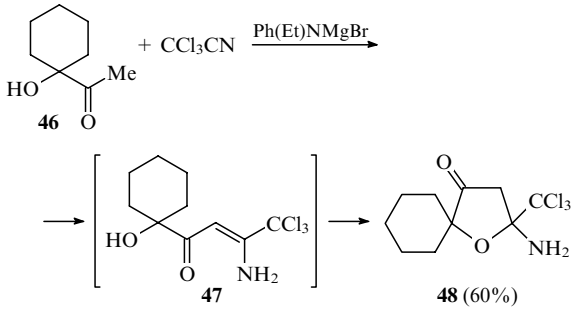
The reaction of trichloro- and trifluoroacetonitrile with acyclic hydroxyalkyl ketones **44** in the presence of (phenyl)ethylaminomagnesium bromide results in the corresponding hydroxy enamino ketones **45**.[43,44]



44 **45** (38%–93%)

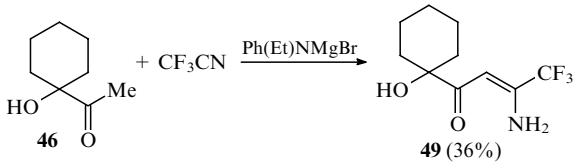
R^1 = Me, Et, Bu^t; R^2 = CCl_3, CF_3.

As in the case of sterically hindered β-hydroxyalkyl methyl ketones, the structures of the products formed in the reactions of nitriles with sterically hindered α-hydroxyalkyl methyl ketones depend on the nature of the halogen which activates the cyano group.[45,46] Thus the condensation of 1-acetylcyclohexan-1-ol (**46**) with trichloroacetonitrile does not afford α-hydroxy enamino ketone **47** as might be expected, but rather gives its cyclic isomer **48**.[45]



46 **47** **48** (60%)

The condensation of α-hydroxy ketone **46** with trifluoroacetonitrile results in α-hydroxy enamino ketone **49** with a geminal amino group and the trifluoromethyl substituent.[46]



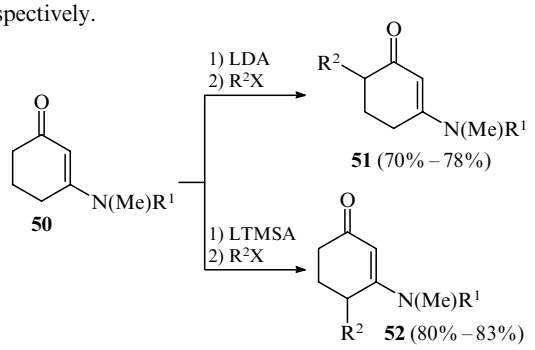
46 **49** (36%)

5. Modification of β-aminovinyl ketones based on the use of their lithium salts

Enamino ketones containing other functional groups in addition to the aminoenone group cannot be prepared in the majority of cases using traditional methods.[2,3,19,21,31–33] Therefore, procedures based on directed introduction of functional groups into more readily accessible AVK acquire special importance. The use of *N*,α′- and *N*,γ-dilithium salts of AVK in reactions with electrophiles is an example of a successful application of synthetic approaches to regio-controlled introduction of functional groups into AVK.

Studies of reactivities of *N*,α′- and *N*,γ-dilithium derivatives with respect to various electrophiles have shown that these are convenient starting compounds for the synthesis of heterocyclic compounds and for the introduction of functional groups into the α′- and γ-positions of AVK.[47–58]

The alkylation of cyclic AVK **50** is the first example of such an approach.[47] It was shown that depending on conditions of preparation of lithium salts (*viz*., the reagent ratios, the nature of a base, temperature), the alkylation predominantly occurs either at position 6 or at position 4 to give the AVK derivatives **51** or **52**, respectively.

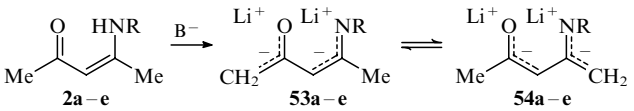


R^1 = Me, C_6H_{11}; R^2 = Bn, Me; X = I, Br; LDA is lithium *N*,*N*-diisopropylamide; LTMSA is lithium bis(trimethylsilyl)amide.

Treatment of the enamino ketone **50** with lithium *N*,*N*-diisopropylamide (LDA) in ether or THF at −78 °C results in deprotonation of the α′-position to afford a kinetically more favourable dianion (termed an α′-dianion); its alkylation gives rise to the cyclic AVK **51**. Deprotonation of the γ-position which gives a thermodynamically more favourable dianion (termed a γ-dianion) occurs upon treatment of compound **50** with lithium bis(trimethylsilyl)amide (LTMSA). Subsequent alkylation results in a practically exclusive formation of AVK **52**.[47] However, this approach could not be used for the alkylation of acyclic AVK, since it gave a mixture of alkylation products irrespective of the base used.[47]

The conditions favouring the preparation of α′- or γ-dilithium derivatives from acyclic β-(*N*-monoalkylamino)vinyl ketones and the factors influencing the regioselectivity of their formation have been studied in detail.[48,49]

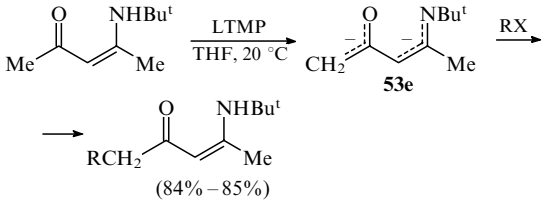
Treatment of 4-(*N*-alkylamino)pent-3-enones **2a–e** with an excess of a strong base (2.5 equiv., THF) gives both α′- (**53**) and γ-dilithium derivatives **54** which exist in a dynamic equilibrium (see Ref. 48).†



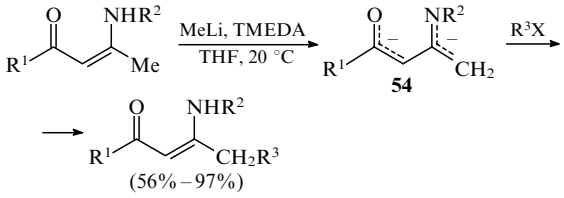
R = Me (**a**), Pr^i (**b**), cyclo-C_6H_{11} (**c**), PhCHMe (**d**), Bu^t (**e**).

Depending on the strength of the base and the substituent R in the starting compound (AVK **2**), the equilibrium can be practically completely shifted towards one of the dianions.[48–51] The α′-dianion **53** which is predominantly formed upon treatment of AVK **2** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) is kinetically more favourable. Thermodynamic calculations demonstrate that under these conditions the conformation of the α′-dianion **53** prevents its isomerisation into a thermodynamically more stable γ-dianion **54**.[48] It should be noted that the regiospecificity of formation of the α′-dianion **53** depends on the size of the substituent at the nitrogen atom. The predominant formation of the α′-dianion **53** is observed only in the case of bulky substituents, such as Bu^t and Ph.[49,51] In the presence of less bulky substituents (R = Me, Pr^i) the γ-dianion **54** is formed together with the α′-dianion **53**.[51] The predominant formation of a thermodynamically more favourable γ-dianion **54** takes place under the action of a stronger base, *viz*., methyllithium, in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Under these conditions, the α′-dianion which is formed first adopts a conformation which allows its rapid isomerisation into a more stable γ-dianion **54**.[48,51] The size of a substituent at the nitrogen atom does not influence the regiospecificity of formation of the γ-dianion **54**.[48] The dianions **53** and **54** can also be prepared from enamino ketones with secondary amino groups.[48–50,54,58]

The reactions of the dianions **53** and **54** with electrophiles proceed at low temperatures (−100 to −20 °C) and take as a rule from 5 min to 2 h. The alkylation of dianions of the type **53** and **54** afforded the corresponding α′- and γ-alkyl-substituted AVK in good yields. It is noteworthy that this reaction proceeds as C-alkylation and does not affect the primary amino group.[48,52]



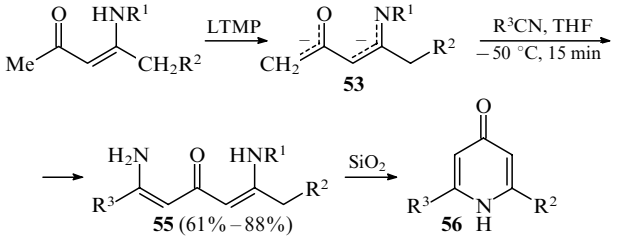
R = Me, Bn; X = Br, I.



R^1 = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; R^2 = Me, Pr^i, Bu^t; R^3 = Me, Et, Pr^i, Bn, n-$C_{10}H_{23}$, $CH_2CH=CH_2$; $CH_2C\equiv CH$; X = Cl, Br, I.

In addition to alkyl halides, allyl and propargyl bromides can be used as alkylating agents.[52]

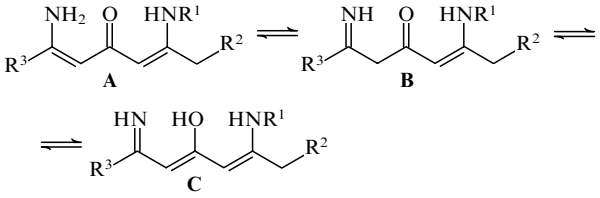
α′-Dianions of the type **53** react smoothly with nitriles under mild conditions to give bis(aminovinyl) ketones **55**. During chromatography on SiO_2, compounds **55** are partly converted into 4-pyridones **56**. This reaction is quantitative when solutions of enamino ketones are kept over SiO_2 for 2 days.[50]



R^1 = Pr^i, Ph; R^2 = Et, Bn, H; R^3 = Ph, Bu^n, 2-ClC_6H_4.

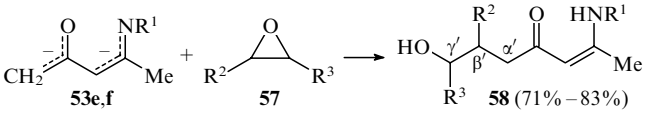
† Hereinafter, for convenience sake we shall refer to the dilithium derivatives **53** and **54** as dianions and omit Li cations in the structural formulae.

According to ^1H and ^{13}C NMR and X-ray diffraction data, compounds **55** exist in both solutions and crystalline state as tautomers **A** containing two enamine fragments, but not as oxo- (**B**) or hydroxy imines (**C**).[50]

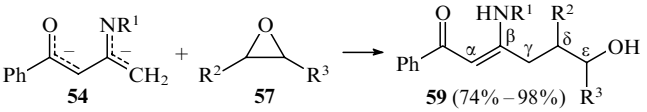


Hydroxy derivatives of enamino ketones were obtained in the reaction of α′- (**53**) or γ-dianions (**54**) with oxiranes,[49] aldehydes, ketones [51, 53] and esters.[54]

The reaction of dianions of the type **53** and **54** with oxiranes **57** is accompanied by the opening of the epoxide ring to give the corresponding γ′- or ε-hydroxy derivatives **58** and **59**. This reaction proceeds as bimolecular S_N2 nucleophilic substitution; non-symmetrical epoxides react at the least substituted carbon atom. The opening of the epoxide ring occurs in a stereo- and regioselective manner resulting in only one of the possible isomers.[49]

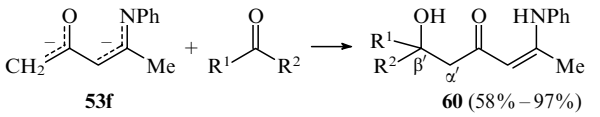


R^1 = Bu^t (**53e**), Ph (**53f**); R^2 = H: R^3 = H, Me, Et, Bu, Ph; R^2-R^3 = $(CH_2)_4$.



R^1 = Me, Bu; R^2 = H, Ph, Me_3Si; R^3 = H, Me, Et, CH_2Cl; R^2-R^3 = $(CH_2)_4$.

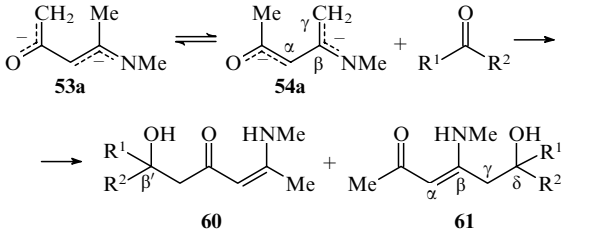
The condensation of the α′-dianion **53f** with aldehydes and ketones was used to obtain β-aminovinyl β′-hydroxy alkyl ketones **60**.[51] Like aminovinyl β′-hydroxyalkyl ketones **34**, these are stable in the acyclic form.



R^1 = H, Me, Ph; R^2 = Me, Pr, Bu^t, n-C_6H_{13}, Ph, $(CH_2)_2Ph$.

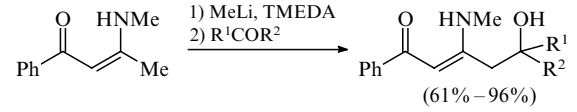
Compounds **60** are produced in high yields even if sterically hindered aldehydes and ketones (trimethylacetaldehyde or benzophenone) and enolisable ketones (*e.g.*, acetophenone) are introduced into the reaction.

In contrast to the α′-dianion **53f**, the condensation of the γ-dianion **54a** with aldehydes and ketones is non-regiospecific and results in the formation of both δ- (**60**) and β′-hydroxyenamino ketones (**61**).[51]



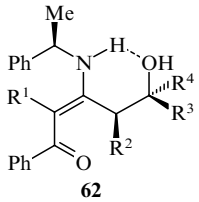
R^1 = H, Me, Ph; R^2 = Me, Pr^n, Bu^t, n-C_6H_{13}, Ph, $(CH_2)_2Ph$, CH=CHPh.

Presumably,[48, 51] the attack of bulky electrophiles, such as carbonyl compounds, at the sterically hindered γ-position of the γ-dianion **54a** which exists in the *syn*-conformation proceeds with great difficulty. However, owing to the presence in the reaction mixture of a small amount of a more reactive α′-dianion **53a** the latter reacts with carbonyl compounds much faster to give a β′-hydroxy derivative, which is accumulated in the mixture due to rapid isomerisation of the anion **54a.** This suggestion is corroborated by the fact that the yield of the undesirable β′-hydroxy ketone **60** increases in the case of sterically more hindered ketones, *e.g.*, benzophenone.[51] Its formation could be completely excluded using an enamino ketone with a phenyl substituent as a starting compound.



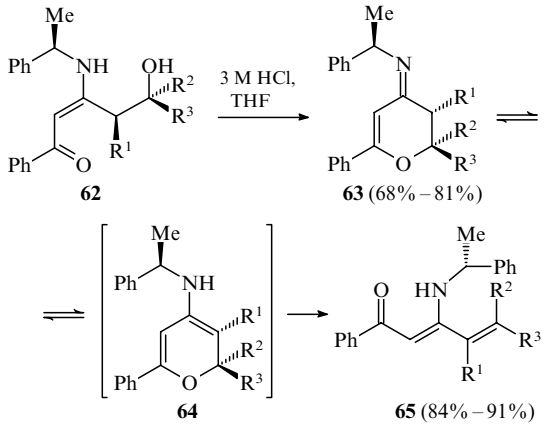
R^1 = H, Me, Ph; R^2 = Me, Et, Ph, cyclo-C_6H_{11}.

Direct aldol condensation of γ-dianions of the type **54** with aldehydes and ketones gave chiral *anti*-β-amino-δ-hydroxyalk-1-enyl ketones **62**.[53] The stereoselectivity of this reaction depends critically on steric factors, being increased in the case of sterically more hindered starting enamino ketones and carbonyl compounds.[53]



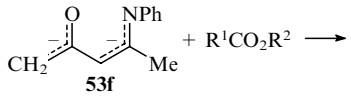
R^1 = H; R^2 = H, Me, Bn; R^1-R^2 = $(CH_2)_2$; R^3 = H, Me; R^4 = Me, $(CH_2)_2Ph$, Bu^t.

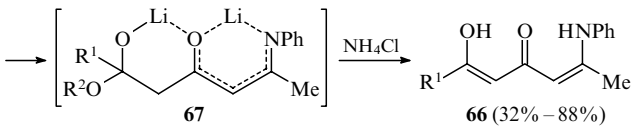
Under conditions of acid hydrolysis, enamino ketones **62** undergo cyclisation into 4-imino-2,3-dihydropyrans **63**. Compounds **63** are stable in acid media, apparently due to the formation of a more stable protonated form **64**. However, in neutral media iminopyrans **63** are unstable and isomerise into enamino ketones **65**.[53]



R^1 = H, Bn, Me; R^2 = Me, Bu^t, Ph; R^3 = H, Me.

The reaction of the dilithium derivative **53f** with esters results in enamino enols **66**.[54]

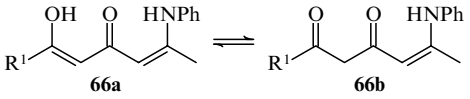




67 **66** (32% – 88%)

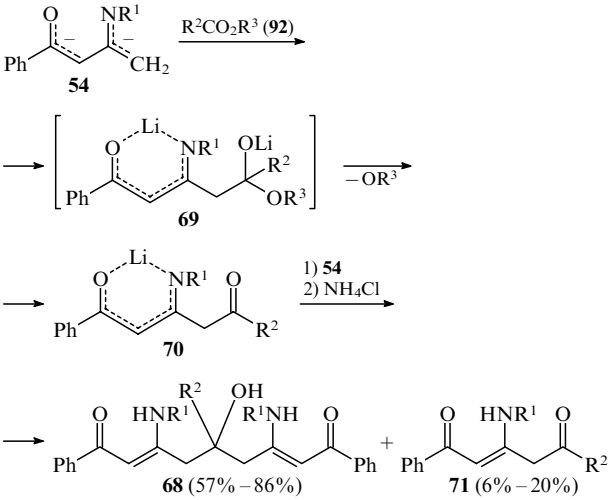
R^1 = Ph, 4-ClC_6H_4, EtCHBr; R^2 = Me, Et, C(Me)=CH_2.

It was proposed [54] that the adduct **67** stabilised by bridging bonds, is the intermediate in this reaction. The yields of compounds **66** are very high in the case of aromatic acid esters, but decrease dramatically if aliphatic acid esters are used. Moreover, the reaction of dilithium derivatives with aliphatic acid esters is accompanied by the formation of ester self-condensation products; their proportion increases with time. It is suggested [54] that a transmetallation reaction between the dilithium derivative **53f** and the ester favours self-condensation of esters. According to ^{1}H NMR spectroscopic data, compounds **66** exist in solutions as two tautomers, *viz*., ketoenols **66a** and diketones **66b**, the equilibrium being markedly shifted towards the enol form **66a**.[54]



66a **66b**

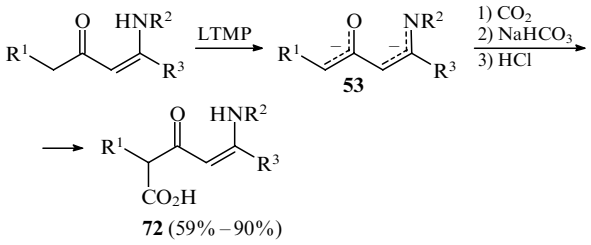
It should be noted that the reaction of dilithium derivatives of the type **54** with esters yields unsaturated amino alcohols **68** as the main product; these are formed as a result of condensation of two molecules of the enamino ketone with one molecule of the ester. Obviously, the intermediate **69** which is formed first is far less stable than the adduct **67** and is decomposed with elimination of the alcoholate anion to give the monolithium derivative **70**. The carbonyl group of the latter is not coordinated with the lithium ion and behaves as the free carbonyl group. Its reaction with the second molecule of the γ-dilithium derivative **54** affords the polyfunctional compounds **68**.[54] The expected products of this reaction, *viz*., enamino diketones **71**, are formed in insignificant amounts.



54 **69** **70** **68** (57% – 86%) **71** (6% – 20%)

R^1 = Pr^i, Me; R^2 = Me, Et, Ph, Pr; R^3 = Me, Et, C(Me)=CH_2.

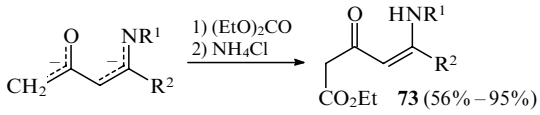
The AVK derivatives **72** with a carboxy group in the α′-position were obtained by the reaction of the α′-dianions **53** with carbon dioxide.[55] For $R^1 \neq H$, the acids **72** are unstable and undergo decarboxylation within several hours to give the starting AVK. For R^1 = H, the acids **72** retain their stability at lowered temperatures over a period of several months. The dianions of the type **54** do not react with carbon dioxide.[55]



53 **72** (59% – 90%)

R^1 = H, Me, Et, Bn; R^2 = Me, Pr^i, Ph, cyclo-C_7H_{12}; R^3 = Me, $Ph(CH_2)_2$.

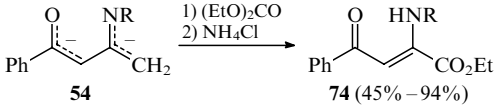
The α′-dianions of the type **53** react with diethyl carbonate to give enamino oxo acids **73**.[55] The maximum yields of compounds **72** and **73** were obtained for compounds with bulky substituents at the nitrogen atom.[55]



73 (56% – 95%)

R^1 = Me, Pr^i, Ph; R^2 = Me, Et.

The γ-dianions of the type **54** react with diethyl carbonate to produce α-amino-β-benzoylacrylates **74**.[55]

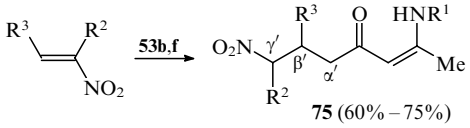


54 **74** (45% – 94%)

R = Me, Pr^i, Ph.

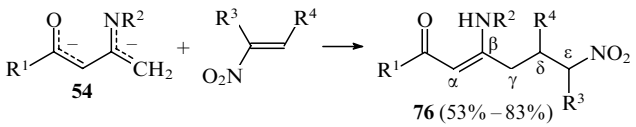
It is noteworthy that the condensation of $(EtO)_2CO$ with the dianions **54** containing an aliphatic substituent instead of a phenyl substituent yields a complex mixture of products.[55]

The dianions **53** and **54** add to the double bond of nitroalkenes to give γ′- (**75**) or ε-nitro-β-enamino ketones (**76**). As a rule, this reaction yields only one of the possible diastereomers.[56]



75 (60% – 75%)

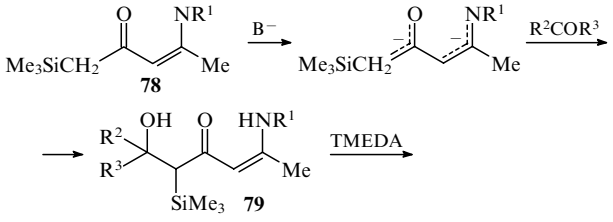
R^1 = Ph (**53f**), Pr^i (**53b**); R^2 = H, Me; R^3 = Ph, Et, $Ph(CH_2)_2$, 4-$MeOC_6H_4$.



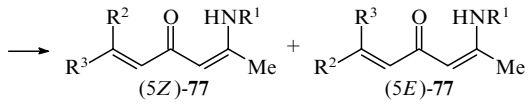
54 **76** (53% – 83%)

R^1 = Ph, Me; R^2 = Me, Pr^i, Ph; R^3 = H, Me; R^4 = Et, Ph, $Ph(CH_2)_2$, 4-$MeOC_6H_4$.

The cross-conjugated enamino ketones **77** were obtained by the reaction of aldehydes and ketones with dianions formed upon treatment of α′-(trimethylsilyl)enamino ketones **78** with bases.[57, 58]



78 **79**

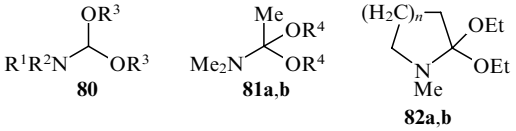


R^1 = Pr^i, Bu^t; R^2 = Ph, PhCH=CH, Et; R^3 = H, Me.

The structures of the products formed depend on the reaction conditions. In tetrahydrofuran, only silyl-substituted hydroxy enamino ketones **79** or their mixture with compounds **77** are isolated. In the presence of tetramethylethylenediamine which binds lithium cations and thus facilitates the elimination of trimethylsilanol only α′,β′-unsaturated amino ketones **77** in a total yield of 53% to 82% are obtained. It is noteworthy that the ratios of the (5*E*)- to (5*Z*)-isomers of compounds **77** depend on the reaction time, *viz*., the (5*Z*)-isomer is mainly formed upon elimination after 2 h, whereas the (5*Z*)-isomer is isomerised into the (5*E*)-isomer with an increase in the reaction time to 20 h.[58]

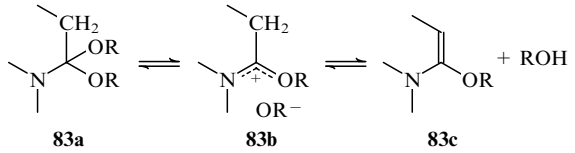
6. Reactions of amide and lactam acetals and ester aminals with compounds containing an activated methylene group

Reactions of amide and lactam acetals and ester aminals with compounds containing an activated methyl or methylene group is one of the most popular approaches to the synthesis of enamines including enamino ketones.[1,59–62] Among amide and lactam acetals and ester aminals synthesised to date,[59,61–66] dialkyl acetals of *N*,*N*-dialkylformamides **80** and *N*,*N*-dimethylacetamide **81** as well as diethylacetals of *N*-methylbutyro- (**82a**) and -valerolactams (**82b**) are the most well-studied and popular synthetic reagents.



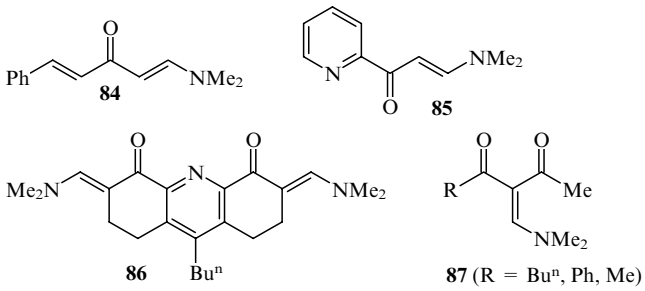
R^1 = R^2 = Et, Me; R^1-R^2 = $(CH_2)_5$; R^3 = Me, Et;
R^4 = Me (**81a**), Et (**81b**); *n* = 1 (**82a**), 2 (**82b**).

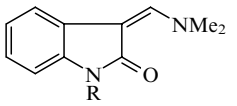
In solutions of amide acetals, an equilibrium exists between acetals **83a**, ambidental cations **83b** and α-alkoxy enamines **83c**.[66–71]



Reactions of nucleophilic substitution of amide acetals proceed in the absence of catalysts, since the abstraction of a proton from an activated methyl or methylene group occurs by virtue of the basic properties of the acetal amide itself. In some cases, azeotropic distillation may be required to remove the alcohol formed.

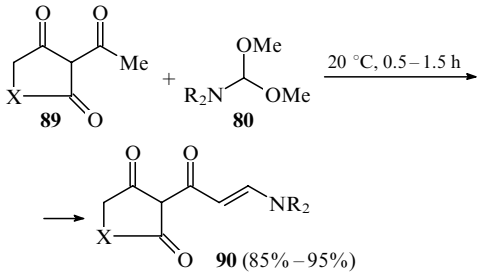
The condensation of dimethylformamide acetal and alkylformate aminal with various ketones (*e.g.*, aromatic, heterocyclic) and diketones gave enamino ketones **84**,[72] **85**,[73], **86**,[74] **87**[75] and **88**.[76]





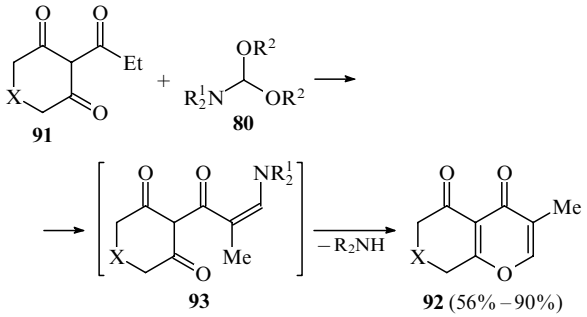
88 (R = H, Et).

Dialkyl acetals of *N*,*N*-dialkylformamides **80**[77,78] react with 2-acetylcycloalkane-1,3-diones **89** exclusively at the acetyl group to give enamino triketones **90**.[77]



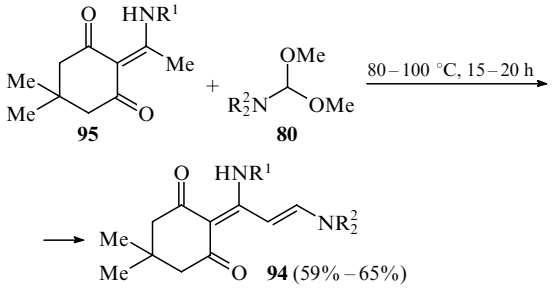
R = Me, Et; X = CH_2, $(CH_2)_2$, CH_2CHMe.

The dioxo derivatives of tetrahydrobenzopyrans **92** formed upon cyclodeamination of enamino triketones **93** are the reaction products of 2-propionylcyclohexane-1,3-diones **91** with *N*,*N*-dialkylformamide acetals **80.**[78]



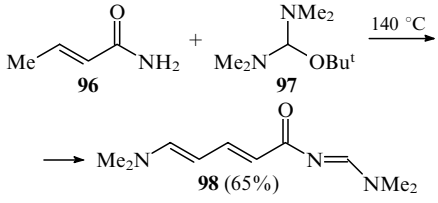
R^1_2N = Me_2N, Et_2N, ; R^2 = H, Me; X = CH_2, CMe_2.

Diaminodienediones **94** were synthesised by heating cyclic enamino β-diketones **95** with an excess of acetals **80**;[79] in this case, the reaction occurs at the methyl group which is separated from the carbonyl function by a double bond. Only few examples of this kind of reactions are documented.[79–81]



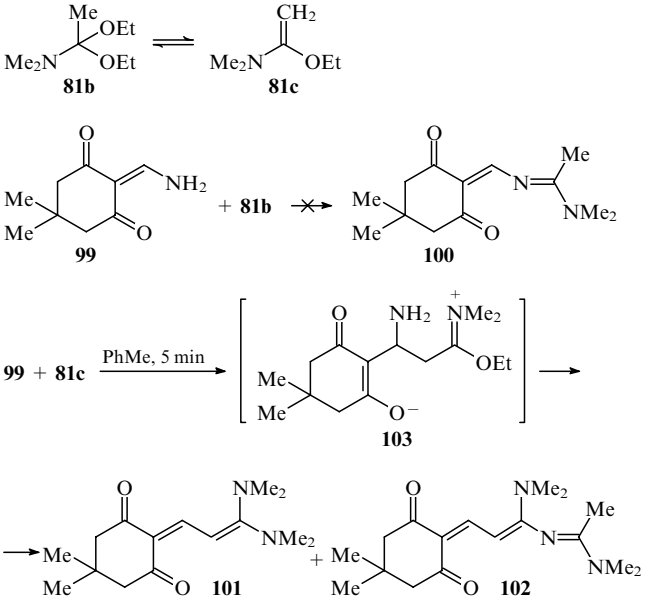
R^1 = Me, Et; R^2 = H, Me.

The condensation of crotonamide **96** with a large excess of *tert*-butylformate bis(*N*,*N*-dimethylaminal) **97** at 140 °C yields



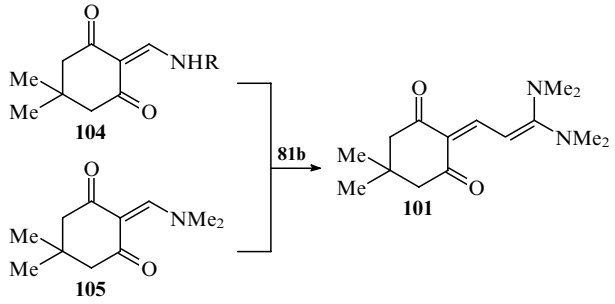
enamidine **98** as a result of reactions at both methyl and the primary amino group.[81]

An unusual reaction was observed in the study of the reactions of *N*,*N*-dimethylacetamide diethyl acetal **81b** and acetals of *N*-methylbutyro- (**82b**) and -valerolactams (**82b**) with enamino diketones.[1, 62, 69–71, 82] Quite unexpectedly, the reaction of the enamino diketone **99** with the acetal **81b** occurs not at the primary amino group to give enamidine **100**,[83] but at the double bond and yields a mixture of diaminodiene diketone **101** and its dimethylaminoethylidene derivative **102**.[1, 62, 69, 82]



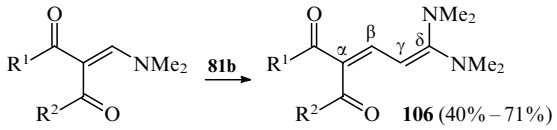
It is assumed that the reaction with enamino diketone **99** involves ketene acetal-aminal **81c** rather than dimethylacetamide acetal **81b** which is in equilibrium with the former. High electron density in the β-position of ketene acetal-aminal **81c**, which is provided by two strong electron-donor substituents, favours its easy addition to the double bond of the enamino ketone **99**. This results in the zwitterion **103** the alkoxy group of which reacts with dimethylamine formed in the course of the reaction to give the diaminodiene **101** or with ammonia and an excess of acetal **81b** to give amidine **102.**[69] It is clear from the scheme presented why the dimethylformamide acetals **80** for which the equilibrium of the type **81b** ⇌ **81c** is impossible do not enter into such reactions.

Obviously, this reaction is ambiguous because of the presence of the primary amino group in the enamino diketone **99**. The introduction of *N*-substituted enamino diketones **104** and **105** into the reaction with acetal **81b** allows selective synthesis of the diamino dienediketone **101**.[69]



R = Ph, Bn.

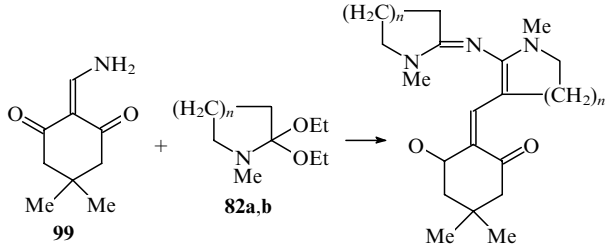
The reaction of *N*,*N*-dimethylacetamide acetal (**81b**) with other cyclic and acyclic enamino dicarbonyl compounds also occurs at the double bond and results in diamino dienediketones **106**.[69, 71]



R^1 = R^2 = Me, Ph; R^1 – R^2 = OCH_2O, $(CH_2)_3$.

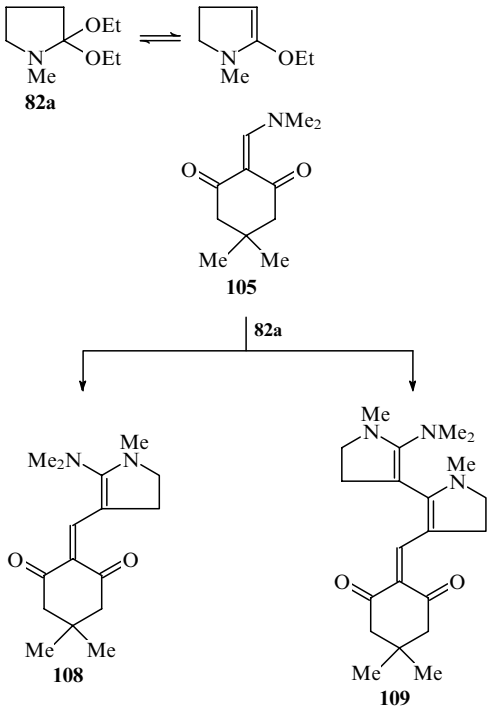
According to ^{1}H NMR spectroscopic data, δ,δ-diamino dienediones **101** and **106** exist predominantly as *s-trans*-conformers with respect to the C(β) – C(γ) bond (J = 14.2 – 14.7 Hz).

N-Methylbutyro- and -valerolactam acetals (**82a**) and (**82b**) [70] react with the enamino diketones **99** and **105** in a similar way. Thus the enamine **99** gives cyclic derivatives of dienediamines **107a**,**b** in high yields.[70]

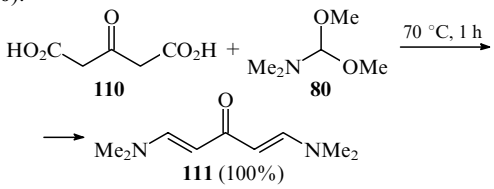


n = 1 (**a**), 2 (**b**).

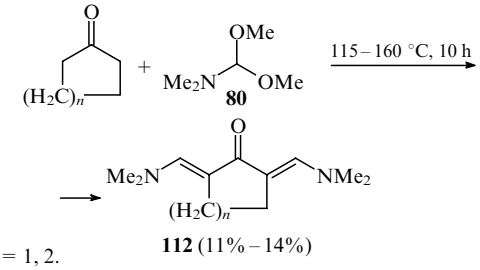
The structure of the reaction product of the lactam acetal **82a** with the enamino diketone **105** depends on the reagent ratio, *viz*., the dihydropyrrole diene **108** is formed in the case of an equimolar ratio, whereas triene **109** is formed in the presence of an excess of the lactam acetal.[70]



Dimethylformamide acetal (**80**) can also be used in the synthesis of di(β-aminovinyl) ketones.[84–87] Thus the synthesis of 1,5-bis(dimethylamino)penta-1,4-dien-3-one (**111**) is based on the reaction of dimethylformamide acetal (**80**) with 3-oxoglutaric acid (**110**).[84, 85]



Di(aminomethylidene)cycloalkanones **112** are formed in the reaction of dimethylformamide acetal **80** with cyclopentanone or cyclohexanone which proceeds under very drastic conditions; the yields of the target products are usually low.[86]



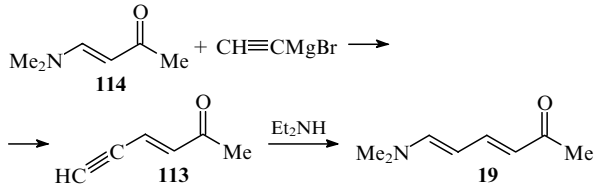
n = 1, 2.

In the presence of 1,5-diazabicyclo[4.3.0]non-5-ene as a catalyst, the yields of compounds **112** increase up to 36% – 50%.[87]

7. Synthesis of δ-aminodienones and α,α′-bis(3-aminopropenylidene)alkanones

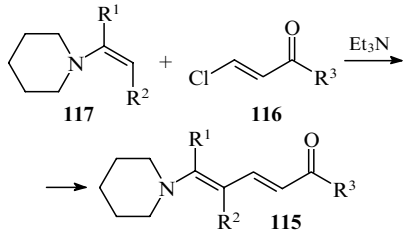
Some examples of the synthesis of δ-amino dienones were described earlier.[88–90] In most cases, the procedures employed for the synthesis of enamino ketones are inapplicable to the synthesis of conjugated δ-amino dienones and, particularly, of polyunsaturated ω-amino ketones where the number of conjugated double bonds between the NMe_2 and CO groups is more than two.

Thus the reaction of the enynone **113** with diethylamine was used for the synthesis of δ-aminodienone **19**. The ketone **113** was synthesised from 4-dimethylaminobut-3-en-2-one (**114**) and ethynylmagnesium bromide.[88]



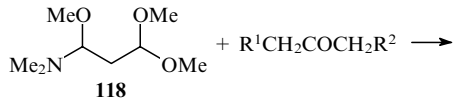
Polyunsaturated amino ketones can, in principle, be synthesised by reiteration of this procedure. However, it has been shown[89] that this approach is ineffective even in the case of trienones.

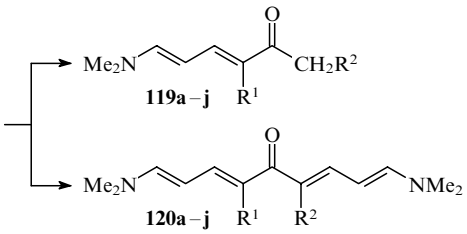
The δ-amino dienones **115** possessing aryl substituents were obtained by the reaction of aryl β-chlorovinyl ketones **116** with enamines **117** in the presence of triethylamine.[90]



R^1 = H, R^2 = Me, Et, Ph; $R^1 - R^2$ = $(CH_2)_3$; R^3 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4.

The condensation of 3-dimethylamino-1,1,3-trimethoxypropane (**118**) (see Ref. 91) with ketones is successfully employed in the synthesis of δ-dimethylamino dienones.[86,92–95] Depending on the conditions, the reaction can be directed towards the formation of ketones containing one (**119a**–**j**) or two (**120a**–**j**) 3-dimethylaminopropenylidene substituents in the α-position.[86,92,93,95]





R^1 = R^2 = H (**a**); R^1 = H, R^2 = Me (**b**); $R^1 - R^2$ = $(CH_2)_2$ (**c**), $(CH_2)_3$ (**d**), $(CH_2)_4$ (**e**), $(CH_2)_2CHMe$ (**f**), $CH_2CH(Me)CH_2$ (**g**), $CH_2CH(Me)CHMe$ (**h**), CH_2OCHMe (**i**), CH_2OCMe_2 (**j**).

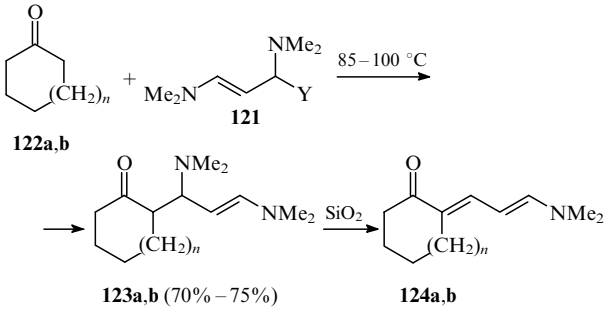
β-Dimethylaminoacrolein acetal-aminals or aminals **121** can be used for the synthesis of compounds **119** and **120** instead of 3-dimethylaminotrimethoxypropane **118**.[96] In both cases, the condensation occurs in the presence of a catalyst and virtually does not result in the formation of by-products. An important advantage of this method is the possibility to synthesise compounds **120** containing two aminopolyenoic chromophores.



Y = OMe, NMe_2.

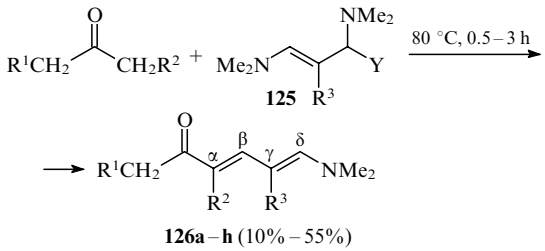
Owing to the interaction of two chromophores through the carbonyl group, the ketones **120** possess specific properties, such as pronounced solvatochromism[97] and thermochromism,[98] fluorescence and the ability to generate laser radiation with high efficiency.[99] The exceptionally easy alkylation and protonation of these compounds at the carbonyl group is accompanied by drastic changes in their colour.[100,101]

The reaction of β-dimethylaminoacrolein acetals or acetal-aminals **121** with cyclic ketones **122a**,**b** gave the intermediate compounds (diamines **123a**,**b**) which are quantitatively converted into α-(3-dimethylaminopropenylidene)cycloalkanones **124a**,**b** in $CHCl_3$ in the presence of SiO_2.[94]



Y = OMe, NMe_2; n = 9 (**a**), 12 (**b**).

The reaction of acetals or acetal-aminals **125**[102] substituted in position 2 with ketones often gives only ketones **126a**–**h** with one 3-dimethylaminopropenylidene substituent.[103–105]

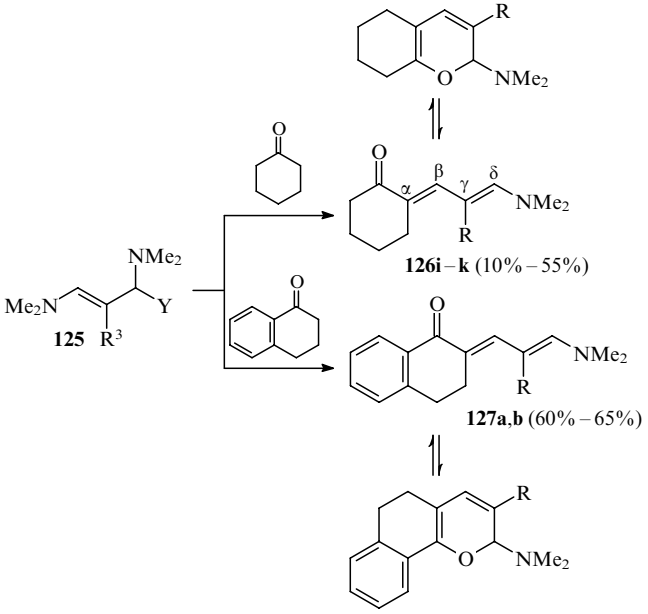


Y = OMe, NMe_2.

Compound **126**	R^1	R^2	R^3	Compound **126**	R^1	R^2	R^3
a	H	H	Me	**e**	$(CH_2)_2$		Me
b	H	H	OEt	**f**	$(CH_2)_2$		Cl
c	H	H	Cl	**g**	$(CH_2)_2$		Br
d	H	H	Br	**h**	$(CH_2)_2$		OEt

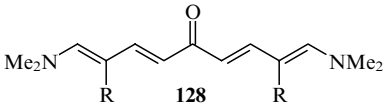
According to ^{1}H NMR spectroscopic data, ketone **126a** has a *trans*-configuration of the α,β-double bond (J = 15 Hz).[105] The cyclic ketones **126e**–**h** represent *E*-isomers with a *trans*-arrangement of the carbonyl group and a substituent in the γ-position ($^3J_{CO-H_\beta}$ = 5.0–5.8 Hz).[103, 104]

In contrast to dienones **126a**–**h**, which exist exclusively in the open form, the γ-substituted compounds **126i**–**k** and **127a**,**b** containing a six-membered ring exist in some solvents in a dynamic equilibrium between the *Z*-isomer of the δ-amino dienone form and the corresponding 2*H*-pyran. Evidence for the existence of both forms is provided by the detection of two sets of signals in the ^{1}H and ^{13}C NMR spectra as well as by absorption bands from both valence isomers in the UV spectra.[103–106]



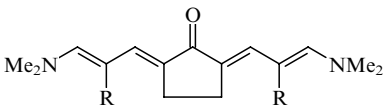
Y = NMe_2, OMe; R = Me (**126i**, **127a**), OEt (**126j**), Cl (**126k**, **127b**).

Bis(ω-dimethylamino) polyenones **128** and **129** containing Me, Ph, Cl and OEt in the γ,γ′-positions were synthesised by the reaction of the corresponding substituted acetals or acetal-aminals **125** with acetone[107, 108] and cyclopentanone.[103, 104, 109] Bis(3-dimethylaminopropenylidene)cyclohexanone **130** was obtained using fluorine-substituted acetals **125**.[110]



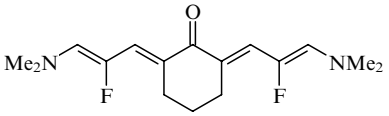
128

R = Me, Ph.



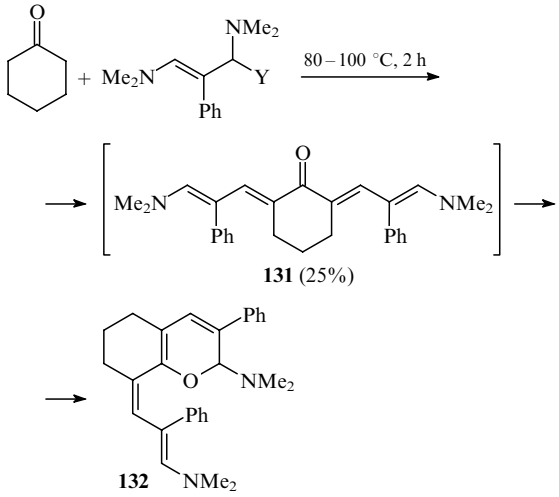
129

R = Me, OEt, Cl.



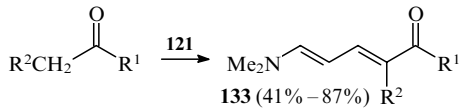
130

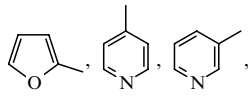
Compound **131** which is formed first was isolated in the form of its valence isomer, *viz*., 2*H*-pyran **132**, in the reaction of α-phenyl-β-dimethylaminoacrolein acetals or acetal-aminals with cyclohexanone.[108]



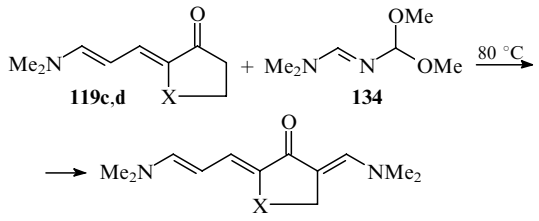
Y = OMe, NMe_2.

δ-Amino dienones **133** containing heterocyclic and heteroorganic substituents were synthesised[111] using β-dimethylaminoacrolein acetals or acetal-aminals **121**.



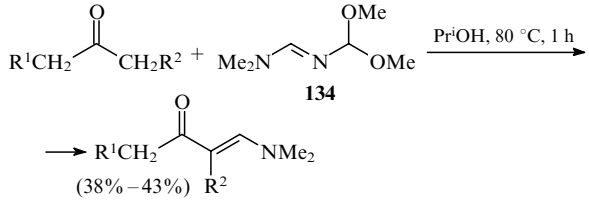
R^1 = Ph, PhCH=CH, , $C_5H_5FeC_5H_4$;
R^2 = H, Me, Ph.

Azaacetal **134** was used for the synthesis of unsaturated amino ketones of various structures. Thus the condensation of cycloalkanones **119c,d** with the azaacetal **134** is accompanied by the cleavage of the C=N bond resulting in non-symmetrical bis(dimethylaminoalkenylidene)alkanones **135**.[112]



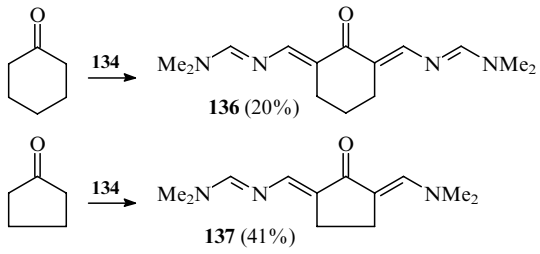
X = CH_2 (**119c**, **135a**), $(CH_2)_2$ (**119d**, **135b**).

The cleavage of the C=N bond also takes place in the reaction of the azaacetal **134** with cycloalkanones and acetone at an equimolar ratio of the reagents.[112]



R^1 = R^2 = H; R^1–R^2 = $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$.

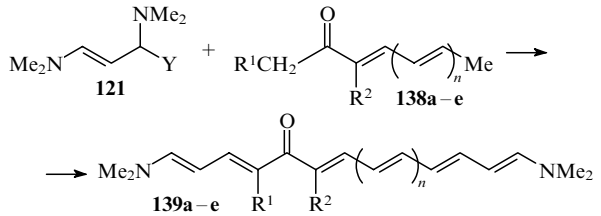
The ketones **136** and **137** containing an azamethine group were synthesised at an cycloalkanone : azaacetal **134** ratio of 1 : 2 (Pr^iOH, 80 °C, 5 h).[112]



III. Conjugated ω-amino polyenones

1. Condensation of α,β-unsaturated ketones with β-dimethylaminoacrolein acetals and acetal-aminals

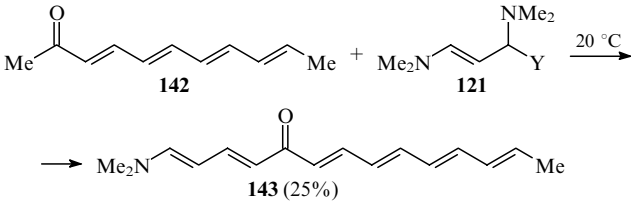
β-Dimethylaminoacrolein **121** acetals and acetal-aminals manifest exceptionally high reactivity. They react with cyclic and acyclic unsaturated ketones **138a**,**d** and their vinilogues **138b**,**c**,**e** containing no more than three double bonds at both the α-methyl (or α-methylene) group and the methyl group separated from the carbonyl function by double bonds to give bis(dimethylamino)-polyunsaturated ketones **139**–**141** (Scheme 1).[113]



Y = NMe_2, OMe.

Compounds **138**, **139**	R^1	R^2	*n*	Yield of **139** (%)
a	H	H	0	54
b	H	H	1	40
c	H	H	2	27
d	$(CH_2)_3$		0	75
e	$(CH_2)_3$		1	48

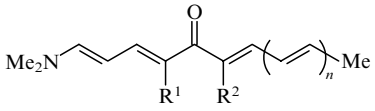
In undeca-3,5,7,9-tetraen-2-one (**142**), the mobility of hydrogen atoms of the methyl group separated from the carbonyl function by four double bonds is insufficient for the condensation with compounds **121**; only the methyl group in the α-position



Y = NMe_2, OMe.

relative to the carbonyl group reacts to yield ketone **143** containing one 3-dimethylaminopropenylidene group.[113]

In conjugated ketones **138a**–**e**, the mobility of hydrogen atoms of the methyl or methylene group vicinal to the carbonyl group is higher than that of the methyl group separated from the carbonyl group by one or several double bonds. This allows one to carry out condensation under milder conditions, *e.g.*, at equimolar ratios of reagents and without heating, which results in selective formation of reaction products involving the α-methylene group.[113]

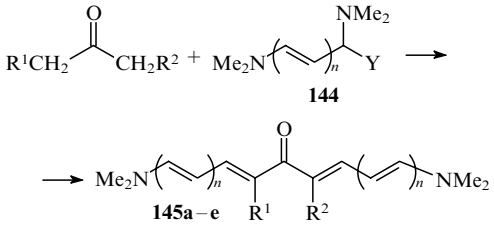


n = 0–2; $R^1 = R^2 = H$; $R^1–R^2 = (CH_2)_3$.

Unfortunately, this method is confined mainly to the synthesis of non-symmetrical polyunsaturated bis(3-dimethylaminopropenylidene)alkanones. Moreover, this requires difficultly accessible unsaturated ketones as starting compounds.

2. Condensation of acetals and acetal-aminals of β-dimethylaminoacrolein vinilogues with ketones

The synthesis of symmetrical polyconjugated α,α′-bis(dimethylaminoalkenylidene)alkanones is based on the use of acetals and acetal-aminals of conjugated ω-dimethylaminopolyenals **144** (*n* = 2, 3) which react with different ketones at both methyl or methylene groups to give bis(dimethylamino)polyunsaturated ketones **145a**–**e**.[114]



Y = OMe, NMe_2.

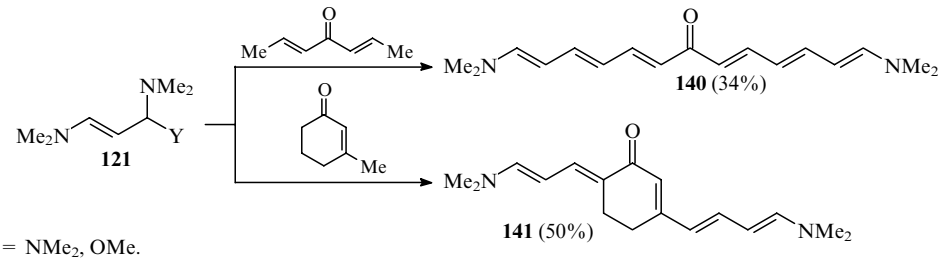
Compounds **145**	R^1	R^2	*n*	Yield of **145** (%)
a	H	H	2	98
b	$(CH_2)_2$		2	62
c	$(CH_2)_3$		2	60
d	H	H	3	3
e	$(CH_2)_2$		3	12

In the case of compounds **144** (where *n* = 3), the reaction proceeds under more drastic conditions where the polyunsaturated ketones formed are unstable. The corresponding derivatives **145d**,**e** could be isolated only in reactions with acetone and cyclopentanone in low yields.[114]

The condensation of acetals or acetal-aminals of δ-dimethylaminodienal **144** (*n* = 2) with enamino, dienamino and trienamino ketones was used for the synthesis of non-symmetrical polyunsaturated bis(dimethylamino) ketones **146**–**148** (Scheme 2).[114, 115]

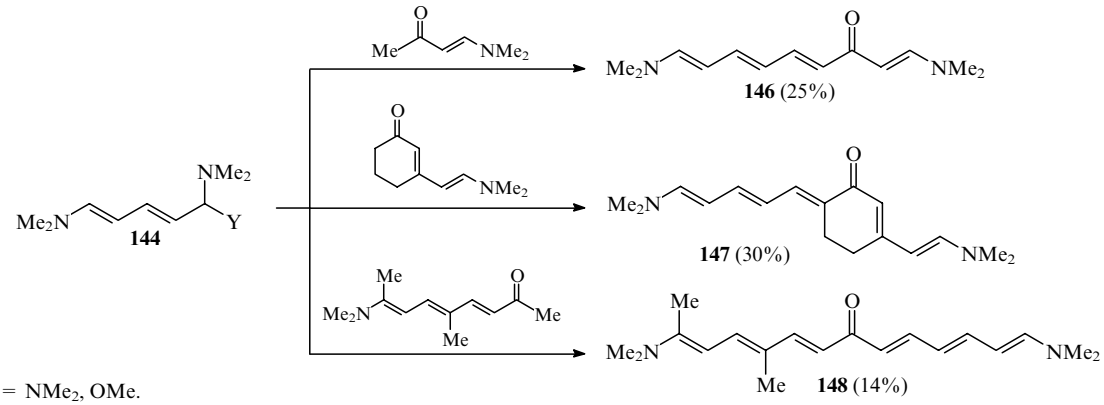
It should be noted that compounds **144** (where *n* = 2) are characterised by sufficiently high reactivities to react with 2-ethylidenecyclohexanone (**149**) at both the α-methylene and the methyl

Scheme 1



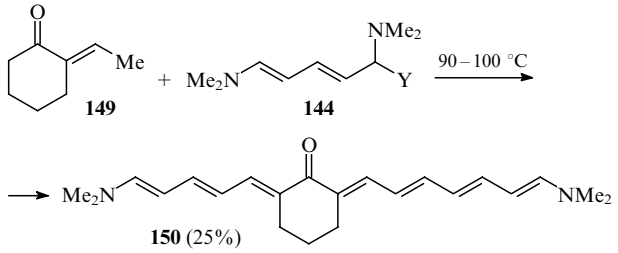
Y = NMe_2, OMe.

Scheme 2



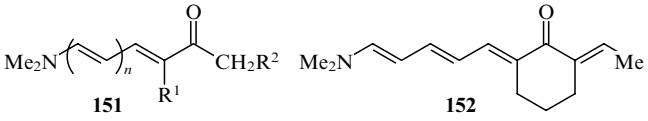
Y = NMe_2, OMe.

group separated from the carbonyl function by a double bond to yield the derivative **150**.[114]

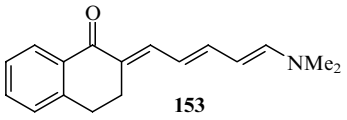


Y = NMe_2, OMe.

With a change in reaction conditions (*viz*., with equimolar ratio of the reactants, gentle, short-term heating), the reaction of acetals and acetal-aminals of ω-dimethylaminopolyenals **144** with ketones occurs in a regioselective manner and yields the polyunsaturated ketones **151**–**153** which contain only one dimethylamino group.[116]

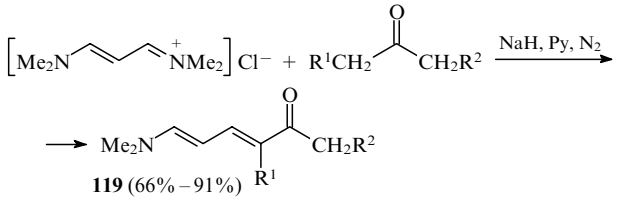


n = 2, 3; $R^1 = R^2 = H$;
n = 2, 3; $R^1 - R^2 = (CH_2)_2$;
n = 2, $R^1 - R^2 = (CH_2)_3$.



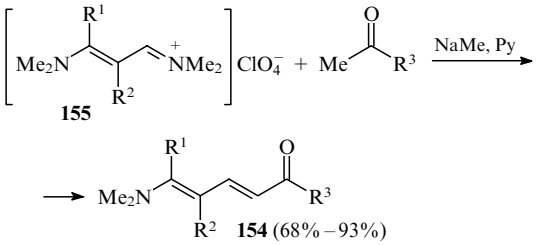
3. Condensation of ketones with polymethine salts

Yet another well-studied approach to the synthesis of ω-amino polyenones, is the condensation of ketones with trimethine or pentamethine salts in the presence of bases, such as $NaNH_2$,[117] MeOK, MeONa or Bu^tOK,[87, 111, 118–120] NaH or LDA.[121–124] As a rule, this reaction is carried out in triethylamine or pyridine.



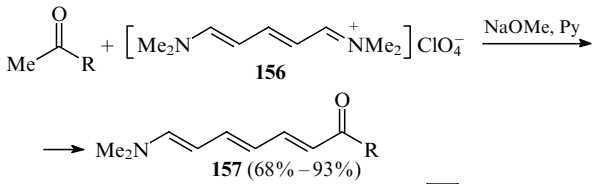
R^1 = Me, Et; R^2 = H, Me; $R^1 - R^2 = (CH_2)_2, (CH_2)_3$.

δ-Dimethylaminoalka-1,3-dienyl ketones **154** having substituents in the aminopolyene chain were prepared by the condensation of aromatic and heteroaromatic methyl ketones with the substituted trimethine salts **155**.[111, 118, 120]



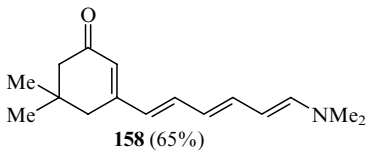
R^1 = H, Ph, ; R^2 = H, OMe, Ph; R^3 = Ph, .

The reaction of the pentamethine salt **156** with methyl ketones makes it possible to synthesise ω-aminopolyunsaturated ketones **157** with a more extended chromophore.[111]

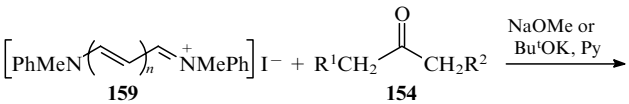


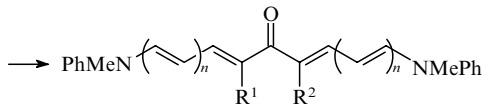
R = Bu^t, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, .

The condensation of isophorone with the pentamethine salt **156** involves the methyl group (rather than the sterically shielded α-methylene group), which affords the aminopolyunsaturated ketone **158** where NMe_2 and CO groups are separated by four double bonds.[111]



The reaction of tri- and pentamethine salts **159** with ketones in pyridine in the presence of MeONa (2 equiv.) or Bu^tOK was used[119] to obtain the symmetrical diamino polyenones **120a**,**c**,**d** and **160a**,**b**. The yields of ξ-dimethylamino trienones **160a**,**b** do not exceed 35%.

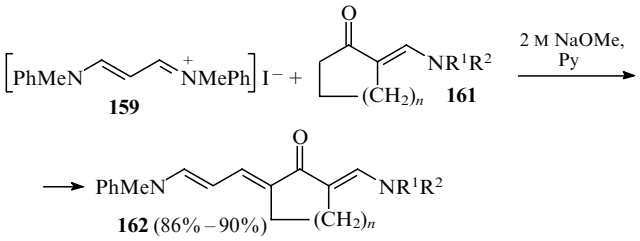




120a,**c**,**d**; **160a**,**b**

Compounds	R^1	R^2	n	Yield (%)
120a	H	H	1	55
120c	$(CH_2)_2$		1	83
120d	$(CH_2)_3$		1	65
160a	$(CH_2)_2$		2	26
160b	$(CH_2)_3$		2	35

The non-symmetrical cyclic polyunsaturated ketones **162** were prepared from cyclic enamino ketones **161**.[87]



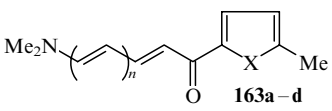
159 **161** **162** (86%–90%)

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

IV. Conjugated ω-amino ketones containing a heterocyclic fragment

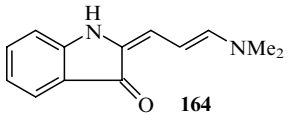
The synthesis of conjugated ω-amino ketones containing a heterocyclic fragment which strongly affects their physicochemical properties has been carried out in the last few years.

Thus the condensation of heterocyclic ketones containing an acetyl or an activated methylene group with acetals and acetalaminals **121** or **144a**,**b** was used to obtain δ-amino dienones **163a**,[113] **164**, **165a**, **166a**,[109] **167a**, **168a** [125] and ξ-amino trienones **163b**, **165b**, **166b**, **167b**, **168b** [125] and **169** [116] containing a heterocyclic fragment.

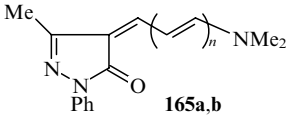


163a–**d**

X = O, S: n = 1 (**a**), 2 (**b**);
X = O: n = 2 (**c**), 3 (**d**).

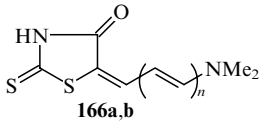


164



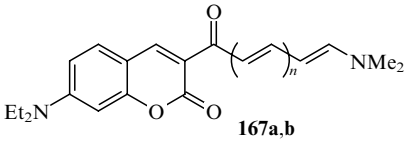
165a,**b**

n = 1 (**a**), 2 (**b**).



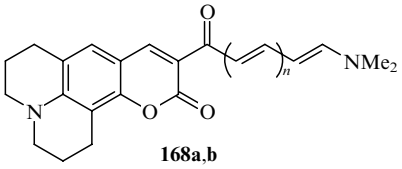
166a,**b**

n = 1 (**a**), 2 (**b**).



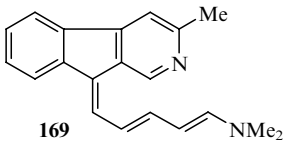
167a,**b**

n = 1 (**a**), 2 (**b**).



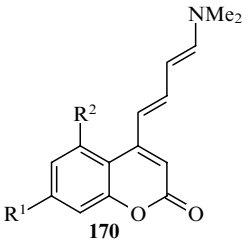
168a,**b**

n = 1 (**a**), 2 (**b**).



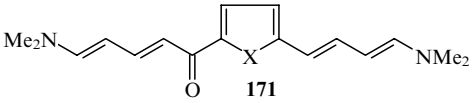
169

High reactivities of compounds **121** enable their reactions with the methyl group separated from the carbonyl group by a double bond or by a heterocyclic fragment to give the ω-amino polyenones **170**–**172**.[113, 125, 126]



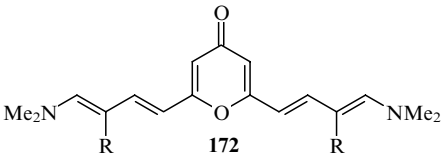
170

R^1 = Me, OH; R^2 = H, OMe.



171

X = O, S.



172

R = H, Me, Ph.

* * *

In conclusion, it may be said that the ω-amino polyenones **168**, **169** and **170** containing a coumarin fragment are very valuable, since coumarin derivatives constitute an important group of organic luminophores and laser dyes which effectively generate radiation in the region of 400–560 nm.[127, 128] In addition, they are widely employed in medicine and biochemistry as fluorescent compounds.[129] 2,6-Bis(4-dimethylaminoalka-1,3-dienyl)-4*H*-pyran-4-ones (**172**) appeared to be very interesting reagents from the spectral and synthetic standpoints.[126]

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