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Captodative aminoalkenes

A Yu Rulev

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Abstract. Procedures for the synthesis of captodative aminoalkenes, which were developed primarily over the last 15 years, are systematised. The influence of the structural and stereoelectronic effects of the substituents both at the nitrogen atom and at the double bond on the reactivity of these systems is considered. Particular emphasis is given to regio- and stereoselectivity of electrophilic, nucleophilic and radical reactions of captodative aminoalkenes as well as to processes of the construction of carbo- and heterocyclic compounds based on these aminoalkenes. A special section is devoted to the chemistry of methylidene- and arylmethylidenequinuclidin-3-ones. The bibliography includes 327 references.

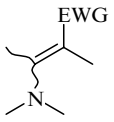
I. Introduction

Two decades ago, Viehe [1–4] proposed the concept of the captodative effect. Later on, the notion of captodative alkenes was introduced for compounds characterised by the simultaneous presence of electron-withdrawing (captive) and electron-donating (dative) substituents at the same carbon atom of the double bond. Alkenes containing the electron-donating and electron-withdrawing substituents in the vicinal position are termed push-pull.

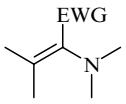
Among captodative alkenes, enamines containing the geminal electron-withdrawing group (EWG) attract the most attention. Since these alkene derivatives possess special chemical properties, they were regarded as a separate group of organic compounds. Recent studies demonstrated that cross-conjugated isomers exhibit specific and much more versatile reactivities as compared to fully conjugated push-pull aminoalkenes.

Many captodative aminoalkenes have already found wide application. It will suffice to mention that these compounds are structural fragments of bioorganic molecules and serve as building blocks in the synthesis of various biologically active heterocycles and analogues of natural compounds. In the solution of some natural-science problems of the prebiotic chemistry and philosophic questions about the origin of life on Earth, much attention has been focused on the simplest representatives of captodative alkenes (see, for example, the studies [5–9] devoted to 2-aminoacrylonitrile).

However, while the chemistry of push-pull aminoalkenes **1** has been studied in sufficient detail and its various aspects were surveyed in a series of fundamental reviews,[10–16] captodative aminoalkenes **2**, on the contrary, remained poorly studied until recent years.



1a – d



2a – d

EWG = CN (**a**), CO_2R (**b**), C(O)R (**c**), CHO (**d**).

The first effort to systematise the main procedures for the preparation of 2-aminocycloalk-2-enones and consider their most remarkable properties was made in the review,[17] which covered the data published up to 1983. In the review [11] devoted to the chemistry of β-aminoenones, a special section was concerned with the data on the chemical behaviour of captodative aminoalkenones (mainly, cyclic), which have been reported only in 30 scientific sources. In the last 15 years, some important aspects of the chemistry of captodative aminoalkenes were developed substantially owing, primarily, to elaboration of simple and efficient procedures for the synthesis of such systems. The present review generalises the data on the chemistry of captodative aminoalkenes. The first section of the review is dedicated to procedures for the preparation of captodative alkenes containing an unsubstituted, mono- or disubstituted amino group and one electron-withdrawing group (carbonyl, alkoxycarbonyl or cyano group) at the same centre. In the second section, the spectroscopic characteristics of captodative aminoalkenes are analysed, including the data on their structures. In the third section, the major types of transformations characteristic of these compounds are classified. A special section is devoted to the chemistry of 2-methylidene- and 2-arylmethylidenequinuclidin-3-ones belonging to bicyclic captodative aminoalkenes, which do not exhibit properties of enamines due to their structural characteristic features. Quinoid structures, which formally contain the $C=C(NR_2)CO$ fragment, and activated alkenes bearing the geminal acylamino group are beyond the scope of the present review. Data on some compounds of this type (in particular, dehydroamino acids) were surveyed in a number of publications (see, for example, the review [18]).

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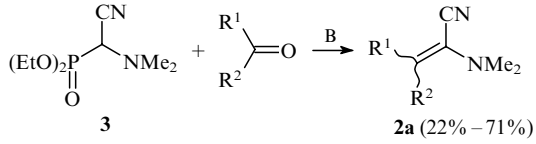
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II. Synthesis of captodative aminoalkenes

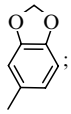
1. Insertion of the double bond into systems containing geminal amino and electron-withdrawing groups

a. Olefination of carbonyl compounds

One of the classical ways for inserting a double bond into a molecule involves Wittig-type olefination of aldehydes and ketones. Various captodative aminoalkenes were successfully prepared according to this procedure. Costisella and Gross demonstrated that cyanophosphonate **3** reacted with aromatic or aliphatic aldehydes and ketones in the presence of a strong base (BuLi, THF;[19] NaH, dioxane or DMSO[20]) to form 1-cyanoenamines **2a** in moderate yields.



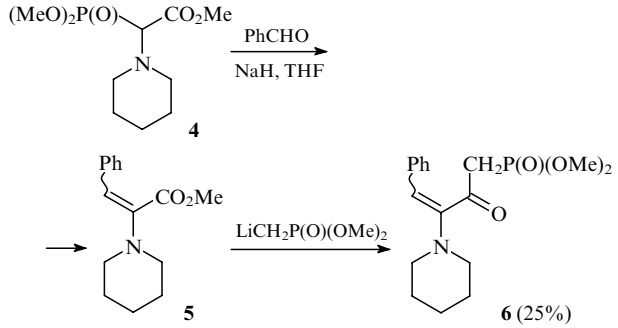
3 **2a** (22% – 71%)

R^1 = H, Me, Et, Pr^i, n-C_6H_{13}, Ph, 4-$NO_2C_6H_4$, $(EtO)_2P(O)CH_2$, ;

R^2 = H, Ph; B is a base.

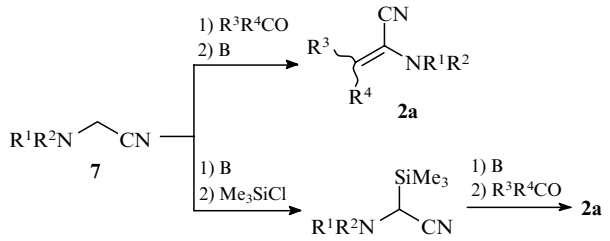
Later on, it was found that this reaction could be performed by electrolysis of phosphonates **3** on platinum or glassy-carbon electrodes,[21] the carbanion being generated on the cathode. This carbanion reacts with the carbonyl compound to give finally the target alkenes **2a** in satisfactory yields.

In addition to the aminonitriles **3**, the reactions were successfully performed with esters. Thus methyl (dimethoxyphosphoryl)piperidinoacetate (**4**) reacted with benzaldehyde to form unstable methyl 3-phenyl-2-piperidinoacrylate (**5**), which was transformed into β-ketophosphonate **6** without isolation.[22]



4 **5** **6** (25%)

The 1-cyanoenamines **2a** were also prepared from aminoacetonitriles **7** and aliphatic (including α,β-unsaturated) or aromatic aldehydes by the Peterson reaction[23–27] or condensation in the presence of a strong base (KH, KOH – K_2CO_3).[24,28] Both procedures appeared to be extremely sensitive to the nature of the amino group in the starting substrate **7**. In the case of dimethylamino-, diethylamino- or pyrrolidinoacetonitriles, the reactions either did not take place at all or proceeded in very low yields.[24] (*N*-Methylanilino)acetonitrile [**7**, NR^1R^2 = N(Me)Ph] proved to be the only substrate, which was almost quantitatively transformed into the corresponding 1-cyanoenamine.



7 **2a**

R^1 = Me, CH_2=$CHCH_2$, MeCH=$CHCH_2$; R^2 = Ph, Bn;

R^3 = H, Me, Pr^n, Pr^i, n-C_5H_{11}, Ph, 4-$MeOC_6H_4$, MeCH=CH, EtCH=CH, PhCH=CH, 2-thienyl, 1-naphthyl;

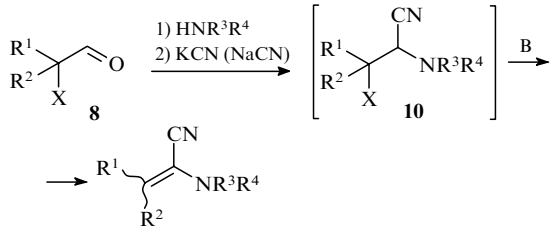
R^4 = H, Me, Et, Ph; B = KH, LDA or KOH – K_2CO_3 – Bu_4NBr.

Aldol condensation of α-aminoketones bearing the active methylene group with aromatic aldehydes afforded the corresponding captodative aminoalkenes **2c**.[29,30]

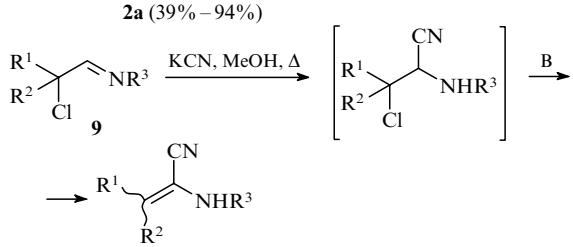
b. Elimination

A wide range of captodative aminoalkenes were prepared by elimination reactions, which very readily proceed in the case of β-heterosubstituted ketones, aldehydes, nitriles and esters.

Elimination of hydrogen halide from α-amino-β-haloketones or derivatives of carboxylic acids is a valuable approach, provided that the corresponding starting compounds are readily accessible. The idea of the use of haloaldehydes as building blocks in the synthesis of captodative aminoalkenes has long been known. More than 40 years ago, Temin[31] developed an original synthesis of α-morpholinoacrylonitrile from chloroacetaldehyde (**8**, R^1 = R^2 = H, X = Cl), which was generated *in situ* from dimethylacetal.[32,33] This classical procedure (with small modifications) continues to be used for the preparation of the 1-cyanoenamines **2a**.[34–36]



8 **10** **2a** (39% – 94%)



9 **2a** (39% – 94%)

R^1 = H: R^2 = Pr^n, Pr^i, Ph; R^1 = Me: R^2 = Et, Ph; R^1 = R^2 = H, Me, Et, Cl; R^1 – R^2 = $(CH_2)_4$, $(CH_2)_5$, CH_2CH=$CHCH_2$; X = Cl, Br;

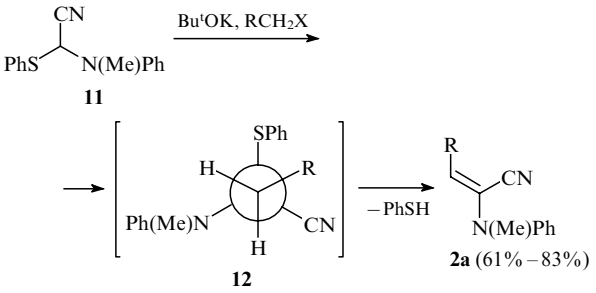
NR^3R^4 = NH_2, NMe_2, NEt_2, , , , N(Me)Ph, N(Me)C_6H_{11}-cyclo; R^4 = H: R^3 = Me, Et, Pr^i, Bu^t, cyclo-C_6H_{11}, CH_2Bn; B = Et_3N or NaOH.

De Kimpe *et. al.*[37,38] extended the scope of application of this method using α-chloroaldimines **9** as the starting compounds. The latter are prepared from aliphatic aldehydes by successive imination with primary amines and chlorination with *N*-chlorosuccinimide. The reactions of the aldimines **9** with KCN in methanol afford the 1-cyanoenamines **2a** in high yields. It was assumed[37,38] that the synthesis proceeded through 2-(*N*-alkylamino)-3-chloro-substituted nitriles as intermediates, which were readily dehydrochlorinated under the reaction conditions.

There are also other examples where the resulting 2-amino-3-halopropiononitriles **10** were subjected to dehydrohalogenation to give the corresponding 1-cyanoenamines **2a**, including those with the unsubstituted,[39] mono-[40] or disubstituted amino group.[41,42] For these reactions, Et_3N[32–36,39–41] or NaOH[31] are the reagents of choice.

An elegant preparative procedure proposed recently for the synthesis of various 1-cyanoenamines **2a** is based on the involvement of (*N*-methylanilino)phenylthioacetonitrile (**11**) in the tandem alkylation – elimination process.[43,44] The reaction proceeds stereospecifically to form the *E* isomer, which is accounted for by

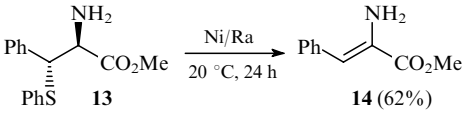
anti-elimination of PhSH from intermediate **12**. The latter was isolated and characterised by spectroscopic methods.[43]



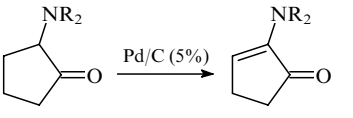
R = H, Me, Pr, Br(CH$_2$)$_2$, I(CH$_2$)$_4$, Ph, CH$_2$=CH, PhCH=CH, MeCH=CH, BrCH=CH, PhSCH$_2$CH=CH, PhSCH=CH;

X = Cl, Br, I.

An attempt to reduce ester **13** with Raney nickel led to unexpected elimination of PhSH giving rise to methyl 2-amino-3-phenylacrylate (**14**).[45]



In my opinion, the above-considered reactions are of considerable synthetic value. In addition, there are other examples of the synthesis of captodative aminoalkenes resulting in elimination of hydrogen halide,[46] alkanethiol,[47] amine,[48] hydrogen cyanide,[49] water [50] or alcohol.[51, 52] Dehydrogenation of *N*,*N*-disubstituted 2-aminocycloalkanones is also worthy of mention. Thus 2-aminocyclopent-2-enones were obtained in high yields by passing gaseous 2-aminocyclopentanones over Pd/C.[53]

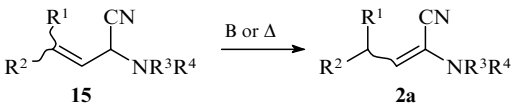


NR$_2$ = NEt$_2$, N⟨ ⟩, N⟨ ⟩O.

c. Rearrangements

In some unsaturated compounds, double-bond migration readily occurs under the action of strong bases. The driving force for this process is the formation of a thermodynamically more stable isomer due to interaction between the π-system of the double bond and the electron-withdrawing group.

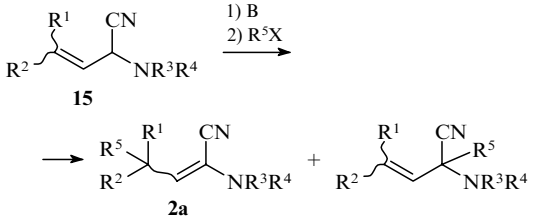
Treatment of β,γ-unsaturated α-aminonitriles **15** with strong bases (Bu^{t}OK or MeONa) under mild conditions afforded the corresponding 1-cyanoenamines **2a**.[26, 27, 54–56] It should be noted that the stereochemistry of the reaction product depends both on the conditions of its preparation and the structure of the starting substrate. In addition, thermally initiated isomerisation can take place in these systems, as, for example, upon distillation of the nonconjugated aminonitriles **15**.[34]



R^1 = H: R^2 = Me, Pr, Ph; R^1 = R^2 = H;

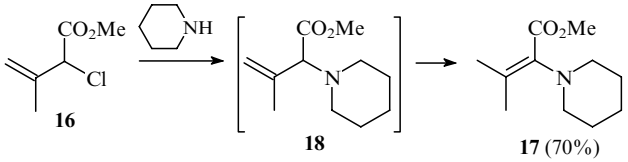
NR^{3}R^4 = N(Me)Ph, N(All)Ph, N(Me)C$_6$H$_4$Br-2; B = Bu^{t}OK, MeONa.

Under the action of strong bases, the β,γ-unsaturated *N*,*N*-disubstituted α-aminonitriles **15** produce ambident anions, which can undergo alkylation either at the α or γ position.[57] This property was used for the preparation of various 1-cyanoenamines **2a**.[54, 58–63] It was established that regioselectivity of alkylation is determined by different factors, among which are the steric parameters of the electrophilic reagent, the amino group and the γ-substituent in the substrate.[58] The formation of the captodative aminoalkenes **2a** is favoured by the presence of a bulky amino group in the substrate molecule. For example, alkylation of the nitriles **15** containing the N(Me)Ph or N(cyclo-C$_6$H$_{11}$)Ph groups always proceeds regiospecifically to form the 1-cyanoenamines **2a**.[61] The stereochemistry of addition depends also on the reaction conditions. Thus the reactions performed at low temperatures (−78 °C) afforded predominantly or even exclusively the *Z* isomers of the compounds **2a**.[60, 61]

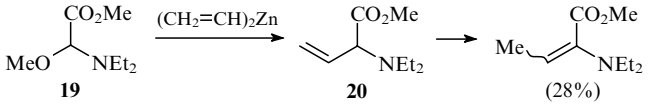


R^1 = H, Me, Ph, MeCH=CH; R^2 = H, Me; NR^{3}R^4 = N(Me)Ph, NMe$_2$, N⟨ ⟩, N⟨ ⟩O ; R^5 = Me, Et, Pr^i, Bu, Bn, All, Br(CH$_2$)$_3$, Cl(CH$_2$)$_3$, 2-BrC$_6$H$_4$CH$_2$; X = I, Br; B = LDA or Bu^{t}OK.

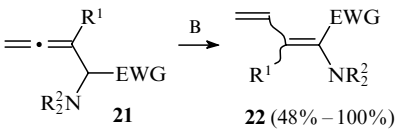
In some cases, the initially formed β,γ-unsaturated α-aminonitriles or esters also undergo double-bond migration to the α,β position with respect to the electron-withdrawing group.[64–67] For instance, the reaction of methyl 2-chloro-3-methylbut-3-enoate (**16**) with piperidine started with the attack on the allylic carbon atom to give finally the conjugated amino ester **17**.[65] It is reasonable to assume that intermediate **18** generated through the replacement of the chlorine atom is isomerised to the more stable alkene **17** under the action of the amine.



When developing a general procedure for the synthesis of esters of β,γ-unsaturated α-amino acids using organozinc compounds, the French research team [66, 67] found that the reaction of aminoacetal **19** with divinylzinc afforded amino ester **20**, which underwent isomerisation to give methyl 2-diethylaminobut-2-enoate.



Prototropic isomerisation of β-allenic amino esters, ketones or nitriles **21** under the action of strong bases [MeONa–DMSO,[68] Bu^{t}OK–HMPA (HMPA is hexamethylphosphoramide) [69] or Bu^{t}OK–THF [70]] proceeded rapidly to give conjugated aminoalkenes **22** in high yields.[68–70]



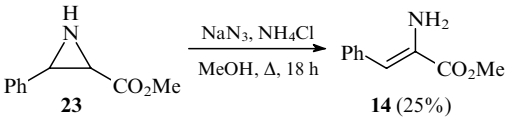
R^1 = H, Me, Et, Pr, Bu, Ph;

NR$^2_2$ = NMe$_2$, NEt$_2$, N⟨ ⟩, N⟨ ⟩, N⟨ ⟩O;

EWG = CO$_2$Me, CO$_2$Et, C(O)Me, CN.

Generally, tautomeric transformations are not considered as preparative reactions. However, unlike simple enamines with unsubstituted or monosubstituted amino groups, which exist predominantly in the imino form, captodative aminoalkenes **2** are much more stable in the enamine form. This allows their isolation either in the individual form or as a tautomeric mixture in which the enamine form dominates. Examples of such syntheses of aminoalkenes containing the activating carbonyl,[71,72] alkoxycarbonyl [73] or cyano group [74] are available in the literature.

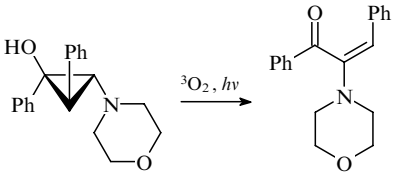
A series of captodative aminoalkenes were prepared from the corresponding substituted aziridines.[45,75–77] In some cases, their formation was absolutely unexpected. For example, treatment of aziridinecarboxylate **23** with sodium azide in methanol gave rise to the unsaturated ester **14** instead of the expected methyl 2-amino-3-azido-3-phenylpropionate.[45]



23 **14** (25%)

It was reported that 2-amino-3-methoxy-1,3-diphenylpropanone was transformed into α-aminochalcone under the action of strong bases.[78] The authors assumed that this reaction proceeded through intermediate aziridinoketones. However, the formation of unsaturated α-aminoketones has not subsequently been confirmed.[79]

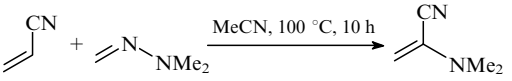
Recently, α-aminoenone **24** was synthesised by photooxidation of cyclopropanol **25**.[80] Photolysis was carried out in the presence of photosensitising agents, *viz*., 9,10-dicyanoanthracene or triphenylpyrylium tetrafluoroborate, for 0.5–5.2 min. It was noted that the enone **24** decomposed when the reaction time was increased.



25 **24** (26%–28%)

2. Insertion of the amino group into the conjugated C=C–EWG system

The reaction of acrylonitrile with formaldehyde dimethylhydrazone produced 2-dimethylaminopropenonitrile regardless of the reaction conditions.[81]



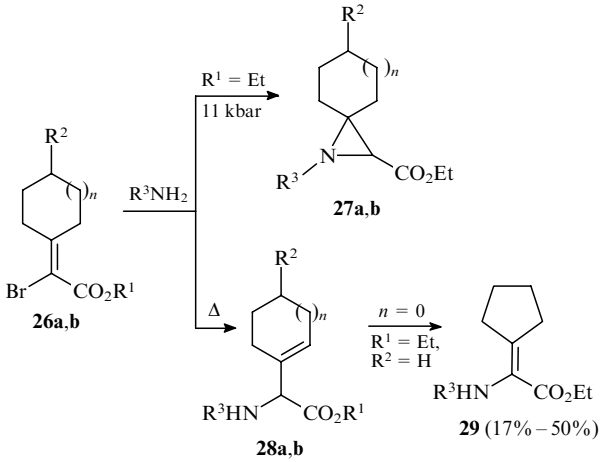
Apparently, this is the only example of the formal synthesis of captodative aminoalkene from unsubstituted activated alkene.

a. Nucleophilic substitution

Nucleophilic substitution of a particular leaving group is most commonly used for the insertion of the amino group into the conjugated C=C–EWG fragment.

Although the replacement of the functional group X in the conjugated C=C(X)EWG system by the amino group seems at first glance to be the shortest pathway to captodative aminoalkenes, the reactions of N-nucleophiles with haloalkenes activated with the geminal electron-withdrawing group are complicated processes and do not necessarily afford the desired products. The results of these studies were critically analysed in the review.[82]

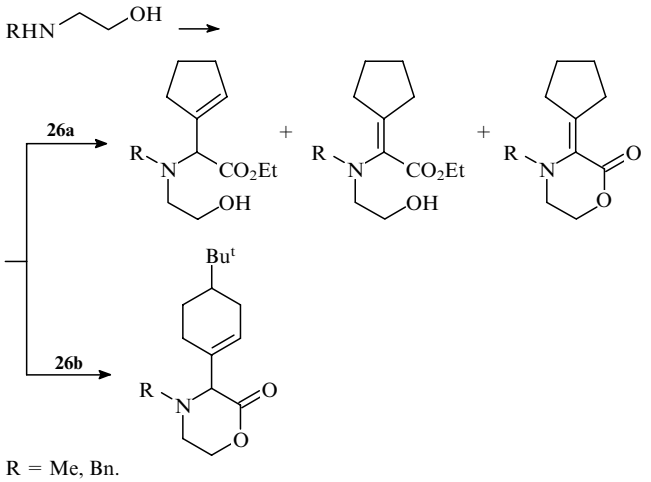
All the aforesaid is clearly exemplified by the data from the recent study,[83] which demonstrated that the results of the reactions of primary amines with bromo(cycloalkylidene)acetates **26a**,**b** depend substantially on the reaction conditions, the nature of the amine and the size of ring in the starting substrate. Under superhigh pressure, these reactions afforded spiroaziridines **27a**,**b** in high yields (and with high diastereoselectivity in the case of the derivatives **27b**). Under the same conditions, amines containing an aromatic or bulky substituent at the nitrogen atom produced predominantly α-amino-β,γ-unsaturated esters **28a**,**b**. Thermal activation of the compounds **26a**,**b** was accompanied by migration of the exocyclic double bond followed by the replacement of the allylic bromine atom to form exclusively the esters **28a**,**b**. Only in the case of the derivatives **28a** containing the five-membered ring, back migration of the endocyclic double bond was observed giving rise formally to *ipso*-substitution product **29**.



n = 0, R^1 = Et, R^2 = H (**a**); n = 1, R^1 = Me, R^2 = Bu^t (**b**);

R^3 = Pr^n, Pr^i, Ph, Bn, PhCHMe.

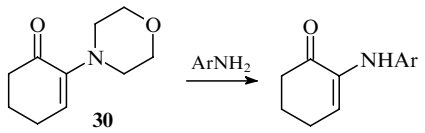
In the reactions with N,N- or N,O-binucleophiles, compounds **26a**,**b** underwent a cascade of transformations. Both upon thermal activation and under high pressure, the reactions involved double-bond migration and substitution of the halogen atom followed by condensation to form oxazinones (in the case of N,O-dinucleophiles) or piperazinones (in the case of N,N-dinucleophiles).[84] As in the case of reactions involving primary amines, the captodative system can be constructed only with the use of the bromo(cyclopentylidene)acetate **26a** and aminoethanol derivatives.[84]



R = Me, Bn.

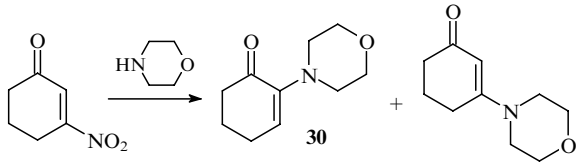
Since the halide ion is one of the best nucleofuges, it is not surprising that this ion is most generally used as the leaving group. Nevertheless, examples of the replacement of other groups at the sp^2-carbon atom are also available in the literature. These reactions often proceed very readily.

In spite of the ambiguous results of the reactions of 2-aminocycloalk-2-enones with N-nucleophiles,[85] 2-morpholinocyclohex-2-enone (**30**) is recognised as a convenient substrate in transamination.[17]

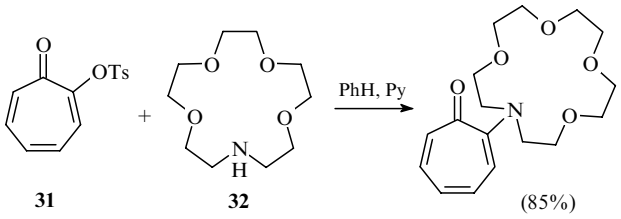


Ar = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-HOC$_6$H$_4$, 2-HO$_2$CC$_6$H$_4$.

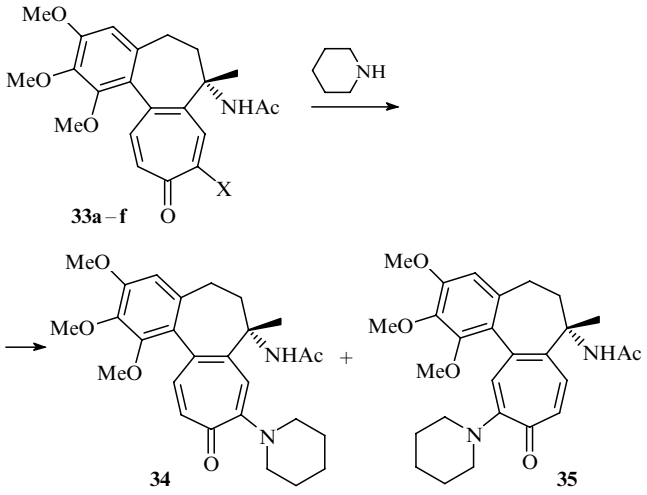
2-Morpholinocyclohex-2-enone (**30**) was prepared by the reaction of 3-nitrocyclohex-2-enone with morpholine, isomeric β-aminoketone being obtained as the minor product.[86]



Refluxing of an equimolar mixture of 2-(*p*-tolylsulfonyloxy)-tropone (**31**) and azacrown ether **32** in benzene in the presence of pyridine afforded the corresponding substitution product.[87]



Competitive *ipso*- and *tele*-substitution of various leaving groups in other troponoid systems has been well studied as well.[88–90] For example, isocolchicides **33a–f** readily reacted with piperidine, the ratio between the *ipso* (**34**) and *tele* isomers (**35**) being determined by the nature of the leaving group X. The reactions of the compounds **33a–c** afforded exclusively the isomers **34**, whereas the compounds **33d–f** produced the *tele* isomers **35** in 10%–25% yields. In the case of colchicides containing a substituent at position 10, only *ipso*-substitution was observed regardless of the nature of the leaving group.[90]

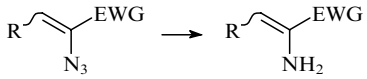


X = Cl (**a**), SOMe (**b**), SMe (**c**), OMe (**d**), F (**e**), OTs (**f**).

Finally, it should be noted that none of the attempts to replace the alkoxy group in α-alkoxyacroleins afforded the α-formyl-substituted enamines **2d**[91] although the reactions of amines with 3-alkoxy- or 3-phenoxypropenals are accepted to be a procedure of choice for the synthesis of their push-pull isomers **1d**.[12, 92, 93]

b. Synthesis of captodative aminoalkenes bearing the unsubstituted amino group

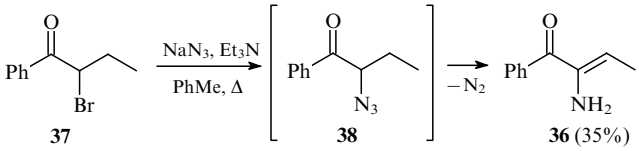
Undoubtedly, captodative aminoalkenes containing an unsubstituted amino group are of particular interest. The classical approach to their synthesis is based on reduction of the corresponding nitro and azido derivatives. It was recommended to use hydrogen on a metal catalyst,[94] hydrogen sulfide[94] or aluminium amalgam[94–96] for reduction of the azido group. In addition, α-amino-α,β-unsaturated ketones and esters were prepared by electrolysis of solutions of ene azides activated with geminal carbonyl or ester groups.[97–100] Refluxing of azidoesters in toluene in the presence of catalytic amounts of iodine also afforded esters of unsaturated α-amino acids.[18, 101, 102]



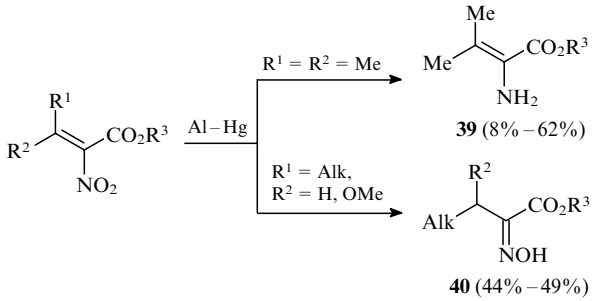
(15%–88%)

EWG = CO_2Me, CO_2Et, MeCO, 4-MeC$_6$H$_4$CO, 4-ClC$_6$H$_4$CO;
R = Me, Et, Pr^n, Pr^i, Ph, PhCH=CH, 4-MeC$_6$H$_4$, 4-HOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,4,6-Me$_3$C$_6$H$_2$, 2-BnC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-Pr^{i}C$_6$H$_4$, 2-furyl, 2-thienyl, 3-thienyl, 3-indolyl.

An unusual synthesis of α-aminoenone **36** from α-bromoketone **37** and sodium azide has been reported.[71] In the first step, the bromine atom was replaced to give azidoketone **38**. Subsequent elimination of N_2 afforded imino ketone, which underwent rapid isomerisation into the unstable alkene **36**.



Nitroalkenes are readily reduced with aluminium amalgam to the corresponding amino derivatives.[103–107] However, this procedure allows the preparation only of esters of β,β-disubstituted α-amino acids **39**. Reduction of β-methoxy-β-alkyl- or β-alkyl-substituted substrates gave rise predominantly to hydroxyimino esters **40**.[104, 107]



R^1 = Me, Et, Pr^n, Pr^i; R^2 = H, Me, MeO; R^3 = Me, Et, Bu^n.

Careful removal of various protective groups also made it possible to prepare the captodative aminoalkenes **2a–c** containing the unsubstituted amino group (see, for example, Refs 108–112).

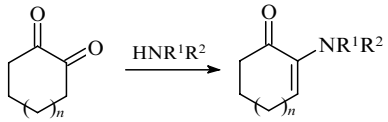
Procedures were developed for the synthesis of captodative aminoalkenes containing the unsubstituted amino group along with the keto, ester or cyano group. The exceptions are the formyl derivatives **2d**. Recent attempts to synthesise these compounds based on 2-haloalk-2-enals and hexamethyldisilazane or (diphenylmethylidene)amine failed.[113] Admittedly, the question about the possibility of the existence of the aminoalkenes **2d** containing the unsubstituted amino group as well as of all aminoaldehydes with the unprotected amino group[114, 115] remains open.

3. Simultaneous insertion of the double bond and the amino group

a. Syntheses based on diketones and ketoesters

One of the most general methods for the synthesis of captodative aminoalkenes is based on condensation of primary and secondary amines with readily enolysable 1,2-dicarbonyl compounds. As a rule, the reactions are carried out at room temperature or on refluxing of equimolar amounts of the reagents in an appropriate solvent (benzene, toluene, more rarely, chloroform or alcohol) in the presence or absence of a base or acid catalyst. The liberated water is removed either by azeotropic distillation or using molecular sieves.

Examples of the syntheses of 2-aminocycloalk-2-enones containing the disubstituted amino group were given in the review [17] and in a number of recent publications.[116–119] The use of chiral pyrrolidines in reactions with five–eight-membered cyclic 1,2-diketones allowed the preparation of optically active α-aminoenones.[120] Primary amines can also produce α-aminoenones in the reactions with cyclic diketones.[121–124] Along with usual alkyl- and arylalkylamines [$BnNH_2$, cyclo-$C_6H_{11}NH_2$, $Ar(CH_2)_2NH_2$], esters of some α-amino acids, such as glycine, alanine and tyrosine, were also successfully used in these reactions.[125, 126]

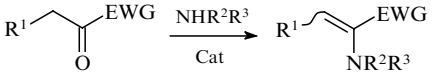


n = 0, 1, 2, 3; R^1 = H, Alk, All, Ar; R^2 = Alk, All, CH_2CO_2Et, $CH(Alk)CO_2Et$.

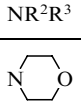
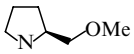
Since acyclic analogues of aminoketones are much less stable, the structures of the starting substrate and the reaction conditions are of particular importance in their synthesis. Acyclic α-aminoketones containing the internal or terminal double bond were prepared from α-diketones according to a classical procedure,[127] the yields being at most 30%. All attempts to purify the products led to their resinification.[128, 129]

Conventional procedures for the preparation of enamines containing the geminal alkoxycarbonyl group offered considerable promise.

It appeared that prolonged refluxing of 2,2-diethoxyethylamine with ethyl (3-chloro-2-nitrophenyl)pyruvate in toluene actually afforded the corresponding enamine in quantitative yield.[130] Taking into account the high sensitivity of alkyl pyruvates both to acidic and basic reagents, Arnold [131] improved this procedure. He proposed that $TiCl_4$, which is traditionally used in the synthesis of enamines, should be changed for softer $AsCl_3$. In essence, this modification allowed the first synthesis of the terminal aminoalkenes **2b** (R^1 = H). In spite of low stability, all products were prepared in the pure form in high yields.



2b,**c**

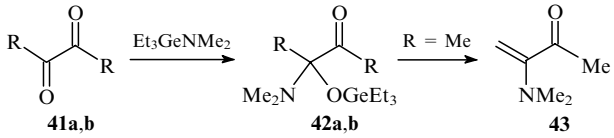
EWG	R^1	NR^2R^3	Catalyst	Yield (%)	Ref.
MeCO	H		$TiCl_4$	–	128, 129
EtCO	H		$TiCl_4$	30	129
EtCO	Me		$TiCl_4$	25	129
PhCO	Ph		$TiCl_4$	–	129
CO_2Me	H	NMe_2	$AsCl_3$	82	131
CO_2Me	H		$AsCl_3$	73	131
CO_2Me	H		$AsCl_3$	75	131
CO_2Bu^t	H	NMe_2	$AsCl_3$	68	131
MeCO	H		$AsCl_3$	100	133

The sole exception is the pyrrolidine derivative, which was not isolated by the author. It should be noted that methyl α-piperidinoacrylate has been obtained previously from the corresponding chlorine-substituted ester and piperidine [132] in very low yield (5%–10%). Later on, the procedure proposed by Arnold [131] was successfully used for the synthesis of optically active acyclic α-aminoenone, *viz*., 3-[(*S*)-2-(methoxymethyl)pyrrolidino]but-3-en-2-one.[133]

The reaction of *o*-phenylenediamine with pyruvic acid in a 0.1 M HCl solution at 20 °C gave rise to a mixture of the corresponding α-amino derivative of acrylic acid and its tautomer with the imine structure.[134] Both isomers can be isolated in the individual form.

An attempt to prepare the captodative enamines **2d** by direct condensation of methylglyoxal with two equivalents of secondary amine was doomed to failure because the reaction proceeded with the involvement of the more reactive aldehyde group.[135]

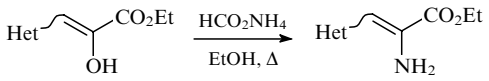
Not only amines but also their derivatives serve as N-nucleophiles in condensation with dicarbonyl compounds giving rise to the aminoenones **2c**.[136, 137] For example, trialkylgermylamines were found to react at one of the carbonyl groups of α-diketones **41a**,**b** to form α-amino-α-triethylgermyloxy ketones **42a**,**b**. The latter compounds appeared to be thermally unstable. Thus the compound **42a** decomposed to give aminoenone **43**.[136]



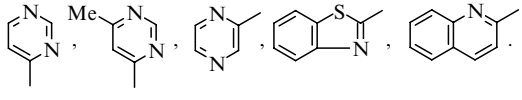
41a,**b** **42a**,**b** **43**

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

Recently, an ingenious procedure was developed for the synthesis of esters of unsaturated amino acids **2b** from esters of hetarylpyruvic acids **44**.[138] The esters **44** exist only in the enol form and are very reactive. These compounds are readily transformed to give the unsaturated amino esters **2b** in high yields upon refluxing with ammonium formate in ethanol. However, all attempts to obtain the compounds **2b** from the esters **44** under the action of other aminating reagents (aniline, benzylamine, ammonium chloride or ammonium acetate) failed.



44 **2b** (71%–85%)

Het = 

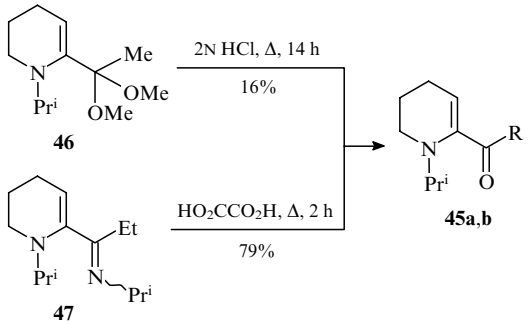
b. Oxirane-ring opening

The oxirane-ring opening under the action of amines is widely used only for the preparation of cyclic aminoenones. These reactions have been surveyed in the review.[17] Since then, no modifications of this procedure were proposed. Noteworthy only are the studies,[139, 140] which were not included in the cited review, and the investigations[141, 142] reported at a later time.

4. Formation of an electron-withdrawing group in aminoalkene

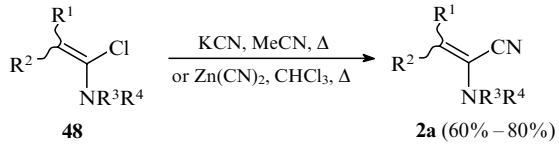
Examples of the insertion or generation of an electron-withdrawing group for the construction of captodative systems are few in number. In addition, these reactions are of limited application and of no particular preparative value.

The formation of the aminoalkenes **2c** containing the geminal carbonyl group was observed upon hydrolysis of enediamines,[143,144] oxidation of enamines [145,146] or aminoalcohols [147] and removal of protective groups.[148,149] Thus analogues of one of the natural components of the smell of freshly backed bread, *viz*., compounds **45a**,**b**, were synthesised by careful acid hydrolysis of the corresponding ketal **46** [148] or azomethine derivative **47**.[149]



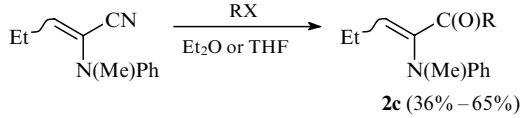
R = Me (**a**), Et (**b**).

A more general and efficient procedure for the synthesis of the 1-cyanoenamines **2a** is based on the nucleophilic substitution of the halogen atom by the cyanide ion.[150,151] For example, prolonged refluxing of 1-chloro-1-(dimethylamino)alkenes **48** with potassium cyanide in acetonitrile or with zinc cyanide in chloroform afforded the 1-cyanoenamines **2a** in good yields.[150] Unfortunately, this procedure is inapplicable to the synthesis of β-monosubstituted analogues of the compounds **2a** (R^1 = H) because the starting chloro derivatives are much less accessible and, in addition, they readily undergo dechlorination under the action of bases or upon heating.



R^1 = Me, Et; R^2 = Me, Ph, Cl; R^3 = R^4 = Me.

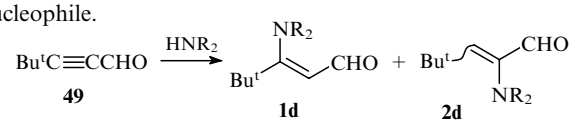
Finally, one activating function in compounds of the type **2** can be transformed into another one. Thus 2-(*N*-methylanilino)-pent-2-enonitrile was transformed into the enamines **2c** containing the geminal carbonyl group under the action of organolithium, -magnesium or -zinc compounds.[54]



R = Me, Bu, Bn, All; X = MgCl, MgI, Li, AllZn.

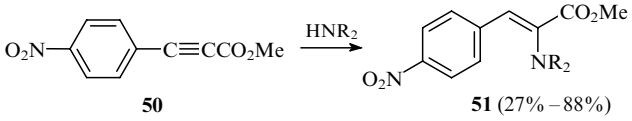
5. Other procedures

Other reactions giving rise to the captodative aminoalkenes **2a**–**d** have also been described in the literature. The results of investigations for a series of activated alkynes were the basis of several publications. It is known that the reactions of ethynylcarbonyl compounds with N-nucleophiles are among procedures most commonly used for the preparation of amino derivatives of the push-pull type **1**.[12] However, it was unexpectedly found that dialkylamines containing bulky substituents added not only at the β position but also at the α position with respect to the aldehyde group of 4,4-dimethylpent-2-ynal (**49**) to give a mixture of the unsaturated aminoaldehydes **1d** and **2d**.[152] Thus the proportion of the isomer **2d** reached 50% and 10% in the reactions of Pr^i_2NH and Bu^n_2NH, respectively. The authors related the regioselectivity of the addition to the spatial structure of the nucleophile.



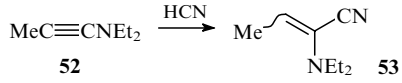
R_2 = Et_2, Pr^i_2, Bu^n_2, Bn_2, Ph_2.

Analogously, the reactions of methyl 4-nitrophenylpropiolate (**50**) with some secondary amines afforded the corresponding α-amino derivatives **51**.[153]

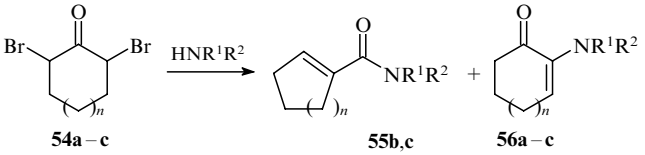


R = $(CH_2)_2OH$, $(CH_2)_2OSO_2Me$, $(CH_2)_2Cl$.

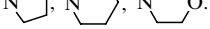
In the synthesis of pyrimidine derivatives from triazines and 1-diethylaminoprop-1-yne (**52**), HCN, which was eliminated in the course of the reaction, added to the starting alkyne to produce 2-diethylaminocrotononitrile (**53**) in yields of up to 76%.[154]



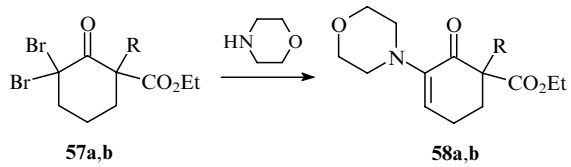
Cyclic α,α′-dibromoketones **54a**–**c** reacted with primary [155] and secondary amines [17,156] to give either Favorskii rearrangement products **55b**,**c** or the corresponding 2-aminocycloalk-2-enones **56a**–**c** depending on the ring size of the ketone and the structure of the nucleophile. The ratio of the reaction products is substantially affected by the nature of the solvent. The formation of the enamines **56a**–**c** is favoured by polar aprotic solvents.



n = 0 (**a**), 1 (**b**), 2 (**c**); R^1 = H, R^2 = Pr^n, Pr^i, Bu^t;

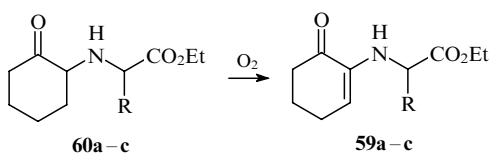
NR^1R^2 = 

In spite of the fact that treatment of α,α-dihaloketones with amines generally afforded the corresponding diamino derivatives,[157] the reactions of ethyl 1-alkyl-3,3-dibromo-2-oxocyclohexanecarboxylates **57a**,**b** with a tenfold excess of morpholine gave rise to aminoalkenes **58a**,**b**.[158]



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

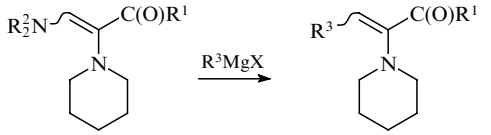
Recently, 2-aminocyclohex-2-enones **59a**–**c** were prepared [126] by oxidation of saturated ketones **60a**–**c**. Oxidation proceeded



R = H (**a**), Me (**b**), 4-$HOC_6H_4CH_2$ (**c**).

even upon storage of the starting substrates without a solvent in air. The same results were obtained by bubbling oxygen through a solution of the ketones **60** in chloroform.

The most reactive captodative aminoalkenes **2d** were first synthesised by L Duhamel and co-workers.[159,160] The reactions of Grignard reagents with formylated or acylated enediamines **61** produced the corresponding aminoalkenes **2c**,**d** in good yields.

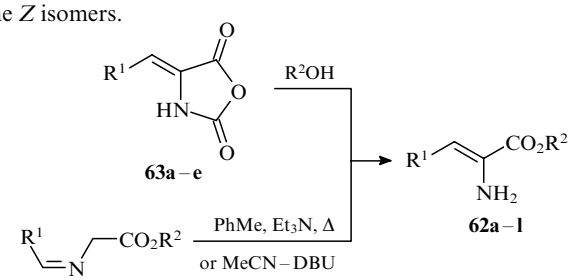


61 **2c**,**d** (43%–90%)

R^1 = H, Me, Ph; NR^2_2 = , NMe_2;

R^3 = Me, Et, Pr^n, Pr^i, Bu^n, Bu^t, Bn, Ph.

Ingenious methods were proposed for the synthesis of esters of dehydroamino acids with the free amino group.[161–164] Alkyl 2-aminoalk-2-enoates **62a**–**e** were prepared by alcoholysis of anhydrides **63a**–**e** under mild conditions.[161,162] In the studies,[163,164] aldimines **64e**–**l** (which were prepared by condensation of glycine esters with aldehydes) were used as the starting reagents, which were transformed into the target compounds **62e**–**l** upon refluxing in toluene in the presence of triethylamine or upon storage in the MeCN–DBU system (DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene) at room temperature. Spectral analysis demonstrated that the esters **62a**–**l** were always generated only as the *Z* isomers.



63a–**e** **64e**–**l**

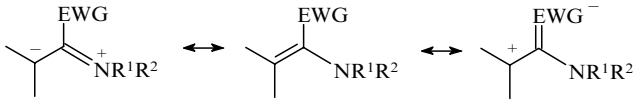
R^1 = Me (**a**), Et (**b**), Pr^n (**c**), Pr^i (**d**), Ph (**e**), $Ph_2C{=}CH$ (**f**), $Me_2C{=}CH$ (**g**), 3-$NO_2C_6H_4$ (**h**), 4-$NO_2C_6H_4$ (**i**), 4-$MeOC_6H_4$ (**j**), 4-ClC_6H_4 (**k**), $(4\text{-}ClC_6H_4)_2C{=}CH$ (**l**); R^2 = Me, Et.

Other reactions giving rise to captodative aminoalkenes have also been reported. However, they are of limited application, cannot be used for preparative purposes, and hence, are beyond the scope of the present review.

III. Structures and spectroscopic characteristics of captodative aminoalkenes

In the analysis of the structures of captodative aminoalkenes, one should first of all answer the question of how the combination of the electron-withdrawing and electron-donating groups is reflected in the degree of *p*,π- and π,π-conjugation in such systems.

Captodative aminoalkenes can be represented by superposition of the structural fragments of enamines, on the one hand, and of α,β-unsaturated aldehydes, ketones or derivatives of carboxylic acids, on the other hand. This approach assumes that three canonical structures must be taken into account in the description of the reactivities of these compounds.



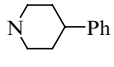
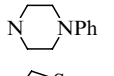
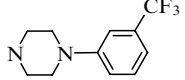
65 **2** **66**

If the structure **65** makes a larger contribution to the total electronic state of the molecule compared to that of the resonance form **66**, the β-carbon atom would be expected to possess higher nucleophilicity. In contrast, if the structure **66** predominates, captodative aminoalkenes must approach the corresponding activated alkenes in their chemical properties.

It is well known that the degree of conjugation between the π-electrons of the double bond and the lone electron pair of the nitrogen atom or the π-system of the activating group is manifested by the chemical shift of the olefinic proton in the ^{1}H NMR spectrum.[165–167] Apparently, this correlation can be made only if the steric parameters of the substituents at the nitrogen atoms are identical or similar to those at the β-carbon atom, whereas the differences in their chemical shifts are rather large. The ^{13}C NMR spectra are less dependent on the influence of the medium and the anisotropic effects and directly reflect the state of both the π and σ electron density in the molecule. For a series of push-pull alkenes, the difference in the chemical shifts of two adjacent carbon nuclei was used for estimating the degree of polarisation of the double bond.[165–167] However, it should be emphasised that ^{13}C NMR spectroscopy provides only qualitative estimates of the degree of polarisation of the double bond in the captodative aminoalkenes **2**. An effort to perform spectral analysis of 2-aminocycloalk-2-enones was made in the studies.[17,168]

The spectroscopic characteristics of captodative aminoalkenes containing the terminal double bond are given in Table 1. In the ^{1}H NMR spectra of these compounds, the signals for the

Table 1. Chemical shifts of the vinyl protons (in $CDCl_3$) in captodative aminoalkenes (**a**–**o**).

Compound	EWG	NR^1R^2	Chemical shifts of the vinyl protons /ppm	Ref.
a	CN	NH_2	4.67, 4.74	39
b	CN	NMe_2	4.33, 4.53 [a]	20
c	CN		4.55, 4.75	33, 169
d	CN		4.63, 4.83	170
e	CN		4.15, 4.42	33
f	CN		4.62, 4.80	170
g	CN		4.67, 4.87	170
h	CN		4.63, 4.83	170
i	CN		4.71, 4.92	170
j	CN	N(Me)Ph	4.64, 4.80	23
k	CO_2Me	NMe_2	4.43, 5.04	131
l	CO_2Me		4.54, 5.11	131
m	CO_2Me		4.63, 5.26	131
n	C(O)Me		4.48, 4.87	see [b]
o	C(O)Me		4.80, 5.20	128

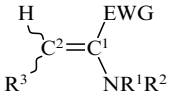
[a] In CCl_4. [b] The author's own data.

protons of the $H_2C=$ group are observed in the 'olefinic region' between the signals typical of vinylamines (δ = 3.40–3.78) [171] and the corresponding activated alkenes (δ = 5.75–6.36).[172–174] It should be noted that the chemical shifts of the olefinic protons depend on the nature of the captodative substituents. For example, the shifts $\delta(H_2C=)$ in the spectra of α-aminoacrylonitriles bearing the nitrogen-containing heterocycles with similar steric parameters (see Table 1, the compounds **c**–**i**) are changed as the electron-donating ability of the amino group changes. As in the series of unsubstituted enamines,[175] the strongest orbital interaction between the lone electron pair of the nitrogen atom and the double bond is observed in the pyrrolidine derivative **e**.

The insertion of the alkyl or aryl substituent at the β position enhances deshielding of the olefinic proton and provides the possibility for the existence of the geometric isomers (Table 2).

As in the case of unsubstituted enamines,[175] the signal for the olefinic proton of the *E* isomers of captodative aminoalkenes is always observed at higher field. The results of the study [48] showed that this regularity is violated by some formyl-substituted enamines. However, I thoroughly checked the molecular geometry by NMR spectroscopy using the Overhauser effect and found that the assignment of the signals made in the cited study [48] was incorrect. To a first approximation, the larger value of $\delta(HC=)$ for the *Z* isomers can be considered a result of strengthening of π,π-conjugation with a simultaneous decrease in *p*,π-conjugation due to the steric interaction between the β-substituent and the tertiary amino group. For this reason, the *Z* isomer is generally thermodynamically more stable.

Factors other than the structural characteristics of the molecule are also responsible for the ratio between the *E* and *Z* isomers.

Table 2. Chemical shifts of the olefinic protons and the carbon nuclei (in $CDCl_3$) in captodative aminoalkenes  (**a**–**s**).

Compound	EWG	NR^1R^2	R^3	Isomer	Chemical shifts of the olefinic protons /ppm	Chemical shifts of the carbon nuclei /ppm		Ref.
						C^2	C^1	
a	CHO		Me	*E*	5.15	122.7	148.8	176
				Z	5.48	140.4	151.8	
b	CHO		Me	*E*	5.80	124.2	147.4	176
				Z	6.20	141.8	150.3	
c	CHO	NEt_2	Me	*Z*	6.50	146.6	149.2	176
d	CHO		Ph	*E*	6.50 [a]	–	–	48
				Z	6.75 [a]	–	–	
e	CHO		Ph	*E* [b]	6.10	–	–	48
				Z	6.50	–	–	
f	CHO	NEt_2	Ph	*E*	6.66	–	–	see [c]
				Z	6.77	139.3	146.9	
g	C(O)Me		Me	*E*	4.80	–	–	129
h	C(O)Et		Me	*E*	4.90	106.9	150.6	129
i	C(O)Me	N(Me)Ph	Et	*Z*	6.55	116.9	147.2	54
j	C(O)Ph		Ph	*E* [b]	5.70	–	–	177
k	C(O)Ph		Ph	*E*	5.90	107.0	146.9	129
				Z [b]	6.06			177
l	C(O)Ph	NEt_2	Ph	*E*	5.57	103.40	145.75	see [c]
				Z	6.12	–	–	
m	CO_2Me		Me	*E*	4.54	102.2	140.4	178
				Z	6.08	127.8	–	
n	CO_2Me	$N(Me)C_6H_{11}$-cyclo	Me	*Z*	6.50	141.9	133.9	178
o	CO_2Me	N(Me)Ph	Et	*Z*	6.94	143.9	135.9	178
p	CO_2Me	N(Me)Ph	Pr	*Z*	6.89	142.5	136.6	178
q	CN	NMe_2	Me	*E*	5.08	113.5	–	20
				Z	5.82	133.3	–	
r	CN	NMe_2	Ph	*E*	5.82	115.3	–	20
				Z	6.18	129.8	–	
s	CN	N(Me)Ph	Et	*E*	5.81	135.6	121.3	179
				Z	6.15	146.4	146.3	

[a] In CCl_4. [b] The assignment to the *E* and *Z* isomers was made based on the author's own data. [c] The author's own data.

Example of *E,Z* isomerisation of captodative aminoalkenes, which proceeded rather readily either in the course of the reactions [48, 128, 129, 177] or upon subsequent purification (for example, upon distillation) [179] and even upon storage over a short period at room temperature,[129] are available in the literature.

For captodative aminoalkenes bearing the internal double bond, the chemical shift of the olefinic proton is also sensitive to variations in the nature of the electron-donating and electron-withdrawing substituents. Generally (although not necessarily), the stronger are the electron-withdrawing properties of the activating group and the weaker are the electron-donating properties of the amino group, the more substantial is the downfield shift of the signal for the olefinic proton. If the nitrogen atom possesses substituents capable of being involved in conjugation with the lone electron pair of the nitrogen atom, the chemical shift of the olefinic proton is increased further by 0.3 – 0.8 ppm. This fact also indicates that in these compounds conjugation between the double bond and the electron-withdrawing group typical of activated alkenes is virtually completely restored.

In the ^{13}C NMR spectra of captodative *N,N*-disubstituted aminoalkenes, the signal for the C^2 atom is observed at a higher field as compared to the signal for the C^1 atom. It should be noted that this regularity is also true for the series of enamines bearing such a powerful electron-withdrawing substituent as the formyl group.[176] The difference in the chemical shifts of the adjacent carbon atoms of the alkene fragment observed in these systems is comparable with that for unsubstituted enamines (30 – 45 ppm). These data are unambiguously indicative of high polarisation of the double bond and are a strong argument in favour of the predominant contribution of the structure **65** to the ground electronic state of the molecule.

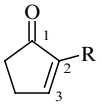
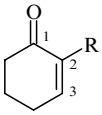
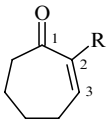
In the case of *N*-methylaniline derivatives containing the geminal electron-withdrawing group, an inversion of the usual order of the chemical shifts of the C^1 and C^2 nuclei is observed. The difference $\delta(C^2)-\delta(C^1)$ reaches +14.3 ppm (see Table 2, compounds **o**, **p** and **s**). The exceptions are enamines bearing the carbonyl group for which the positions of the resonance signals for the carbon nuclei are less dependent on the nature of the amino group (see Table 2, compounds **h**, **i**, **k** and **l**). A satisfactory explanation for this phenomenon is lacking.

The presence of conjugation in the C=C–EWG system of the carbonyl-containing captodative aminoalkenes **2d** is evidenced by the presence of intense absorption bands at 1655 – 1690 (C=O) and 1585 – 1620 cm^{-1} (C=C) in their IR spectra.[180] The former spectral region is close to the stretching vibration frequencies characteristic of the conjugated carbonyl group, whereas the frequencies belonging to the latter region are somewhat lower than the vibration frequencies of the double bond in the corresponding unsubstituted enals and enones and are noticeably lower than the vibration frequencies of the C=C bond in simple enamines.

Analysis of the IR spectra of captodative carbonyl-containing enamines by comparing the intensities of the absorption bands of the C=C and C=O groups led Arnould *et al.*[177] to the conclusion that the *E* isomer in the ground state adopts the *s-cis* conformation, whereas the *Z* isomer has the *s-trans* conformation.

Finally, the efficiency of *p,π*-conjugation in 2-aminocycloalk-2-enones depends dramatically on the ring size (Table 3). For example, the shifts δ(HC=) in the ^1H NMR spectra of piperidine and morpholine derivatives of cycloalkenones increase substantially on going from seven- to six- and then to five-membered rings. As in the spectra of acyclic enamines bearing the geminal carbonyl group, the resonance signals for the C^3 atom in the spectra of 2-aminocycloalk-2-enones containing mono- and disubstituted amino groups are shifted upfield as compared to the signals for the C^2 atom. The difference between the chemical shifts

Table 3. Chemical shifts of the olefinic protons in 2-aminocycloalk-2-enones.

Compound	R	Chemical shifts of the olefinic protons /ppm	Solvent	Ref.
	$NHPr^i$	5.98 [a]	$CDCl_3$	155
	$NHBu^t$	5.83 [b]	$CDCl_3$	155
		5.91	CCl_4	181
		6.42	$CDCl_3$	182
		5.70 [c]	CCl_4	156
		5.86 [d]	$CDCl_3$	86
		5.23	CCl_4	183
		5.13	CCl_4	183

The chemical shifts of the carbon nuclei: [a] $\delta(C^3)$ = 120.61, $\delta(C^2)$ = 145.13 (see Ref. 155); [b] $\delta(C^3)$ = 121.04, $\delta(C^2)$ = 142.62 (see Ref. 155); [c] $\delta(C^3)$ = 126.1, $\delta(C^2)$ = 148.1 (see Ref. 146); [d] $\delta(C^3)$ = 133.7, $\delta(C^2)$ = 150.8 (see Ref. 146).

of the β- and α-sp^2-hybridised carbon atoms varies between −22 and −27 ppm, whereas this difference for unsubstituted cyclic α,β-unsaturated ketones ranges from 21 to 33 ppm. Undoubtedly, this effect should be related to the fact that *p,π*-conjugation between the nitrogen atom and the double bond dominates over the π,π-interaction between the double bond and the carbonyl group. All the aforesaid send one in the critical review of the conclusion made previously [17] that the canonical structure **66** is more appropriate for the description of the ground state of 2-aminocycloalk-2-enones.

Hence, the spectroscopic data provide evidence for the presence of competitive *p,π*- and π,π-conjugation in the captodative aminoalkenes **2a** – **d**, the efficiency of the conjugation being determined by the nature of the functional groups. In the general case, the compounds under consideration are intermediate between unsubstituted enamines and α,β-unsaturated aldehydes, ketones or derivatives of carboxylic acids. What this means is these systems would be expected to exhibit dual reactivity with respect to nucleophilic and electrophilic reagents.

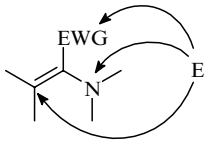
IV. Reactions of captodative aminoalkenes

Being polyfunctional systems, the captodative aminoalkenes **2a** – **d** are not only valuable starting reagents for organic synthesis but are also excellent models for solution of some problems of alternative reaction centres. Analysis of the data available in the literature shows that insignificant (at first glance) changes in the structure of the substrate or the reagent and variations in the reaction conditions can give rise to radically different reaction products. In addition, the polyfunctional properties of the compounds under consideration are often responsible for their unexpected and surprising cascade transformations.

1. Reactions with electrophilic reagents

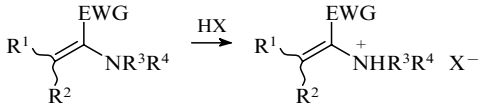
a. Protonation and hydrolysis

Apparently, the nitrogen atom, the β-carbon atom and the heteroatom of the activating group serve as the nucleophilic centres in captodative aminoalkenes. Consequently, the regioselectivity of the electrophilic attack is the central problem of the reactions of the compounds **2a–d** with electrophilic reagents.



Protonation serves as the simplest test for the reactivity of such systems. Unlike simple enamines generating stable immonium salts[175] and the push-pull aminoenones **1c**, which are protonated predominantly at the oxygen atom,[10] the captodative aminoalkenes **2a**,**c**,**d** can add the proton at each of three major nucleophilic centres depending on the structure of the substrate, the nature of the protonating reagent and the reaction conditions.

Thus the reactions of mineral or strong carboxylic acids with the aminoalkenes **2**, which are activated by the geminal cyano,[184] carbonyl,[185] formyl[186,187] or azomethine group,[188] generally afford the corresponding enammonium salts **67a**,**c–e**. It should be emphasised that the hydrochlorides **67a**,**c**,**d** (X = Cl) were isolated and completely characterised.



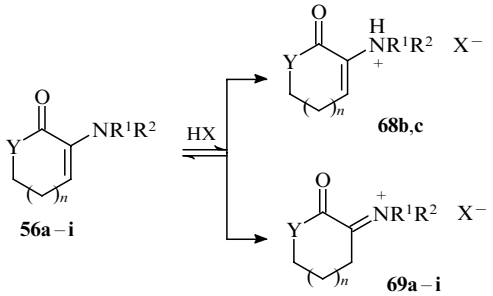
2a,**c–e** **67a**,**c–e**

EWG = CN (**a**), C(O)Ph (**c**), CHO (**d**), CH=NMe (**e**);

R^1 = H, R^2 = Me, Ph; $R^1–R^2$ = $(CH_2)_5$;

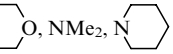
NR^3R^4 = $NHBu^t$, NEt_2, , ; X = Cl, CF_3CO_2, CCl_3CO_2.

The regioselectivity of protonation of the 2-aminocycloalk-2-enones **56a–i** is determined by the ring size and the nature of the amino group.[121,189] For example, the reaction of a solution of trifluoroacetic acid in $CDCl_3$ with morpholinocyclohexenone **30** afforded exclusively enammonium salt **68b** (NR^1R^2 is morpholino), whereas the reaction with the seven-membered homologue **56c** (NR^1R^2 is morpholino) performed under the analogous conditions led to protonation both at the heteroatom to give compound **68c** (NR^1R^2 is morpholino) and at the β-carbon atom to generate the corresponding immonium salt **69c**.[121] Protonation of aminocyclopentenones (**56a**) as well of the cyclohexenone **56b** containing the monosubstituted amino group (NR^1R^2 = NHC_6H_4Me-4) afforded immonium salts **69a**,**b**, which underwent subsequent enolisation.[121] The dependence of the regioselectivity



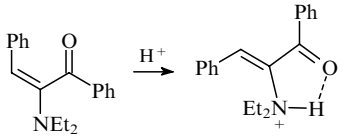
56a–i

Y = CH_2: n = 0 (**a**), 1 (**b**), 2 (**c**); Y = CHMe: n = 0 (**d**), 1 (**e**), 2 (**f**);

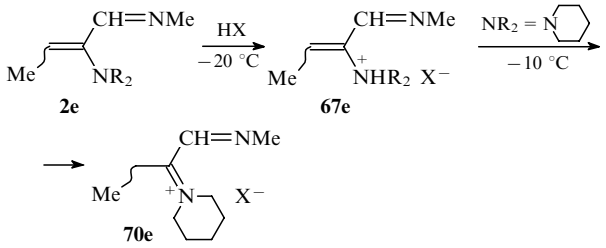
Y = NH: n = 0 (**g**), 1 (**h**), 2 (**i**); NR^1R^2 = NHBn, NHC_6H_4Me-4, , NMe_2, ; X = CF_3CO_2, Cl.

of protonation on the ring size was also observed in the case of the enaminolactams **56h**,**i**.[190,191]

The formation of nitrogen-protonated captodative aminoalkenes is a rare example of the existence of enammonium salts, which, as a rule, readily undergo isomerisation to the corresponding immonium salts.[175] A rather stable enammonium salt was first synthesised in 1976.[192,193] However, really stable compounds with the enammonium structure were prepared only upon protonation of the captodative aminoalkenes **2c**,**d**. Apparently, their stability is associated with the powerful influence of the electron-withdrawing geminal substituent and the stabilising effect of the intramolecular hydrogen bond that is formed.† This assumption is supported by the fact that protonation of (*s-cis*-diethylamino)-benzylideneacetophenone gave rise to the enammonium salt adopting the *s-trans* conformation.[185]



The salts **67d** are so stable that they were not transformed into immonium salts at all.[186,187] As shown in the previous section, a decrease in the electron-withdrawing ability of the activating group in the captodative aminoalkenes **2** leads to an increase in the proportion of the resonance form **65** bearing a negative charge on the β-carbon atom. As a consequence, these aminoalkenes exhibit properties of simple enamines. Actually, unlike the formyl-substituted enamines **2d**, their azomethine analogues **2e** generated the enammonium salts **67e**, which underwent slow isomerisation in $CDCl_3$ solution to give the more stable C-protonated derivatives **70e**.[188]



2e **67e**

NR_2 = , ; X = CF_3CO_2, CCl_3CO_2.

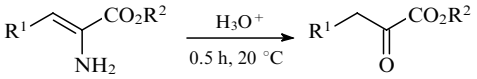
The result of the reaction of the acyclic aminoenones **2c** with acids depends substantially on the nature of the protonating reagent and the reaction conditions. Thus the reaction with anhydrous HCl was accompanied predominantly by protonation at the nitrogen atom, whereas the formation exclusively of immonium salts was observed in a solution of trifluoroacetic acid.[185] The difference in the behaviour of inorganic and carboxylic acids is accounted for by the bifunctional catalytic action of carboxylic acids in the course of proton transfer from the nitrogen atom to the carbon atom.[194]

In the enammonium salts **67**, *p*,π-conjugation becomes impossible. Moreover, the donor fragment NR^3R^4 is transformed into the acceptor $N^+HR^3R^4$ upon quaternisation. The formation of the system with the geminal electron-withdrawing substituents results in the essential electron density redistribution. This is the reason that the multiplicity of the C=C bond is somewhat decreased and, as a consequence, the barrier to rotation about this bond is substantially lowered. Examples of *E*,*Z* isomerisation of enammonium salts (**67c–e**), which proceeded very readily, were cited in Refs 185–188.

In spite of the fact that enammonium salts do not necessarily undergo tautomeric transformations into immonium salts, the

† The author's own data.

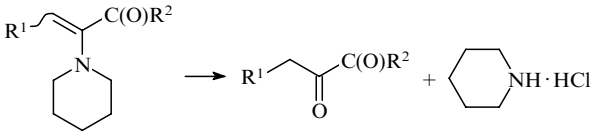
captodative aminoalkenes **2b–d** are hydrolysed to give the corresponding α-dicarbonyl compounds. For example, the aminoesters **62a–e** were virtually quantitatively transformed into esters of 2-oxocarboxylic acids **71a–e** in a 1 M solution of hydrochloric acid at room temperature during 0.5 h.[162]



62a–e **71a–e**

R^1 = Me (**a**), Et (**b**), Pr^n (**c**), Pr^i (**d**), Ph (**e**); R^2 = Me, Et.

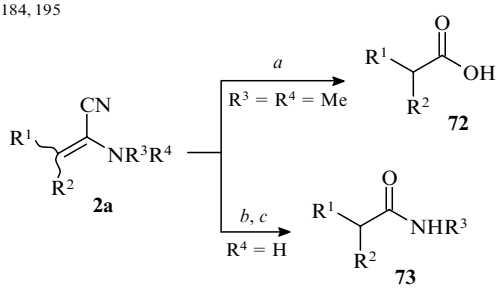
The acyl- and formyl-substituted enamines **2c**,**d** are also hydrolysed in an acidic medium.[160,186] Various α-diketones can be prepared from the compounds **2c** by varying the substituents in the starting substrate.



2c,**d**

R^1 = Alk, Ar; R^2 = H, Alk, Ar.

Protonation and hydrolysis of the captodative aminoalkenes **2** are used in a number of simple and efficient synthetic procedures. An example is hydrolysis of the 1-cyanoenamines **2a** containing the unsubstituted, mono- or disubstituted amino group to give the corresponding carboxylic acids **72**.[20,110,150] The reactions of the cyanoenamines **2a** with Lewis acids ($AlCl_3$ or $ZnCl_2$) in ethanol followed by hydrolysis gave rise to monosubstituted amides **73**.[184,195]



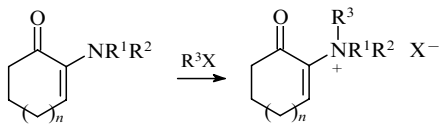
2a **72** **73**

R^1 = H, Me, Et; R^2 = Me, Et, Ph, 4-$MeOC_6H_4$; $R^1–R^2$ = $(CH_2)_5$; R^3 = R^4 = Me; R^4 = H: R^3 = H, Me, Pr^i, Bu^t, cyclo-C_6H_{11}.

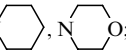
(*a*) H_2O, H^+, (*b*) $AlCl_3$, EtOH or HCl, PhH; (*c*) H_2O.

b. Alkylation and acylation

Alkylation of captodative aminoalkenes requires more drastic conditions and affords the corresponding enammonium salts regardless of the nature of the alkylating reagent. It is not surprising that the nature of the amino group exerts a pronounced effect on the ease of the reaction. Thus prolonged refluxing of 2-aminocycloalk-2-enones **56a**,**b** with alkyl halides afforded *N*-alkyl derivatives **74a**,**b**.[181,189]



56a,**b** **74a**,**b**

n = 0 (**a**), 1 (**b**); NR^1R^2 = NMe_2, ; R^3 = Me, Et; X = I, Cl, BF_4.

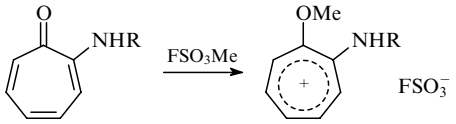
The cyanoenamines **2a** containing a bulky substituent on the monosubstituted amino group do not react with alkyl halides or alkyl *p*-toluenesulfonates. However, aminoalkenes bearing the disubstituted amino group can be prepared with the use of stronger alkylating reagents, for example, of dialkyl sulfates, alkyl fluorosulfonates or triethyloxonium tetrafluoroborate.[196] In the latter case, alkylation proceeded under mild conditions and was not accompanied by side processes.



(62%–95%)

R^1 = Me, Et; R^2 = Me; $R^1–R^2$ = $(CH_2)_5$; R^3 = Me, Pr^i, Bu^t, cyclo-C_6H_{11}.

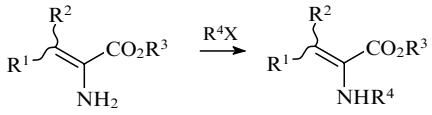
'Magic methyl' was successfully used for quantitative *O*-alkylation of 2-aminotropone (**75a**) and 2-methylaminotropone (**75b**).[197] It is reasonable to assume that the driving force for this reaction is the formation of the aromatic system of tropylium cation **76a**,**b**.



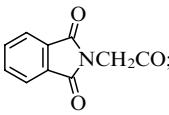
75a,**b** **76a**,**b** (100%)

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

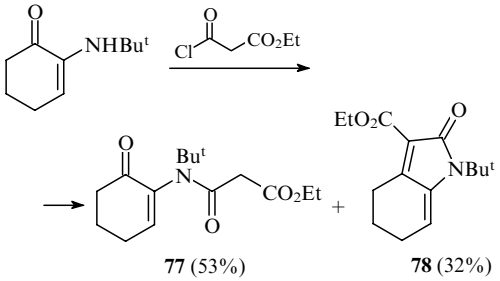
The primary, secondary and tertiary captodative aminoalkenes **2** are difficult to acylate. Thus attempts to perform the reactions of the primary aminoalkenes **2b** with acetyl chloride or acetic anhydride failed.[138] However, some reactions of the compounds **2b** with acid chlorides or anhydrides of strong carboxylic acids produced *N*-acylated products in moderate yields.[95,96,104,105,107,198–200] These reactions were used in the peptide synthesis.[200–204]



2b (8%–60%)

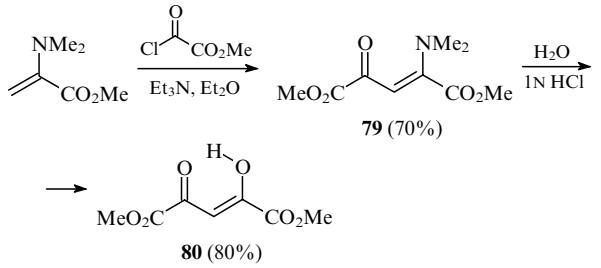
R^1 = H, Me; R^2 = Me, Et, Pr^n, Pr^i, Ph, $MeOCH_2OC_6H_4$, Het; R^3 = Me, Et; R^4 = $ClCH_2CO$, BnOCO, 4-$MeC_6H_4SO_2$, CF_3CO, ; X = Cl, CF_3CO_2.

N-Acylation of 3-aminocoumarin derivatives was successfully carried out under the action of phthalic anhydride and 2-chloronicotinoyl chloride.[205,206] Perfluoroacyl fluorides proved to be excellent acylating reagents for the formyl-substituted aminoalkenes **2d**.[207] The reaction of 2-*tert*-butylaminocyclohex-2-enone with ethyl chlorocarbonylacetate in the presence of pyridine and 4-dimethylaminopyridine afforded a mixture of *N*-acylated derivative **77** and the product of its subsequent intramolecular condensation **78**.[208]

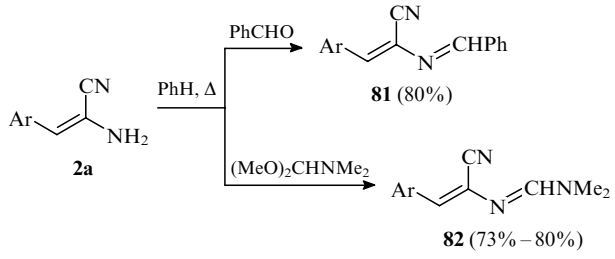


77 (53%) **78** (32%)

The formation of diester **79** in the reaction of methyl 2-dimethylaminoacrylate with methoxalyl chloride is a rare example of C-acylation of captodative aminoalkenes. The compound **79** is readily hydrolysed to the symmetrical ester of dioxo acid **80**.[131]

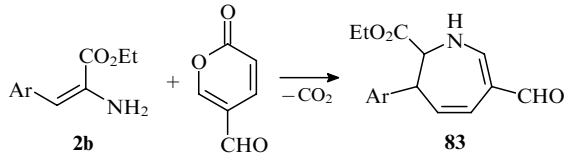


Unsymmetrical amino groups in captodative aminoalkenes are sufficiently basic and nucleophilic that they can be subjected to condensation with carbonyl compounds. These aminoalkenes smoothly react with aldehydes or dimethylformamide dimethyl acetal to form the corresponding azomethines.[94, 106, 110, 138, 209] Even the unstable cyanoenamines **2a** were readily transformed into 2-aza-3-cyanobuta-1,3-dienes **81** and **82** upon refluxing in benzene with azeotropic distillation of water.[110]



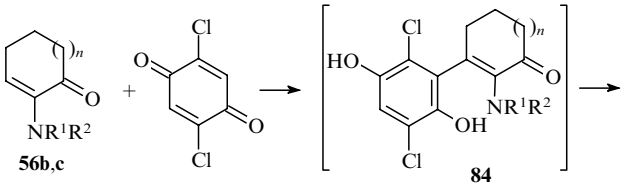
Ar = Ph, 4-$MeOC_6H_4$.

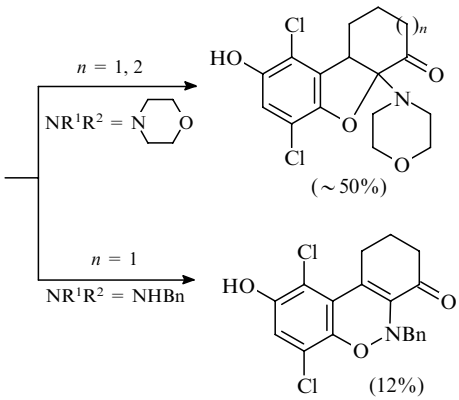
The reactions of the aminoalkenes **2b** with 5-formylpyran-2-one, which begin with the ring opening, provide the convenient means for preparing dihydroazepines **83**.[210]



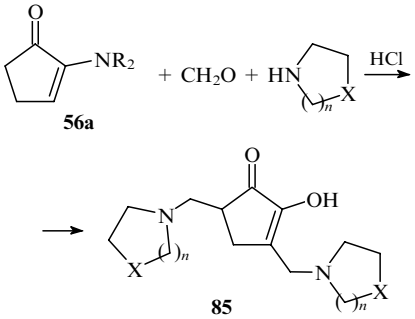
Ar = Ph, 4-ClC_6H_4.

In reactions with some carbonyl compounds, captodative aminoalkenes containing mono- and disubstituted amino groups act as C-nucleophiles. For example, the reactions of the 2-aminocycloalk-2-enones **56b**,**c** with quinones afforded various heterocyclic compounds.[122] Their structures depend on the ring size and the nature of the amino group of the substrate. It was believed [11, 122, 211, 212] that the first step of the reaction gave rise to derivative **84**.

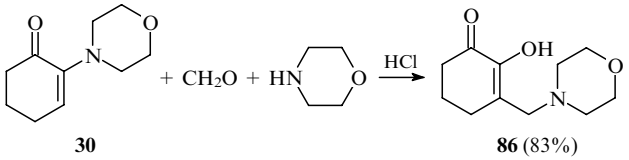




The first investigations into the involvement of the captodative aminoalkenes **2** in aminomethylation demonstrated that the structure of the resulting Mannich base depends dramatically on the ring size of the substrate and the reaction conditions.[181, 213] Thus the 2-aminocyclopent-2-enones **56a** produced bis-aminomethylated compounds **85** in moderate yields,[181] whereas the reaction of the aminoalkene **30** gave rise only to monoaminomethylated product **86** even in the presence of a twofold excess of paraformaldehyde and morpholine hydrochloride.[213]

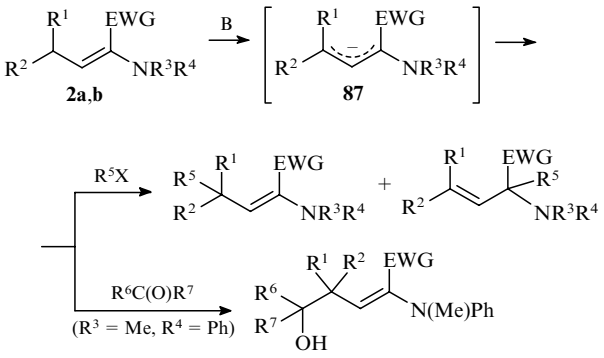


n = 1, X = CH_2; n = 2, X = CH_2, O.



c. Reactions of electrophilic reagents with carbanions generated from captodative aminoalkenes

As mentioned above, the β-substituted captodative aminoalkenes **2a**,**b** are capable of being deprotonated under the action of strong bases to give allylic anions **87**, which can react with various electrophilic reagents (alkyl halides, aryl halides and carbonyl compounds) either exclusively at the γ-carbon atom or simultaneously at the α- and γ-carbon atoms.[34, 57, 151, 178, 214–218] The fact that the attack proceeds predominantly at the γ-position is attributed primarily to the steric characteristics of the substrate and the electrophile. These reactions are preparatively valuable because they allow modifications of captodative aminoalkenes to obtain compounds, which are used in the synthesis of various polyfunctional systems.

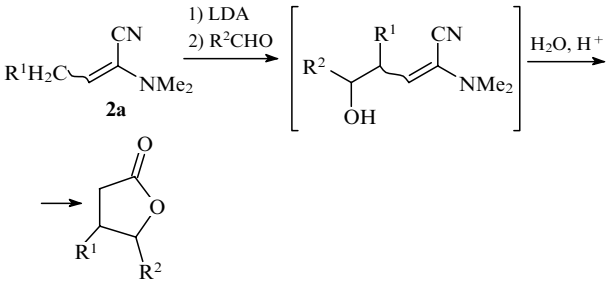


EWG = CN (**a**), CO_2Me (**b**); R^1 = H, Me, PhS, $PhSO_2$; R^2 = H, Me;

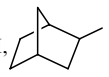
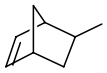
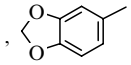
NR^3R^4 = NMe_2, NEt_2, , N(Me)C_6H_{11}-cyclo, N(Me)Ph;

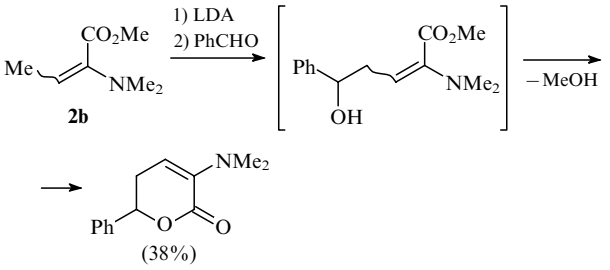
R^5 = Me, Et, Pr^i, Bu^n, n-C_5H_{11}, Ph, Bn, CH_2=$CHCH_2$, MeCH=$CHCH_2$, Me_2C=$CHCH_2$; X = Hal; R^6 = H, Me; R^7 = Me, Pr^i, Ph; R^6–R^7 = $(CH_2)_5$; B = Bu^nLi, LDA, Bu^tOK.

Some tertiary enamines **2a**,**b** react with aldehydes in the presence of strong bases to give five- or six-membered lactones depending on the nature of the activating group.[20, 214]



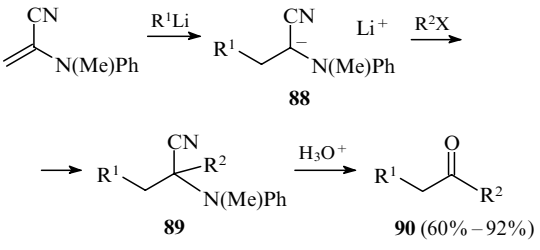
(18%–46%)

R^1 = H, Me; R^2 = Ph, $Me(CH_2)_3$, $Me(CH_2)_5$, MeCH=CH, , , .



(38%)

The Michael addition of various anions to 2-(*N*-methylanilino)acrylonitrile afforded initially anions **88**.[23, 35, 58] Their subsequent reactions with electrophiles gave rise to bifunctional



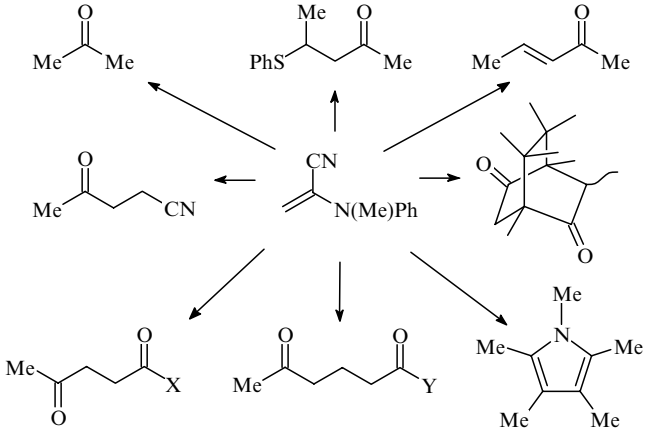
88

89 **90** (60%–92%)

R^1 = Bu^t, Ph, $PhCOCH_2CH_2$, PhCH=CHCHPh, $Bu^tC(O)CH_2$; R^2 = H, Me, Et, Bn; X = OH, I. Br.

derivatives **89**, which were hydrolysed to the corresponding carbonyl compounds **90**.[23, 35, 58]

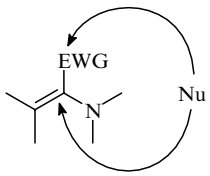
When developing this methodology and varying the nature of the electrophile and the organolithium derivative, Ahlbrecht and co-workers unveiled the considerable synthetic potential of one of the simplest captodative aminoalkenes, *viz*., 2-(*N*-methylanilino)acrylonitrile. This compound proved to be a versatile and readily accessible starting reagent for the one-pot synthesis of ketones,[23] β-, γ- and δ-diketones,[179, 219–221] γ- and δ-oxoaldehydes,[221, 222] β-phenylthioketones, which were transformed into α,β-unsaturated carbonyl compounds[223] upon pyrolysis, as well as of derivatives of oxocarboxylic acids (nitriles,[224, 225] esters and amides[226]). The efficient syntheses of bicyclic diketones[220] and pyrroles[179] based on 2-(*N*-methylanilino)acrylonitrile are worthy of notice.



X = H, Alk, Ar, OR, NR_2; Y = H, Alk, Ar.

2. Reactions with nucleophilic reagents

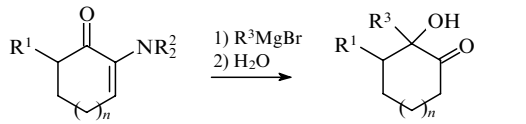
Taking into account the electronic structure of captodative aminoalkenes, one would expect that these compounds will act as poor Michael acceptors and the attack of nucleophilic reagents will proceed predominantly either at the electrophilic centre of the activating group or at the α-carbon atom.



Actually, attempts to perform the 1,4-addition of some C- and N-nucleophiles to 2-aminocycloalk-2-enone have not met with success. Only nitroalkanes produced Michael adducts in moderate yields (see Ref. 17).

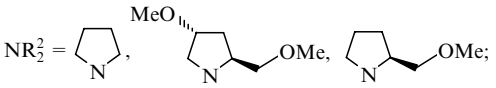
In the study on the cyanoenamines **2a**,[54] it was concluded that the direction of the addition of nucleophiles generally follows the rule of hard and soft acids and bases (HSAB). However, some of nucleophilic reactions of captodative aminoalkenes do not obey the HSAB principle.

The 1,2-addition of organometallic compounds to form a new C–C bond is the most extensively used nucleophilic reaction of captodative aminoalkenes. The reactions of the 2-aminocycloalk-2-enones **56a**–**d** with Grignard reagents proceeded regiospecifically to produce 2-hydroxycycloalkanones **91a**–**d** in good yields.[120, 227–230]



56a–c, j **91a–c, j** (35%–88%)

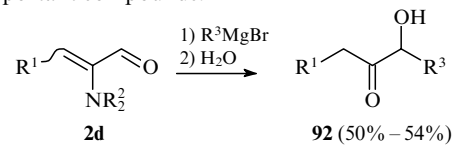
n = 0 (**a**), 1 (**b**), 2 (**c**), 3 (**j**); R^1 = H, Me;



R^3 = Me, Et, Ph, CH_2=CH, CH_2=CMe.

1,4-Adducts were detected in no cases. The reactions with the use of chiral substrates afford hydroxyketones with high enantioselectivity, which depends on the solvent used. Thus the enantiomeric excess (*ee*) achieved in the reaction of the aminoenone **56a** [R^1 = H, NR^2_2 is (2*S*)-2-methoxymethylpyrrolidino] with CH_2=CHMgBr in tetrahydrofuran was only 33%, whereas it reached 84% in a Et_2O–THF mixture (9 : 1).[230] Interestingly, the absolute configuration of the optically active α-hydroxycycloalkanones **91** depends on the nature of the substituent R^2. For example, the aminoenone **56b** [R^1 = H, NR^2_2 is (2*S*)-2-methoxymethylpyrrolidino] reacted with methyl- or ethylmagnesium bromide to give the compounds (2*R*)-**91b** (R^3 = Me or Et) with an optical purity of 92%–95%, whereas the hydroxyketones **91b** (R^3 = CH_2=CH, Ph), which were obtained by the reactions of the same substrate with vinyl- or phenylmagnesium bromide, adopt an opposite configuration (*ee* 58%–95%).[120] The authors attributed these stereochemical results to the difference in the structure of an intermediate complex of the organometallic compound with the aminoenone.

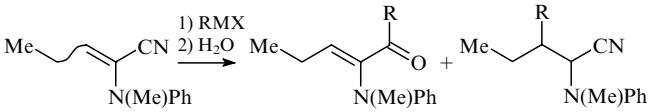
Like 2-aminocycloalk-2-enones, acyclic captodative aminoalkenes react with organometallic compounds to form predominantly 1,2-adducts. Thus the formyl-substituted enamines **2d** are readily transformed into acyloins **92**, which provides the basis for a new efficient procedure for the preparation of these synthetically important compounds.‡



2d **92** (50%–54%)

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

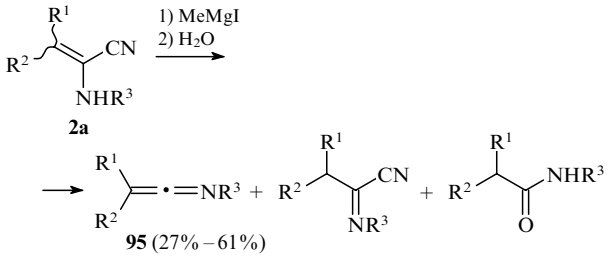
Analogously, the reactions of 2-(*N*-methylanilino)pent-2-enonitrile with organomagnesium and organozinc reagents proceed as the 1,2-addition. However, the reaction of the same substrate with benzylmagnesium bromide gave rise to 1,4-addition product **94b** along with 1,2-adducts **93b** in comparable amounts.[54]



93a–c (5%–60%) **94b** (19%)

RMX = MeMgI, BnMgCl, AllZnBr; R = Me (**a**), Bn (**b**), All (**c**).

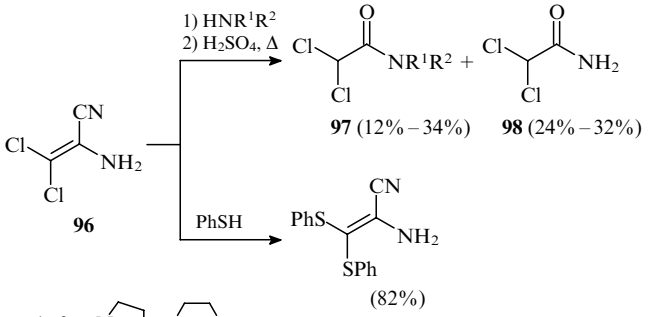
In the case of the secondary cyanoenamines **2a**, Grignard reagents serve as strong bases. These reactions afford trialkylketenimines **95** as the major reaction products.[231]



95 (27%–61%)

R^1 = R^2 = Me, Et; R^3 = Pr^i, Bu^t.

In the reactions with captodative aminoalkenes, N-nucleophiles attack either the electrophilic centre of the activating group or the α-olefinic carbon atom. For example, 2-amino-3,3-dichloroacrylonitrile (**96**) reacted under mild conditions with primary and secondary amines to give amides **97** and **98**.[232] The mechanism of formation of these compounds involves the nucleophilic attack at the carbon atom bound to the cyano group followed by hydrolysis of the amidines generated in the first step. Curiously, the chlorine atoms were not replaced even in the presence of a fourfold excess of the amine (*cf.* Ref. 82). At the same time, the reaction of the substrate **96** with more nucleophilic thiophenol proceeded regiospecifically with the replacement of both chlorine atoms.[232]

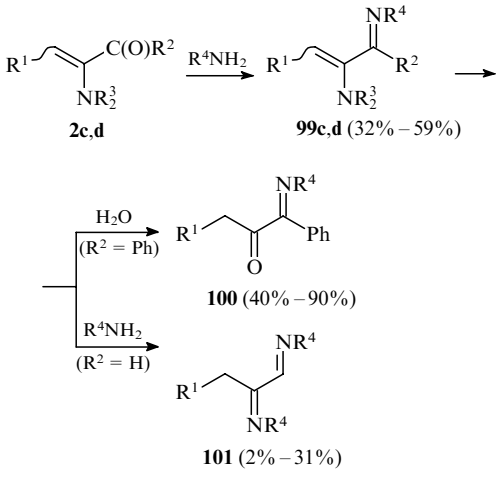


97 (12%–34%) **98** (24%–32%)

96 (82%)

NR^1R^2 = , , NHPr.

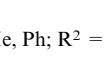
Condensation of primary amines and hydrazine derivatives with the captodative aminoalkenes **2c,d** proceeded exclusively at the carbonyl group. Under the action of the liberated water, the initially formed azomethinoenamines **99c** were hydrolysed in a basic medium to give oxo derivatives **100**.[233] Under these conditions, the compounds **99d** were converted into bis-azomethines **101**. The ratio **99d** : **101** depends on the reaction conditions and the nature of the starting reagents.[234] Under analogous conditions, guanidine and thiourea did not react with the aminoalkenes **2c**.[233]



2c,d **99c,d** (32%–59%)

100 (40%–90%)

101 (2%–31%)

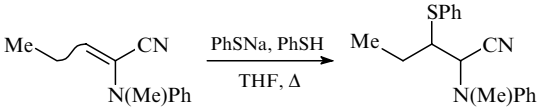
R^1 = Me, Ph; R^2 = Ph (**c**), H (**d**); NR^3_2 = NEt_2, ;

R^4 = Me, Bu, NH_2, NHEt.

‡ The author's own data.

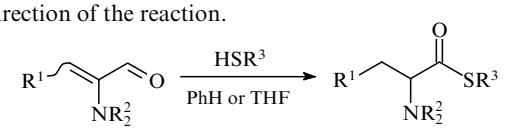
2-Morpholinocyclohex-2-enone (**30**) undergoes condensation with ethanolamine acting as a N-nucleophile to give the corresponding azomethine derivative.[235] As mentioned in Section II.2.a, 2-aminocycloalkenones are involved in *ipso*-substitution reactions under the action of primary aromatic amines and even ammonia.[17,88]

Unlike N-nucleophiles, S-nucleophiles can be involved in the intra- or intermolecular conjugated addition to captodative aminoalkenes. For example, prolonged refluxing of 2-(*N*-methylanilino)pent-2-enonitrile with sodium thiophenoxide and thiophenol in THF gave rise to 1,4-addition product **102**.[54]



102 (70%)

The reactions of the aminoalkenes **2d** with alkane- or arenethiols or dithiols afforded neither 1,2- nor 1,4-adducts; instead, the compounds **2d** were unexpectedly transformed into the corresponding thiol esters of α-amino acids **103** in yields of up to 87%.[236] Neither changes in the structures of the reagents nor variations in the reaction conditions have an effect on the direction of the reaction.

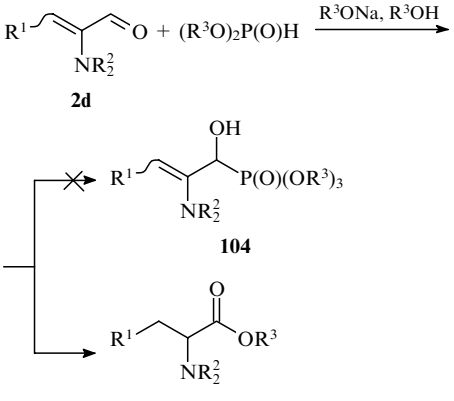


2d **103** (40% – 87%)

R^1 = Me, Ph; NR^2_2 = NEt_2, N⟨⟩; R^3 = Et, Bu, Ph, CH_2CH_2SH.

This methodology, which allows the construction of the $CH(NR_2)CO$ fragment, was further developed in the synthesis of esters of α-amino acids containing the disubstituted amino group. It is well known that these compounds are important precursors for the design of new pharmaceuticals and for the preparation of polyfunctional compounds.

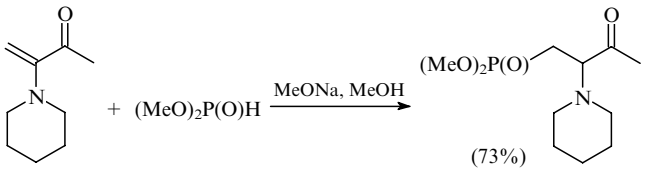
It appeared that the reactions of the formyl-substituted enamines **2d** with an equimolar amount of dialkyl phosphonate in the presence of sodium alkoxide afforded esters of *N*,*N*-disubstituted α-amino acids **105** rather than the expected phosphonates **104**.[237–239] The moderate yields of the esters **105** were accounted for by competitive anionic polymerisation of the starting substrate or one of the intermediates under the action of sodium alkoxide. In the absence of the catalyst, the reaction of the phosphonate with the aminoalkene **2d** did not take place.



105 (30% – 37%)

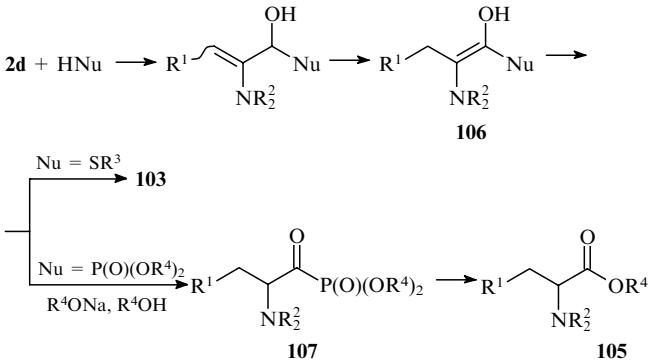
R^1 = Me, Pr, Ph; NR^2_2 = NEt_2, N⟨⟩, N⟨⟩O; R^3 = Me, Et.

Unlike the formyl-substituted enamines **2d**, the aminoenones **2c** containing the terminal double bond are involved in the regiospecific 1,4-addition to dimethyl phosphonate. Thus 3-piperidinobut-3-en-2-one smoothly produced the Michael adduct.[239] The 1,2-adduct was not detected even in trace amounts. 2-Diethylaminobenzylideneacetophenone did not react with dimethyl phosphonate.



(73%)

The scheme providing an explanation for the generation of the amino acid derivatives **103** and **105** was proposed in the studies.[236–240] Undoubtedly, the first step involves the addition of the nucleophile to the formyl group of the aminoalkene **2d**. The key step of the scheme involves isomerisation of the initially formed 1,2-adduct to give thermodynamically more stable tetrasubstituted alkene **106**, which is rapidly transformed into the thiol ester **103** (in the case of S-nucleophiles) or ketophosphonate **107** (in the case of P-nucleophiles). Heterolysis of the C–P bond in the intermediate **107** readily proceeds under the action of alkoxides to give the ester of α-amino acid **105**.

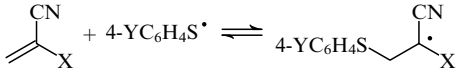


The proposed hypothesis was strongly supported by isolation of the enol **106** [Nu = $P(O)(OMe)_2$] as a stable silyl ether generated in the reaction of the α-formyl-substituted enamine **2d** (R^1 = Ph, NR^2_2 = NEt_2) with dimethyl trimethylsilyl phosphite.[239] The above-described reaction of the substrates **2d** with dialkyl phosphonates is one of the first examples of the vicarious nucleophilic addition. From the practical standpoint, the reactions of soft nucleophiles with the aminoalkenes **2d** provide a new convenient procedure for the one-pot synthesis of derivatives of *N*,*N*-disubstituted α-amino acids.

3. Radical reactions

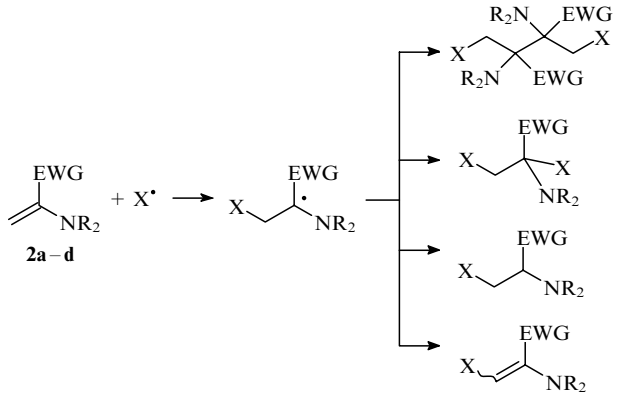
Aminoalkenes containing a geminal activating group are excellent radicalophiles. The stabilising effect of captodative substituents on the radical centre has been postulated more than 20 years ago [1] and was subsequently confirmed by numerous experiments.

Ito *et al.*[241] carried out the kinetic study of the addition of arylthiyl radicals to acrylonitriles bearing the electron-donating group X at the α position. It appeared that the rate constant of this reaction decreases in the series NR_2 > OR > Cl > OAc > Me > H. This sequence correlates well with their electron-donating ability and indicates that captodative substituents exert the synergistic effect on stability of the radical. It should be noted that the relative activity of amino derivatives is ~20 times higher than that of their alkoxy analogues and ~550 times higher than the reactivity of unsubstituted acrylonitrile. Consequently, the aminoalkenes **2** proved to be the most efficient radical traps of all the known compounds.



X = N⟨⟩O, OEt, Cl, OAc, Me, H; Y = H, Me, Bu^t, OMe, Cl, Br.

This ability of captodative systems finds versatile synthetic applications.[4, 132, 242] Below are given the possible pathways of transformations of the radical intermediate giving rise to various polyfunctional compounds with high selectivity.

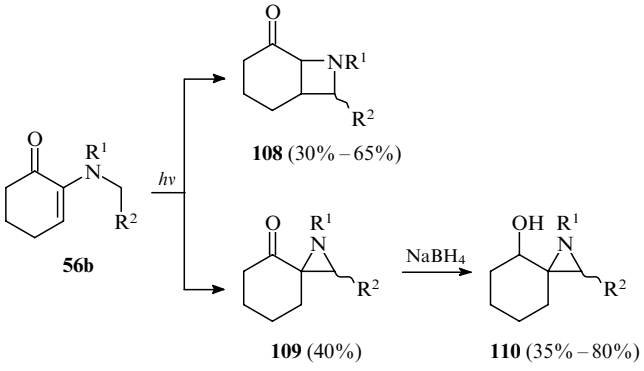


2a–d

EWG = CN (**a**), CO_2R (**b**), C(O)R (**c**), CHO (**d**); R = Alk, Ar.

The behaviour of captodative aminoalkenes in photolysis is very sensitive to insignificant structural changes in the substrate and primarily to the nature of the substituents at the nitrogen atom. Conceivably, that is why it is difficult to make generalisations and predict the direction of the reaction based on the available data.

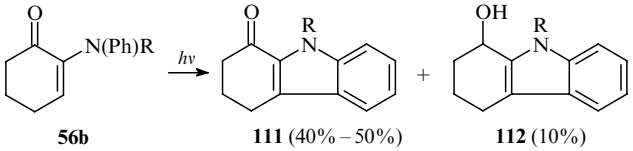
In most cases, photolysis of the 2-aminocyclohex-2-enones **56b** [R^1 = Et, R^2 = Me; $R^1–R^2$ = $(CH_2)_4$, $(CH_2)_2OCH_2$] containing the α-hydrogen atoms in the substituents at the nitrogen atom is accompanied by elimination of one of these hydrogen atoms. Subsequent cyclisation of the resulting biradical intermediate affords bicyclic azetidine derivatives **108**.[189, 243] Analogues of the compounds **56b** bearing the methyl group at position 3 produced the azetidines **108** in low yields.[189] In some cases, the reactions of the aminoalkenes **56b** performed under the same conditions unexpectedly gave rise to spiroaziridines **109**, which were isolated as alcohols **110** after reduction of the carbonyl group.[119, 244] It is believed that the aziridines **109** were formed through α-hydrogen abstraction followed by the rearrangement of unstable azabicyclooctenol.[119]



56b **108** (30%–65%) **109** (40%) **110** (35%–80%)

108: R^1 = Et, R^2 = Me; $R^1–R^2$ = $(CH_2)_4$, $(CH_2)_2OCH_2$;
109, **110**: R^1 = H, R^2 = Ph; R^1 = Bn, R^2 = Ph;
R^1 = Me, All, R^2 = CH=CH_2.

Photochemical cyclisation of *N*-arylaminocycloalkenones afforded carbazole derivatives **111** and **112**.[140]

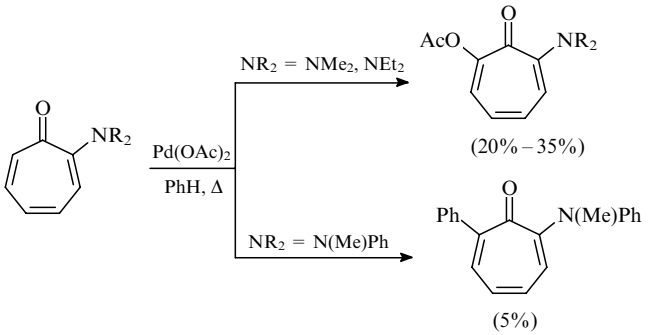


56b **111** (40%–50%) **112** (10%)

R = Me, Et.

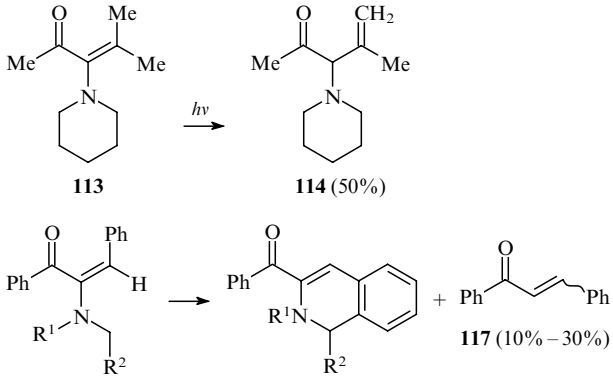
Radical cyclisation of 2-(haloarylethyl)aminocycloalk-2-enones proceeds both at the C^2 atom of the enone fragment to form aminoalkenes, which are azepine derivatives, and at the nitrogen atom to produce compounds of the indole series.[245]

The reactions of 2-aminotropones with palladium acetate, which are considered to be a catalytic radical process, differ essentially from the reactions of other troponoid compounds performed under the same conditions.[246] Depending on the substituents at the nitrogen atom, either acetoxylation (NR_2 = NMe_2, NEt_2) or arylation [NR_2 = N(Me)Ph] were observed.



(20%–35%) (5%)

The photochemical behaviour of the acyclic aminoalkenones **2c** differs from that of the 2-aminocyclohex-2-enones **56b**. Thus in photolysis of aminoalkenone **113** in ether or pentane, allylic hydrogen abstraction proceeded more efficiently to give isomeric nonconjugated alkene **114** as the only reaction product.[177] In the absence of the allylic hydrogen atom, for example, in aminoalkene **115**, the substrate underwent rapid *E*,*Z* isomerisation followed by slow formation of a mixture of compounds consisting primarily of cyclisation product **116** and elimination product **117**.[177]



113 **114** (50%) **115** **116** (40%–55%) **117** (10%–30%)

R^1 = Et, R^2 = Me; $R^1–R^2$ = $(CH_2)_4$, $(CH_2)_2OCH_2$.

Intramolecular photocyclisation of 2-anilinoalkenonitriles gave rise to 2-cyano-1-methyl-3-R-indoles (R = Me, Ph, CH=CHMe). Under the action of Bu_3SnH in the presence of azoisobutyronitrile, radical cyclisation of 2-anilinoacrylonitriles containing the haloalkyl (alkenyl) substituent at position 3 gave rise to substituted cycloalkanes or cycloalkenes.[63, 247]

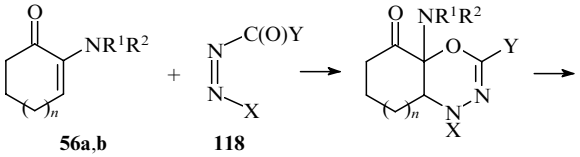
4. Captodative aminoalkenes in the synthesis of carbo- and heterocyclic compounds

Due to the presence of multiple carbon–carbon and carbon–heteroatom bonds, captodative alkenes can be used in the synthesis of carbo- and heterocyclic compounds. Cycloaddition reactions are apparently the most important transformations of captodative aminoalkenes. These reactions have been extensively studied in the last decade. The aminoalkenes **2a–c** can be involved in [2+2]-, [3+2]- and [4+2]-cycloaddition reactions, the latter reactions being most common.

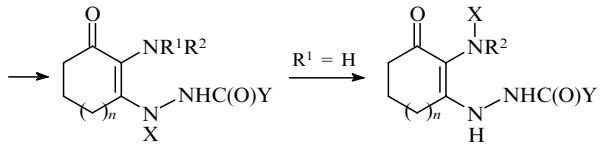
It is well known that dienophiles containing electron-withdrawing substituents are readily involved in the Diels–Alder

reactions with electron-rich dienes. It is not surprising that [4 + 2]-cycloaddition of simple enamines to nonactivated dienes occurs very rarely. Unlike simple enamines, captodative aminoalkenes successfully react with various dienes, including nonactivated compounds.

The reactions of the 2-aminocycloalk-2-enones **56a**,**b** with electrophilic diazenes **118** are formally classified as [4 + 2]-cycloaddition.[248–253] Stability of 1,3,4-oxadiazines **119** thus formed depends both on the nature of the amino group and the ring size of the substrate as well as on the presence of the functional groups in the diazene **118**. Generally, aminoenones bearing a disubstituted amino group form rather stable cyclic derivatives **119**, which are slowly transformed into acyclic isomers **120** at room temperature or upon heating.[248–250] Analogous [4 + 2]-adducts were also obtained from *N*-aryl-substituted aminocycloalkenones.[252] In other cases, the formation of the heterocycles **119** is not necessarily detected and the enediamines **120** are the only reaction products, which are readily rearranged into more stable isomers.[251–253] Benedetti *et al.*[251] assumed that the compounds **120** can also be formed immediately from the starting substrates.



56a,**b** **118** **119** (21%–95%)

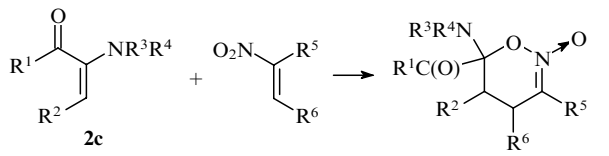


120 (21%–100%)

n = 0 (**a**), 1 (**b**); R^1 = H; R^2 = Bu^n, Bu^t, Ph; NR^1R^2 = , ;

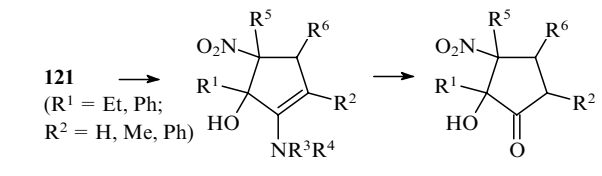
X = Ph, 4-$NO_2C_6H_4$, PhCO, CO_2Me, CO_2Et; Y = Ph, 4-$NO_2C_6H_4$, OEt.

The reactions of the cyclic and acyclic aminoalkenones **56b** and **2c** (as dienophiles) with nitroalkenes (as heterodienes) were used for the synthesis of various carbo- and heterocyclic systems, *viz.*, tetrahydroindoles,[141] polyquinanes[254,255] and pentalenes.[129,256–258] In most cases, the authors of the cited studies postulated that 1,2-oxazine *N*-oxides **121** were formed as intermediates whose subsequent transformations depend primarily on the nature of the substituents and the reaction conditions. Some heterocyclic derivatives **121** were so stable that they can be isolated in quantitative yields.[141,257–259] In a number of studies,[129,141] [2 + 2]-cycloaddition products or Michael adducts were detected along with the compounds given below.



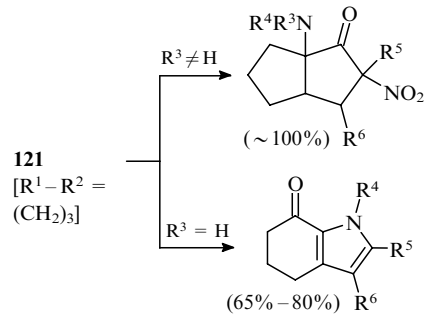
2c **121** (70%–100%)

R^1 = Et, Ph; R^2 = H, Me, Ph; R^1–R^2 = $(CH_2)_3$; NR^3R^4 = $NHBu^n$, $NHBu^t$, NHPh, , , ; R^5, R^6 = H, Me, Ph.



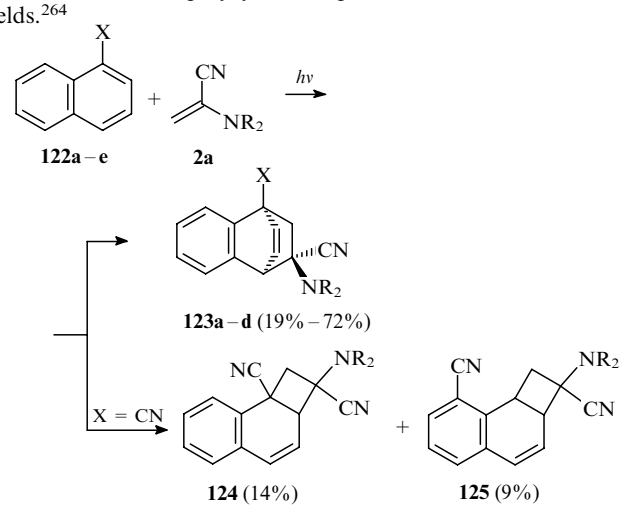
(70%–96%) (62%–96%)

R^5 = H, Me, Ph; R^6 = H, Me.



R^5 = H, Me, Ph; R^6 = Me, Ph.

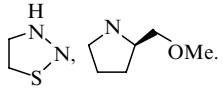
Döpp and co-workers[260–264] performed extensive studies on cycloaddition of various captodative alkenes to unsaturated systems over many years. The Diels–Alder reactions of the cyanoenamines **2a** with 1-naphthaldehyde (**122a**), 1-acetonaphthone (**122b**), 1-naphthophenone (**122c**) or methyl 1-naphthoate (**122d**) proceeded with high regio- and stereoselectivity to form adducts **123a**–**d**.[36,170,261–263] By-products of [2 + 2]-cycloaddition were obtained in negligible yields (< 1%) (in some cases, these compounds were not detected at all). In contrast, the cyanoenamine **2a** (NR_2 is morpholino) is involved in [2 + 2]-cycloaddition with naphthalene-1-carbonitrile **122e** to give a mixture of isomeric polycyclic compounds **124** and **125** in low yields.[264]



122a–**e** **2a** **123a**–**d** (19%–72%) **124** (14%) **125** (9%)

X = CHO (**a**), C(O)Me (**b**), C(O)Ph (**c**), CO_2Me (**d**), CN (**e**);

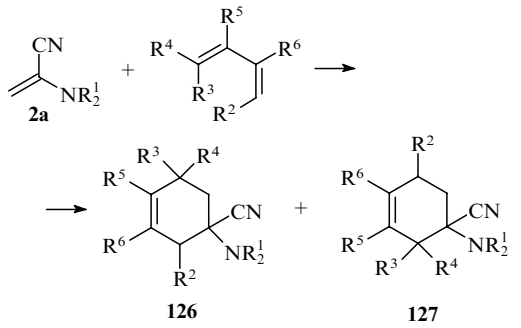
NR_2 = , , Ph, NPh, $NC_6H_4CF_3$-3,



The reactions of the aminoalkene **2a** (NR_2 is morpholino) with substituted 1-acetonaphthones afford the [2 + 2]- and [4 + 2]-cycloaddition products in a ratio which depends on the position of the substituent. The reaction with 2-methoxy-1-acetonaphthone produced only the [2 + 4]-adduct, whereas derivatives bearing a substituent at position 4 gave rise to [2 + 2]-cycloaddition products.[265] Under the conditions of photolysis, 2-morpholinoacrylonitrile was involved in the [2 + 2]-cycloaddition reaction with 3-acetylthianaphthene.[266]

Unlike unsubstituted enamines, the cyanoenamines **2a** react with a number of nonactivated conjugated dienes to give [4 + 2]-cycloaddition products **126** and **127** (Scheme 1). The acrylonitrile **2a** (NR_2 is morpholino) proved to be more reactive as a dienophile than its analogue containing the aromatic amino group, the regioselectivity of the addition being dependent on the nature of the substituents in the diene (see Scheme 1).

Scheme 1

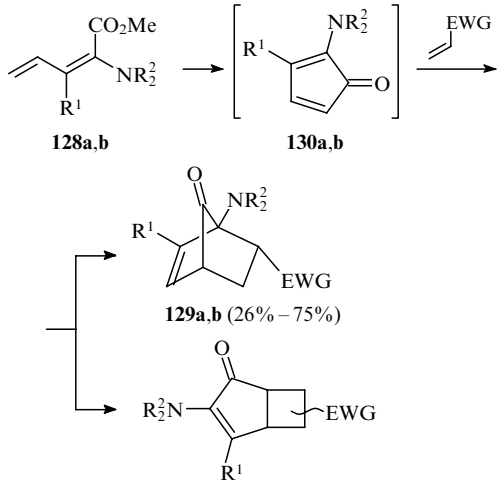


126 **127**

NR_2^1	R^2	R^3	R^4	R^5	R^6	Total yield (%) (ratio **126** : **127**)	Ref.
	H	H	H	Me	H	62 – 72 (8 : 2)	32, 267
N(Me)Ph	H	H	H	Me	H	24 (10 : < 1)	32
	H	H	H	Me	Me	81 – 92	32, 267
N(Me)Ph	H	H	H	Me	Me	18	32
	CH_2		H	H	H	54	32
N(Me)Ph	CH_2		H	H	H	55	32
	$(CH_2)_2$		H	H	H	92	32
N(Me)Ph	$(CH_2)_2$		H	H	H	65	32
	H	F	F	$OSiPh_3$	H	81 (10 : < 1)	268

The above-considered reactions clearly demonstrate that captodative aminoalkenes are good dienophiles, which are much superior to the corresponding alkoxy and thio analogues in reactivity.[269] These compounds are equally efficient as dienes provided that the β-substituent contains one or several multiple bonds.[25, 26, 270]

The reactions of dienes **128a**,**b** with derivatives of acrylic acid afforded unexpected cyclisation products.[69, 271] Aminonorbornenones **129a**,**b** were formed through the [4 + 2]-cycloaddition of methyl acrylate or acrylonitrile to aminocyclopentadienones **130a**,**b** generated upon intramolecular condensation of the dienamino esters **128a**,**b**. The [2 + 2]-cycloaddition products **131a**,**b** were obtained as by-products. The proportion of the [4 + 2]-cycloaddition products **129a**,**b** depends on the nature of the



128a,**b** **130a**,**b**

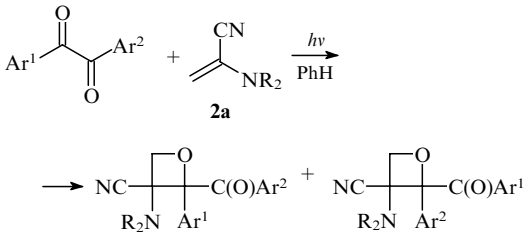
129a,**b** (26% – 75%)

131a,**b** (10% – 30%)

EWG = CO_2Me, CN; R^1 = Me (**a**), Et (**b**); NR_2^2 = NMe_2, NEt_2, .

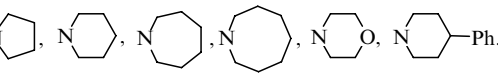
amino and activating groups, *viz*., the highest yields were achieved in the case of the dienes **128a**,**b** containing the piperidine substituent.

The captodative alkenes **2a** – **d** are excellent substrates in [2 + 2]-cycloaddition. The reactions of these compounds with substituted alkenes or carbonyl compounds produced respectively cyclobutanes [272] or oxetanes (the Paterno – Büchi reaction).[273, 274] Thus the addition of symmetrical 1,2-diketones to the cyanoenamines **2a** proceeded regio- and stereospecifically to give head-to-head [2 + 2]-adducts with the *cis*-oriented amino and aryl groups (the configuration of the resulting diastereomer determined in the study [273] is, apparently, in error). Under irradiation of a mixture of unsymmetrical diones and the cyanoenamines **2a**, the addition at the carbonyl groups proceeded with comparable rates to give a mixture of isomeric oxetanes in 9% – 90% yields.[274]

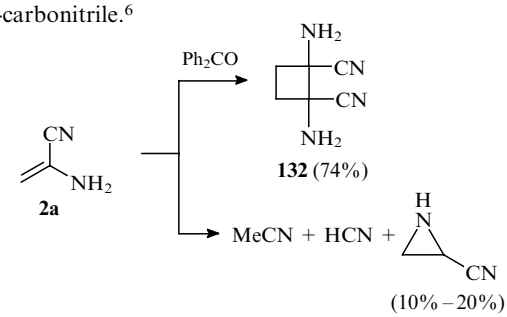


2a

$Ar^1 = Ar^2$ = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 2-$C_{10}H_7$; Ar^1 = Ph: Ar^2 = 4-$MeOC_6H_4$; 2-$C_{10}H_7$;

NR_2 = .

Examples of head-to-head and head-to-tail photochemical dimerisation of captodative aminoalkenes are available in the literature,[5, 6, 275] the type of dimerisation being dependent on the structure of the substrate. The result of the reaction depends also on the reaction conditions. For instance, 2-aminoacrylonitrile underwent dimerisation in the presence of benzophenone as a photosensitising agent to form a mixture of diastereomers **132**.[5] However, the formation of the cyclobutanes **132** was not observed in the absence of Ph_2CO. In the latter case, the main reaction involved fragmentation of the starting substrate to yield HCN and MeCN accompanied by competitive isomerisation into aziridine-2-carbonitrile.[6]



2a

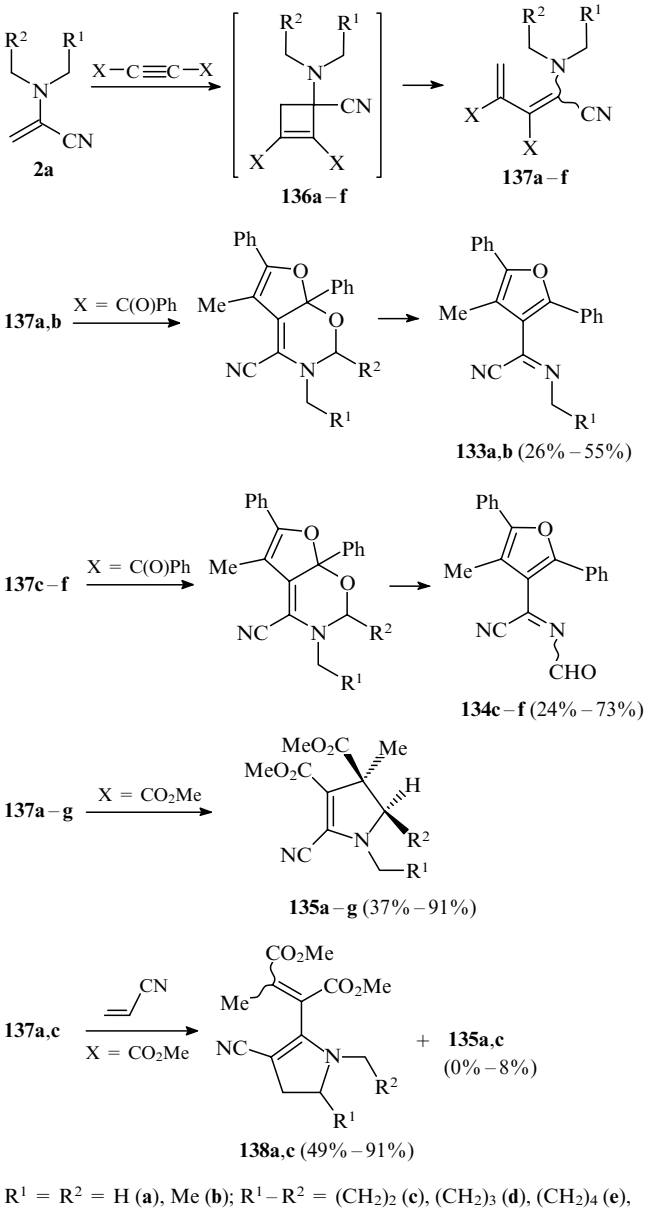
132 (74%)

MeCN + HCN +

(10% – 20%)

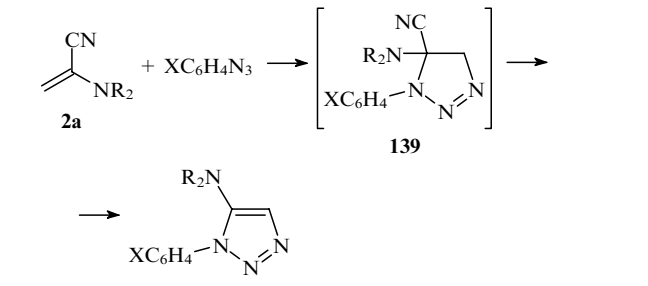
The captodative aminoalkenes **2a** are much more reactive than their push-pull isomers **1a**. These compounds react with dimethyl acetylenedicarboxylate or dibenzoylacetylene by being involved in the so-called 'α-cyclisation of tertiary amines'.[276 – 278] Depending on the nature of the amino group in the aminoalkenes **2a** and the activating group in the acetylene derivative, either furans **133a**,**b** and **134c** – **f** or dihydropyrroles **135a** – **g** were obtained as the final reaction products. The preparation of dihydropyrroles, which were formed with high stereoselectivity, required more drastic conditions (refluxing in acetonitrile or DMSO).[276, 279] The reaction mechanism includes [2 + 2]-cycloaddition and rapid recyclisation of adducts **136** into dienes **137**, which are the key intermediates for all products. The dienes **137a**,**c** are involved in 1,3-dipolar addition reactions with dipolarophiles, such as acrylonitrile, yielding finally a mixture of cycloadducts **138a**,**c** and the dihydropyrroles **135a**,**c** (Scheme 2).[278]

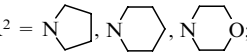
Scheme 2



$R^1 = R^2 = H$ (**a**), Me (**b**); $R^1–R^2 = (CH_2)_2$ (**c**), $(CH_2)_3$ (**d**), $(CH_2)_4$ (**e**), $(CH_2)_5$ (**f**), CH_2OCH_2 (**g**); X = C(O)Ph, CO_2Me.

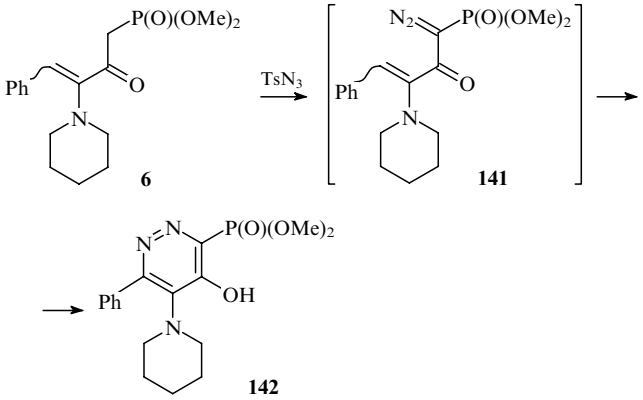
In [3 + 2]-cycloaddition, captodative aminoalkenes behave analogously to common enamines. Like enamines,[175] these compounds add aryl azides to give the corresponding dihydrotriazoles.[11, 33, 280, 281] However, some of these cyclic derivatives are unstable and cannot be isolated. For example, dihydrotriazoles **139** formed in the reactions of the cyanoenamines **2a** underwent



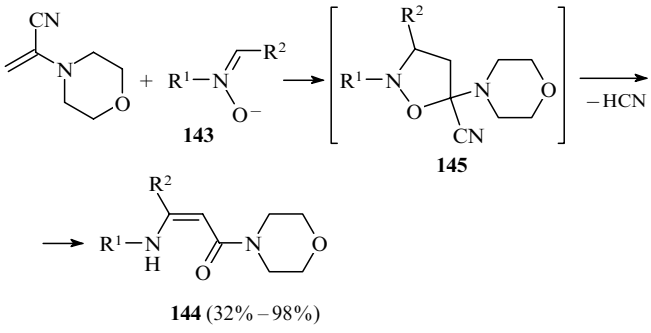
NR^2 = ; X = H, 4-Me, 3-NO_2, 4-Br, 3-Cl.

spontaneous HCN elimination to generate 1,2,3-triazoles **140**.[3, 280] The reactions always proceed regiospecifically to yield the only isomer.

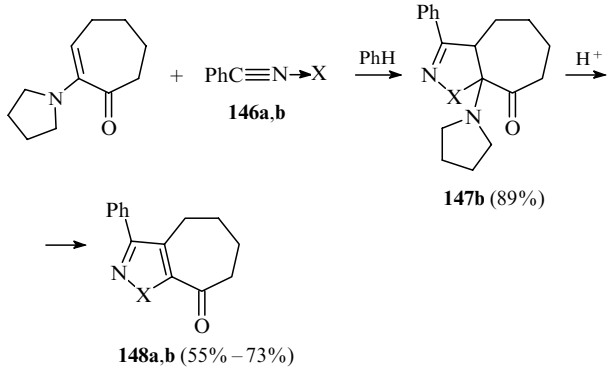
Like enamines, the β-oxophosphonate **6** reacted with tosyl azide to give diazo compound **141**, which underwent cyclisation into pyridazine **142**.[22]



In spite of the fact that the reactions of 2-morpholinoacrylonitrile with aldonitrones **143** afforded morpholides **144**, Döpp and Walter [282] considered these reactions as 1,3-dipolar cycloaddition. Actually, the formation of the amides **144** can be attributed to elimination of HCN from intermediate isoxazolidine **145** followed by the ring opening. Hence, this cycloaddition reaction is also regiospecific, the terminal carbon atom of the starting aminonitrile being nucleophilic. Keto nitrones did not react with 2-morpholinoacrylonitrile.[282]



Cycloaddition of 1,3-dipolar compounds **146a,b** to 2-pyrrolidinocyclohept-2-enone afforded initially compound **147b**, which lost amine upon acid treatment to form pyrazolone derivative **148a** or isoxazolone derivative **148b**.[283]



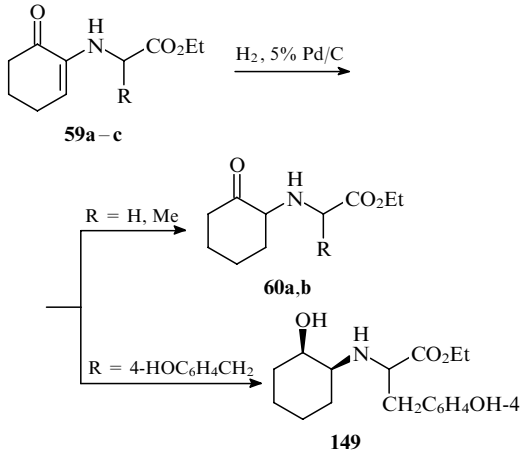
X = NPh (**a**), O (**b**).

5. Other reactions most typical of captodative aminoalkenes

The captodative aminoalkenes **2a–c** are involved in some reactions, which cannot be unambiguously classified with the above-considered types. The most typical reactions, which are not

associated with the presence of a particular specific substituent, are considered in this section.

The aminoalkenes **2a**–**c** are rather readily subjected to hydrogenation. Under traditional conditions of heterogeneous catalysis, selective reduction of the C=C double bond generally takes place.[17, 126, 284] In some cases, the reactions are accompanied by simultaneous reduction of the activating group. For example, the addition of hydrogen to the enamines **59a**,**b** afforded the corresponding 2-aminocyclohexanones **60a**,**b**. However, hydrogenation of the substrate **59c** performed under the same conditions gave rise to a mixture of diastereomers of *cis*-1,2-aminoalcohols **149** in quantitative yield.[126]



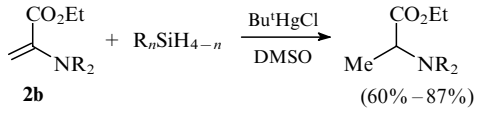
59a–**c**

60a,**b**

149

R = H (**a**), Me (**b**), 4-$HOC_6H_4CH_2$ (**c**).

Of a wide variety of different activated alkenes, only the captodative aminoalkenes **2b** appeared to react with hydrosilanes with reduction of the C=C double bond.[285]

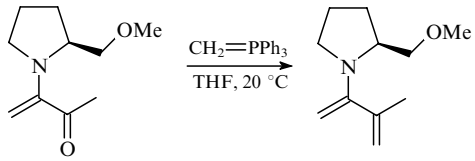


2b (60%–87%)

NR_2 = NEt_2, ; n = 1–3.

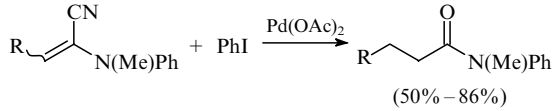
The reactions with the use of metal aluminium hydride or borohydride as reducing agents either proceeded only at the activating group (C=O or CN)[17, 150] or resulted in simultaneous reduction of both functional groups.[159]

Wittig olefination of optically active 2-(methoxymethyl)pyrrolidinobut-3-en-2-one afforded chiral 2-amino-substituted buta-1,3-diene **150**. This compound is the first representative of the compounds, which have previously been difficult to access.[133]



150 (59%)

Noteworthy are the palladium-catalysed reactions of 2-(*N*-methylanilino)alkenonitriles with iodobenzene.[286] Owing to the studies performed by De Kimpe and co-workers,[184, 195] this transformation of cyanoenamines became an efficient procedure for the synthesis of the corresponding amides.



(50%–86%)

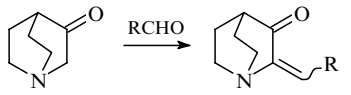
Captodative aminoalkenes readily undergo isomerisation. As mentioned above, the aminoenones **2c** and the aminoenals **2d** can be very readily subjected to *Z*,*E* isomerisation, which either occurs in the course of their preparation or subsequent transformations or takes place upon storage. In addition to *Z*,*E* isomerisation, examples of rearrangements of these compounds under the action of both acidic[287] and basic reagents[183] are available in the literature.

Analysis of the most typical transformations of the captodative aminoalkenes **2a**–**d** shows that these compounds can exhibit the properties of either enamines or activated alkenes depending on various factors. The balance in favour of the canonical structure of enamine can be rather easily disturbed upon insignificant changes in the nature of the activating or amino group.

V. Methylidene- and arylmethylidenequinuclidin-3-ones

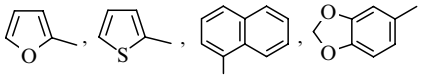
Methylidene- and arylmethylidenequinuclidin-3-ones **151** not only serve as the key intermediates in the design of new pharmaceuticals but are also of interest in theoretical organic chemistry. These compounds can formally be considered as bicyclic captodative aminoalkenes. However, they cannot exhibit properties of enamines because of the fixed spatial orientation of the lone electron pair of the nitrogen atom. This is the essential distinction between the compounds **151** and the above-considered systems.

The 2-arylmethylidenequinuclidin-3-ones **151** are generally prepared by base-catalysed condensation of quinuclidin-3-one **152** with various arene- or hetarenecarbaldehydes.[288–299] The compounds **151** are obtained as individual isomers or as mixtures of geometric isomers in yields from moderate to quantitative. The same methodology was successfully applied to the synthesis of ferrocenylmethylidene-substituted[300] and tricyclic analogues of quinuclidinone.[301]

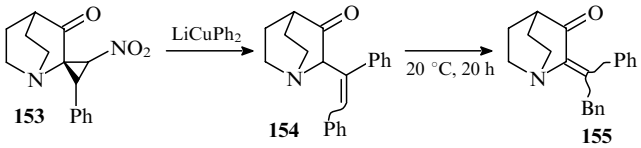


152 **151** (37% — ~ 100%)

R = Ph, 2-PhC_6H_4, 2-HOC_6H_4, 2-$MeOC_6H_4$, 2-FC_6H_4, 2-ClC_6H_4, 3-HOC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$Me_2NC_6H_4$, 4-$PhOCH_2CH_2OC_6H_4$, 2,4-$(MeO)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, $BnOC_6H_4$, $C_5H_5FeC_5H_4$,



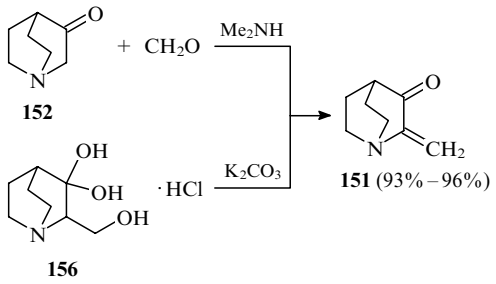
The cyclopropane-ring opening in spirocyclic quinuclidinone derivative **153**, which occurs under the action of C-, N- or O-nucleophiles, provides an interesting example of the preparation of β,β-disubstituted methylidenequinuclidones.[302] Thus the reaction of the compound **153** with lithium diphenylcuprate afforded a mixture of isomers **154** and **155**. The compound **154** was completely transformed into the quinuclidinone **155** during 20 h (the ratio $Z:E$ = 3:1).[302]



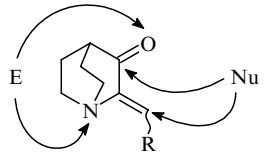
153 **154** **155**

The quinuclidinone **151** (R = H) containing the terminal double bond was smoothly generated from the ketone **152** under the conditions of the Mannich reaction[303] as well as by dehydra-

tion of 2-hydroxymethyl-3,3-dihydroxyquinuclidine hydrochloride (**156**).[304]

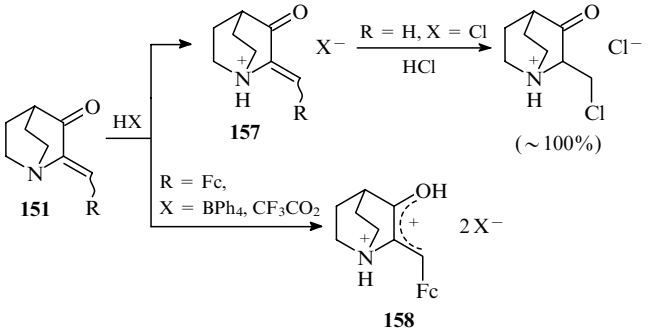


The orthogonal arrangement of the lone electron pair of the nitrogen atom hinders *p,*π-conjugation as a result of which the amino group exerts only the inductive effect on the double bond. This characteristic feature of the arylmethylidenequinuclidinones **151** is reflected in the observed downfield shifts of the signals for the olefinic proton (δ = 6.80 – 7.50) in the ^{1}H NMR spectra and for the β-carbon atom (δ = 125 – 146) in the ^{13}C NMR spectra as compared to the signals of the above-considered captodative aminoalkenes **2c** or **56b**. Hence, the quinuclidinones **151** would be expected to exhibit properties of strong amines in reactions with electrophilic reagents and properties of Michael acceptors in reactions with nucleophiles.



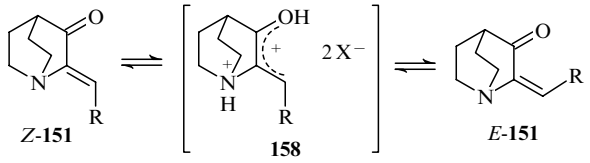
Like captodative aminoalkenes, the arylmethylidene- and ferrocenylmethylidenequinuclidinones **151** are protonated and alkylated at the nitrogen atom.[299, 305 – 307] However, the same regioselectivity of the electrophilic attack is accounted for by different reasons. Thus enammonium salts of captodative aminoalkenes are highly stable due primarily to the stabilising effect of an intramolecular hydrogen bond, whereas *N*-protonation (alkylation) of the quinuclidinones **151** is associated only with the basicity of the nitrogen atom.

Bubbling of dry HCl through a solution of methylidenequinuclidinone led to quaternisation of the nitrogen atom to form compound **157** (R = H) along with the anti-Markovnikoff addition of hydrogen halide to the double bond.[305] In the case of the ferrocenylmethylidenequinuclidinones **151** (R = Fc), two heteroatoms are simultaneously protonated. The formation of the dications **158** was confirmed by NMR spectroscopy.[299, 307]



R = H, Ph, 4-FC_6H_4, 2,4-$(MeO)_2C_6H_3$, Fc;
X = Cl, BPh_4, $PhCO_2$, CF_3CO_2.

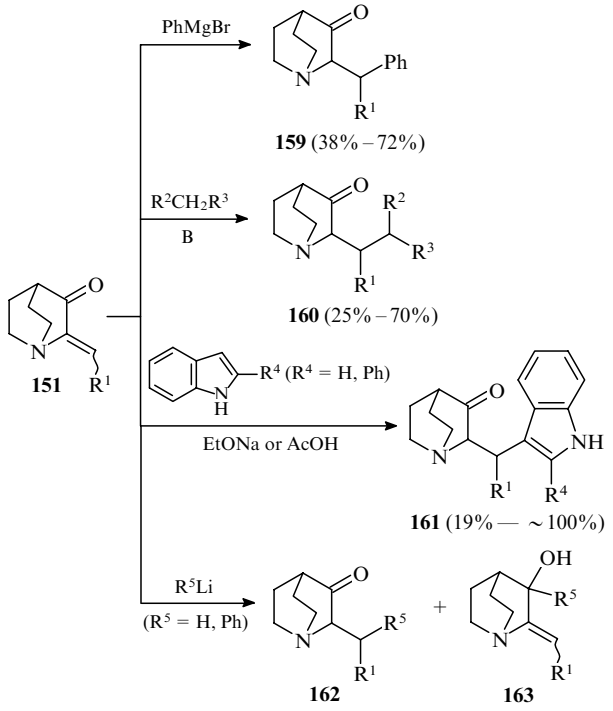
Under the action of gaseous HCl in chloroform [288, 290, 295, 308] or of $NaBPh_4$ in acetic acid,[299, 307] the compounds **151** underwent reversible *Z,E* isomerisation. For example, *Z*-2-arylmethylidene- and *Z*-2-ferrocenylmethylidenequinuclidinones are readily (often quantitatively in a matter of minutes) transformed into the corresponding *E* isomers.[295, 299, 307] In this case, there is the evident analogy with enammonium salts of captodative aminoalkenes, *viz*., isomerisation becomes possible due to a decrease in the double-bond character of the alkene fragment.[299] These transformations of the quinuclidinones **151** provide the means of performing the selective synthesis of their individual geometric isomers, which is of importance in studying the structure – properties relationships (including, the structure – biological activity relationships).



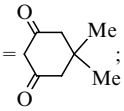
The fact that the quinuclidinones **151** cannot exhibit the properties of enamines is reflected in their reactions with nucleophilic reagents. For example, the majority of the reactions of the compounds **151** and their tricyclic analogues with various C-nucleophiles proceed as conjugated 1,4-addition.[294, 301, 302, 309 – 314] In some cases, Michael adducts **159** – **162** are obtained in moderate yields, which is attributable to competitive 1,2-addition giving rise to compounds **163**. The latter compounds were obtained as the major products in the reactions of the quinuclidinones **151** with aryl- or alkyllithium derivatives (Scheme 3).[299, 300, 307, 315, 316] As mentioned above, numerous attempts to perform the Michael addition to captodative aminoalkenes failed almost without exception (see Section IV.2).

Alcohols serve as O-nucleophiles in the Michael addition reactions with methylidenequinuclidin-3-one, the reactions pro-

Scheme 3

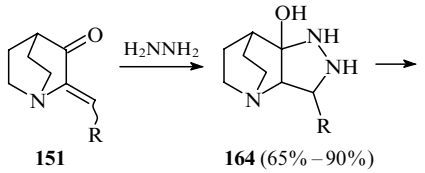


R^1 = H, Ph, 2-ClC_6H_4, 4-$MeOC_6H_4$, Fc; R^2 = CO_2Me, R^3 = CN;
R^2 = Ph, R^3 = CN; R^2 = Ph, R^3 = N=CHPh; R^2 = H, R^3 = NO_2;
R^2 = C(O)Me, R^3 = CO_2Et; R^2 = C(O)Me, R^3 = C(O)Ph;

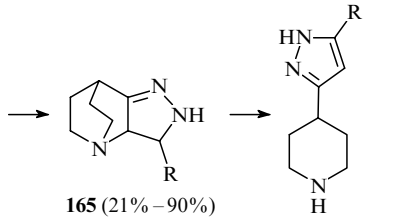
$R^2 = R^3$ = C(O)Me, $R^2R^3CH_2$ =  ; B = NaOH, MeOH, BuLi.

ceeding slowly.[306] As expected, aniline forms the corresponding Schiff's base with the latter compound.[317]

The presence of two electrophilic centres, *viz*., the carbon atom of the carbonyl group and the β-carbon atom of the double bond, allows the use of the quinuclidinones **151** for the construction of various heterocyclic systems. For example, the reactions of the ketones **151** (R = H, Ph or Fc) with hydrazine afforded quinuclidine derivatives **164** or **165** depending on the reaction conditions. Under the action of basic reagents (KOH or an excess of hydrazine), the latter compounds were decomposed upon heating to give pyrazoles **166**.[290–292, 296, 297, 300, 317, 318] Analogous transformations were observed in the reactions of the compounds **151** with thiosemicarbazide.[318] Phenylhydrazine reacts analogously to primary amines to produce phenylhydrazone.[290]



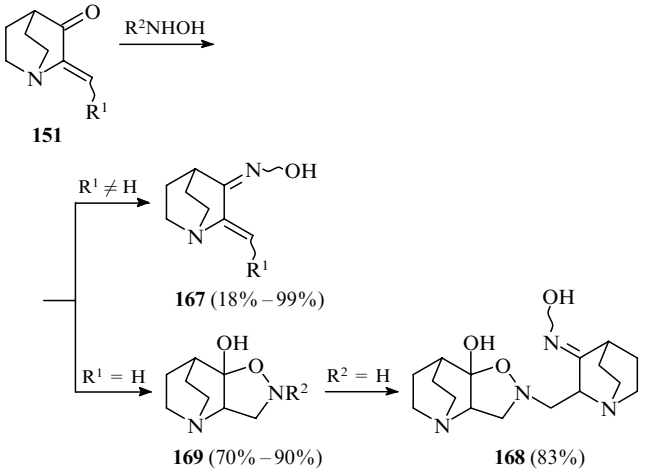
151 **164** (65% – 90%)



165 (21% – 90%) **166** (68% – 88%)

R = H, Ph, Fc.

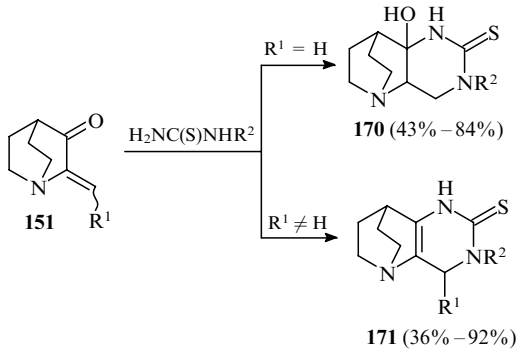
The reactions of hydroxylamines with the arylmethylidenequinuclidinones **151** bearing a substituent at the double bond afforded oximes **167**,[298, 319, 320] whereas the reaction of the unsubstituted methylidenequinuclidin-3-one **151** (R^1 = H) with hydroxylamine gave rise to oxime **168**, which was isolated as dihydrochloride.[321] It was assumed that this reaction proceeded through the intermediate formation of 4*a*-hydroxyisoxazolidino[4,5-*b*]quinuclidine **169**. The *N*-substituted derivatives of the isoxazolidine **169** were prepared in high yields by the reactions of quinuclidinone **151** (R^1 = H) with *N*-arylhydroxylamines.[321]



151 **167** (18% – 99%) **169** (70% – 90%) **168** (83%)

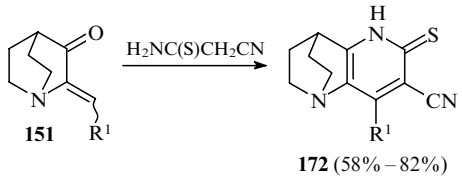
R^1 = H, Ph, 2-HOC_6H_4, 3-HOC_6H_4, 4-HOC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-$NO_2C_6H_4$;
R^2 = H, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4.

The compounds **151** equally readily reacted with thiourea and phenylthiourea to produce pyrimidinethiones **170**[318] or **171**.[290, 300, 322] Finally, cyclisation of the ketones **151** with cyanothioacetamide gave rise to the corresponding thiones **172**.[323]



151 **170** (43% – 84%) **171** (36% – 92%)

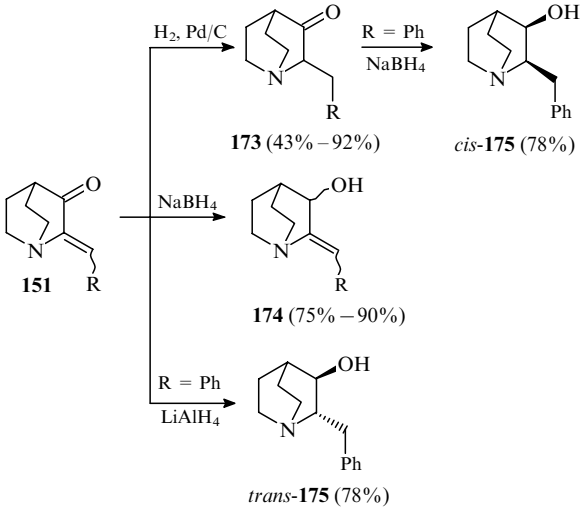
R^1 = H, Ph, 4-$MeOC_6H_4$, Fc; R^2 = H, Ph.



151 **172** (58% – 82%)

R^1 = Ph, 4-FC_6H_4.

As in the case of captodative aminoalkenes, reduction of methylidene- and arylmethylidenequinuclidinones can be directed with high selectivity toward either the C=C double bond or the carbonyl group by varying the nature of the reducing agent. When subjected to platinum- or palladium-catalysed hydrogenation, methylidene- and arylmethylidenequinuclidinones were transformed into saturated ketones **173**.[288, 291, 292, 298, 305] The corresponding allylic alcohols **174** were selectively obtained with the use of $NaBH_4$.[288, 308, 324, 325] Stereospecific reduction of both functional groups in the benzylidenequinuclidinone **151** (R = Ph) with lithium aluminium hydride afforded benzylquinuclidinol *trans*-**175** (R = Ph).[326] Catalytic hydrogenation of the same compound **151** (R = Ph) followed by reduction with $NaBH_4$ gave rise to *cis*-**175** (R = Ph).[308]



151 **173** (43% – 92%) *cis*-**175** (78%) **174** (75% – 90%) *trans*-**175** (78%)

R = H, Ph, 2-ClC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$.

VI. Conclusion

Recent progress in the chemistry of captodative alkenes allows the preparation of many aminoalkenes containing the geminal activating group, which can be considered as polyfunctional building blocks. Various transformations characteristic of this type of compounds, such as electrophilic or nucleophilic addition and, in particular, cyclisation, can be used in organic synthesis. Unlike the push-pull enaminocarbonyl compounds **1c** for which a special type of non-cyclic aromatic stabilisation was assumed,[327] the cross-conjugated aminoalkenes **2a – d** act as 'chemical chame-

leons'. The latter compounds are able to exhibit the properties of either enamines or activated alkenes resulting from insignificant changes in the structure of the substrate and the reaction conditions. Owing to these properties, captodative aminoalkenes are unique building blocks and there is reason to hope that they will find increasing use in organic synthesis.

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