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Haloalkenes activated by geminal groups in reactions with N-nucleophiles

A Yu Rulev

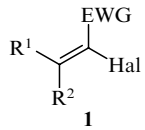
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Abstract. Reactions of nitrogen nucleophiles with haloalkenes in which the halogen atom occupies α-position with respect to an **electron-withdrawing group are considered. Primary attention is devoted to the elucidation of the dependence of the reaction path on the nature of the nucleophile and substrate and on the reaction conditions. Possible mechanisms of nucleophilic substitution of vinylic halogen atoms in alkenes with activating and leaving groups attached to the same carbon atom are discussed. The bibliography includes 169 references.**

I. Introduction

Modern strategy of organic synthesis is based on the use of polyfunctional but relatively simple building blocks in chemo-, regio-, and stereo-selective syntheses of complex molecules. In recent years, the methodologies of tandem and domino transformations have been actively developed. This makes it possible to minimise the number of synthetic steps, the expense, and the amount of wastes and to accelerate as much as possible the advance to the target objects.[1,2] In the design of diverse complicated molecules, it is useful to proceed from compounds with so-called 'compositional functional groups'.[3] Thus 'symbiosis' of a carbonyl (or cryptocarbonyl) group and a halogen atom at the α-carbon atom in a substrate not only activates each functional group but also opens up new prospects for the use of such substrates in synthesis.[4,5] This type of compound is represented, for example, by haloalkenes **1** containing a geminal electron-withdrawing group (EWG). These derivatives are often used as the initial compounds in the syntheses of amino acid derivatives, various biologically important nitrogen-containing heterocycles, and analogues of natural compounds.



1

EWG = CN, COOR, C(O)R.

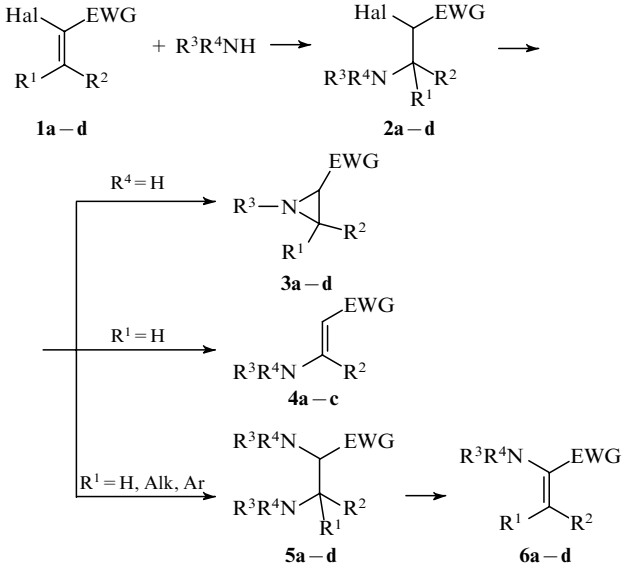
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The studies on reactions of haloalkenes activated by a geminal group with nitrogen-containing nucleophiles (referred to below as N-nucleophiles) began apparently in 1904, when Watson [6] discovered the ability of piperidine to react with bromo(benzyl-idene)acetophenone yielding mono- and di-amino-derivatives. Further progress in this field appears to be a series of trials and errors, findings and delusions as follows from subsequent critical analyses of the early publications.[7–9]

In this review, we attempt to trace the general regularities of the reactions of the haloalkenes **1** activated by geminal substitution with N-nucleophiles, which were mainly reported during the last 15 years.

In most cases, interaction of the haloalkenes **1** with N-nucleophiles can be represented by the following simplified scheme:



Hal = Cl, Br; EWG = CN (**a**), COOR (**b**), C(O)R (**c**), CHO (**d**).

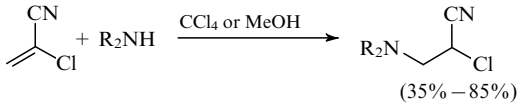
The reaction products include Michael adducts **2**, substituted aziridines **3**, aminoalkenes with a vicinal (**4**) or geminal (**6**) activating group, and α,β-diamino-derivatives **5**. Other routes of transformations involving the activating group or the functional groups in the substituent are also possible. Even slight changes in the structure of the initial substrate or in the nature of the nitrogen-containing nucleophile, variation of the temperature, the solvent, the molar ratio and the order of mixing of the

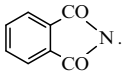
reactants, *etc*. often result in the formation of absolutely different reaction products. Despite certain difficulties of prediction, some general rules governing the reactivity of the haloalkenes **1** in reactions with N-nucleophiles have been discovered. Thus the nature of the activating EWG is a crucial factor in all the cases considered. Analysis of the published data makes it possible to claim that the reactivity of the haloalkenes **1** with geminal substitution increases with increase in the electron-withdrawing properties of the EWG. In terms of their activating capacity, these groups can be arranged in the sequence $CN \leqslant COOR < C(O)R < CHO$,[10] which shows a good correlation with the activity series of unsaturated compounds of the $CH_2=CH-EWG$ type in the Michael reaction with amines.[11]

II. Reactions of haloalkenes activated by geminal groups with N-nucleophiles

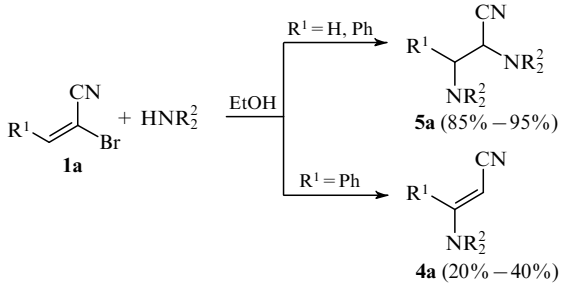
1. Haloalkenes activated by a cyano group

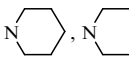
As should be expected, haloalkenes **1a** with a *gem*-cyano group enter into the Michael reaction with secondary amines yielding initially β-amino-α-halo-derivatives **2a**. The chloro-derivatives have been isolated in a pure state.[12] Secondary amines and phthalimide add to α-chloroacrylonitrile on refluxing in methanol.[13] The addition of diphenylmethylideneamine to the same substrate occurs under mild conditions and gives no side products.[14]



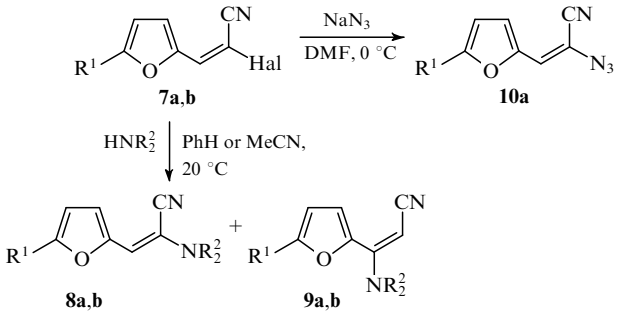
$R_2N = Me_2N, Et_2N, Pr_2N, Bu_2N, Ph_2C{=}N,$ 

The replacement of chlorine in the initial nitrile by bromine decreases the stability of the Michael adducts to such an extent that the corresponding β-amino-α-bromo-derivative **2a** cannot be even detected. In this case, the addition of amine is accompanied either by substitution of the halogen atom giving α,β-diamino-derivative **5a** or by elimination of hydrogen bromide giving rise to substituted β-aminoacrylonitriles **4a**.[15]

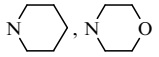


$R^1 = H, Ph$; $NR_2^2 = NMe_2, NEt_2,$ 

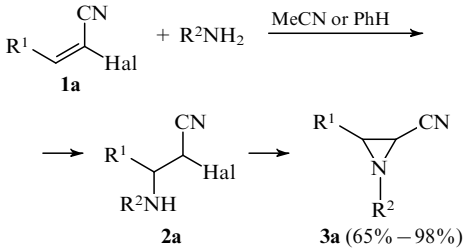
The use of sterically hindered amines (benzimidazole, 1,2,4-triazole) or substrates containing bulky substituents at the β-position usually results in the formation of β-aminoacrylonitriles **4a** as the only [16–18] or predominant [19,20] products. However, there are some exceptions. For example, treatment of furylhaloacrylonitriles **7a**,**b** with secondary amines (piperidine, morpholine, diethylamine) yields mixtures of α-amino- (**8a**,**b**) and β-amino- (**9a**,**b**) derivatives,[19,20] whereas treatment with azides affords α-substituted acrylonitriles **10a** as the only products.[21]



$R^1 = NO_2$, Hal = Cl (**7a**); R^1 = Br, Hal = Br (**7b**);

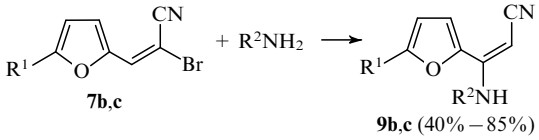
$NR_2^2 = NEt_2,$ 

Reactions of the cyanoalkenes **1a** with primary amines generally occur according to the scheme given above. However, in this case, there is a possibility of intramolecular cyclisation of the products **2a** to the corresponding aziridines. In fact, primary aliphatic and aromatic amines and even ammonia readily react with α-haloacrylonitriles **1a** to give aziridines **3a** in high yields.[22–26] The stereochemistry and the mechanism of the addition have been studied.[22,26]



Hal = Cl, Br; R^1 = H, Me, Ph, glycosyl residue;
R^2 = H, Me, Pr, Pr^i, Bu^t, Am, C_6H_{13}, cyclo-C_6H_{11}, Bn, Ph, Ar.

The fact that the aziridine derivatives **3a** are actually formed *via* the Michael adduct **2a** was proved by detecting the latter by spectroscopy [22] and by isolating it as a salt.[27] However, some examples have been reported in which the expected aziridines were not formed, and the adduct **2a** either remained unchanged [13,28] or was converted upon dehydrohalogenation into 3-aminoacrylonitrile of type **4a** with a secondary amino group. This rare situation is realised, for example, for the nitriles **7b**,**c**, which react with primary amines giving only β-aminoacrylonitriles **9b**,**c** in good yields.[29]

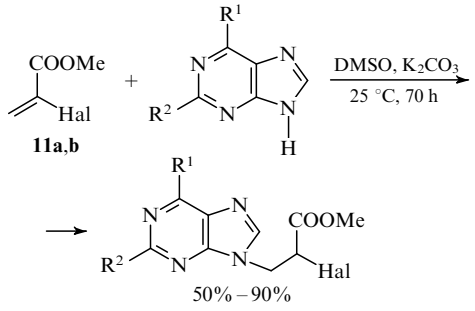


R^1 = Br (**b**), NO_2 (**c**); R^2 = H, Bu, Bn, $HOCH_2CH_2,$ 

2. Haloalkenes activated by an ester group

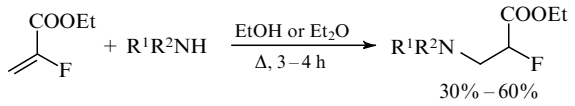
Similar transformations have been observed in the series of haloalkenes **1b** activated by a geminal ester group. A distinctive feature of this type of reaction is that in some cases, the activating group also reacts with amines. As in the series of α-haloacrylonitriles **1a**, the outcome of the reaction depends on the nature of the amine, the structure of the substrate (the presence of substituents, the nature of the halogen), and the experimental conditions.

The use of bulky or weakly basic nucleophiles as well as very active Michael acceptors leads to termination of the reaction at the initial stage, when the products of the addition at the double bond have been formed. For example, the reaction of purine bases with methyl α-chloroacrylate (**11a**) or α-bromoacrylate (**11b**) affords the corresponding Michael adduct in high yield.[30]



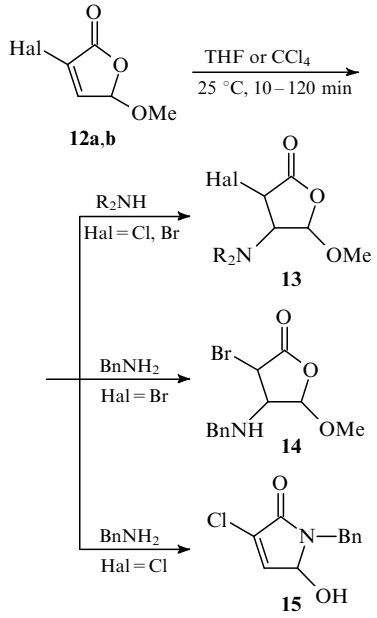
Hal = Cl (**a**), Br (**b**); $R^1 = NH_2$, $R^2 = H$; $R^1 = Cl$, $R^2 = H$; $R^1 = R^2 = Cl$.

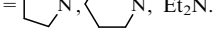
A similar situation is observed when haloacrylates containing weakly nucleofugal fluorine are used. The suggestion[31] that the ester group in α-fluoroacrylates might undergo ammonolysis by secondary and primary amines and by ammonia proved to be faulty. The attack by the N-nucleophile is directed at the β-carbon atom of the double bond and results in the formation of esters of *N*-mono- or *N*,*N*-di-substituted α-fluoro-β-alanine.[32] No amides have been found among the reaction products.



R^1, $R^2 = (CH_2)_5$, $(CH_2)_2$; $R^1 = R^2 = Et$; $R^1 =$ cyclo-C_6H_{11}, $R^2 = H$.

A mixture of diastereomeric products of conjugated addition **13** was obtained upon the interaction between equimolar amounts of a secondary amine and 3-chloro(or bromo)-5-methoxy-5*H*-furan-2-one (**12a**,**b**). In this case, the attack by the nucleophile occurs mostly from the side opposite to the methoxy group.[33]

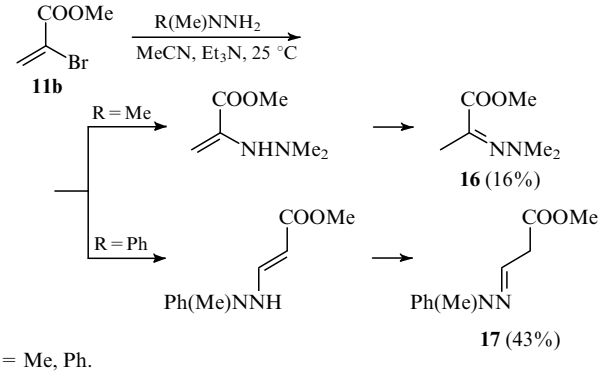


$R_2N =$  Et_2N.

Primary amines and ammonia readily react with α-haloacrylates **1b** normally yielding the corresponding aziridines of type **3b**.[34–38] The formation of the addition products was detected by NMR spectroscopy,[33] and in the case of α-haloacrylic acids, the adducts were isolated as salts.[39]

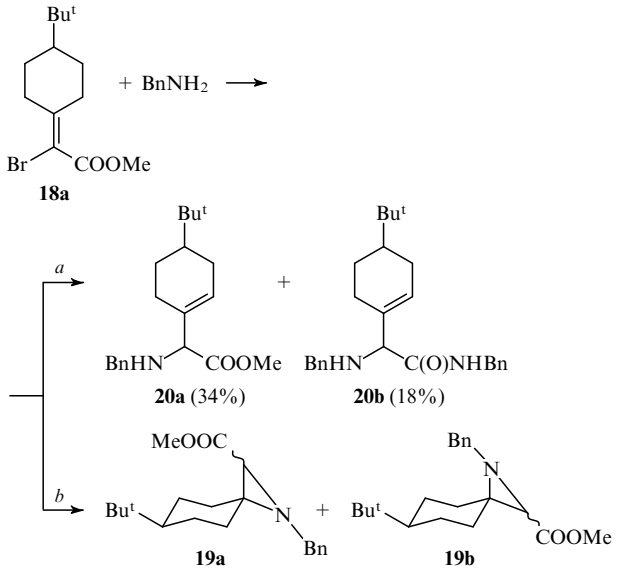
It should be emphasised that the structures of the substrate and the nucleophile as well as experimental conditions influence the reaction pathway so strongly that even slight variations often have fundamentally significant consequences. Thus replacement of bromine by chlorine in bromofuranone **12b** changes the direction of the nucleophilic attack: the reaction of 3-chloro-5-methoxy-5*H*-furan-2-one **12a** with benzylamine yields unexpectedly pyrrolinone **15** rather than the Michael type adduct **14** as the major product.[33]

Methyl α-bromoacrylate prepared from methyl α,β-dibromopropionate reacts with 1,1-disubstituted hydrazines to give hydrazones **16** or **17** depending on the basicity of the N-nucleophile.[40]



R = Me, Ph.

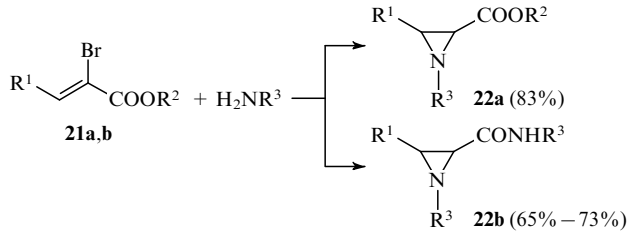
The influence of the experimental conditions on the reaction of α-haloacrylates with N-nucleophiles is clearly illustrated by the reaction of methyl bromo(4-*tert*-butylcyclohexylidene)acetate **18a** with benzylamine. At room temperature and atmospheric pressure, isomeric spiroheterocyclic compounds **19a**,**b** are formed as the only reaction products (yield 83% – 85%). High pressure markedly increases both the rate and stereoselectivity of the reaction: the ratio of diastereomers with equatorial (**19a**) and axial (**19b**) orientation of the nitrogen atom ranges from 1.7 : 1 under ordinary pressure to 10 : 1 at 11 kbar. Refluxing a methanolic solution of the ester **18a** with two equivalents of benzylamine gives rise to a mixture of α-amino ester **20a** and the corresponding amide **20b**.[36–38]



(*a*) MeOH, Δ, 18 days; (*b*) MeOH, 11 kbar, 25 °C, 4 days.

Aziridine derivatives can be easily obtained by reaction of primary amines with α-halo α,β-unsaturated esters.[41–43] The ratio of *cis*- and *trans*-aziridines depends substantially on the solvent used. For example, the reaction of methyl α-bromocinna-

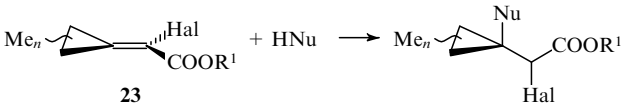
mate **21a** with primary amines in methanol yields *cis*-**22a** as the main product, whereas in benzene, the proportion of the corresponding *trans*-isomer increases to 45%.[41,42] In the case of substrates **21b** containing a fluoroalkyl group at the β-position, closure of the aziridine ring is accompanied by amidation giving rise to compounds **22b**. This result has been attributed[43] to the influence of the electron-withdrawing polyfluoroalkyl substituent, which considerably enhances the reactivity of the ester group.



21a,**b** **22a** (83%) **22b** (65% – 73%)

R^1 = Ph, R^2 = Me (**a**); R^1 = CF_3, CHF_2CF_2; R^2 = Et (**b**);
R^3 = Me, C_6H_{13}, Bn.

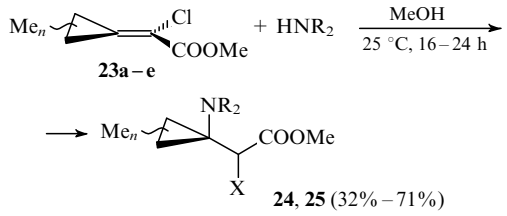
Interesting results along this line have been obtained by de Meijere *et al.*[44–46] As models, these researchers chose 2-halocyclopropylideneacetates **23**, which are highly reactive Michael acceptors. The higher reactivity of these compounds compared to other 3,3-disubstituted acrylates has been rationalised[3,45,47] by the fact that the formation of the Michael adduct relieves the overall strain of the system, because during this reaction the *sp* hybridised carbon atom in the ring goes into the sp^2 hybridisation state. In fact, esters **23** easily add one equivalent of an N-nucleophile giving rise to 1′-substituted 2-chloro(or bromo)-2-cyclopropylacetates usually in good yields and with no side products.[14,47–50]



23

n = 0 – 4; Hal = Cl: R^1 = Me, Bn, Bu^t; Hal = Br: R^1 = Me;
HNu = NH_2R^2, NHR^2_2, $HNAc_2$, HN=CPh_2, HN=CAr_2, HN=C(R)Ar, phthalimide.

However, in the case of primary amines, smooth addition to the substrates **23** is often accompanied by secondary reactions involving the chloromethine or alkoxycarbonyl group. Acetamide and phthalimide, which are less nucleophilic, either do not react at all or give Michael adducts in low yields.[47] The best results were obtained in the reactions of chloro-substituted esters **23** with highly basic secondary amines and with diphenylmethylideneamine in methanol. Aprotic and less polar solvents (DMF, Et_2O, CH_2Cl_2) markedly decreased the rate of addition.[14] The halogen atoms in the Michael adducts tend to be substituted by other nucleophiles including amines. Thus the reaction of methyl chloro(cyclopropylidene)acetates **23a**–**e** with a five- or sevenfold excess of secondary amines leads to addition – substitution products **25** in good isolated yields.[51]

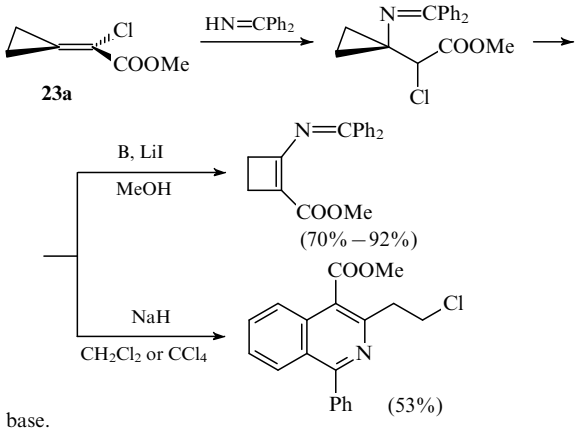


23a–**e** **24**, **25** (32% – 71%)

n = 0 (**23a**), 1 (**23b**), 2 (**23c**), 3 (**23d**), 4 (**23e**);
X = OMe (**24**), NR_2 (**25**); NR_2 = NMe_2, NEt_2, .

The outcome of the reactions of the esters **23a**–**e** with diethylamine, which is the bulkiest among the nucleophiles used, depends on the number of substituents in the cyclopropane ring of the substrate. Tetramethyl-substituted chloro(cyclopropylidene)-acetate **23e** does not react with diethylamine even on prolonged refluxing (24 h, 70 °C). The substrate **23d** with three methyl groups in the ring is converted into **24** (R = Et). The formation of this product was rationalised by assuming the initial addition of diethylamine followed by substitution of the chlorine atom by methanol. The reaction of the dimethyl derivative **23c** with diethylamine under the same conditions affords two products, **24** and **25**. Finally, methyl chloro(cyclopropylidene)acetate **23a** with a non-substituted ring reacts with diethylamine giving rise to the Michael adduct and diamino ester **25** (n = 0, R = Et).

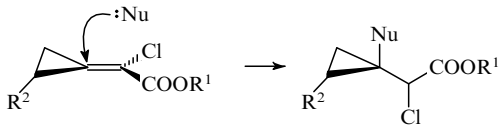
Methyl chloro(cyclopropylidene)acetate **23a** readily adds diphenylmethylideneamine to give the corresponding adduct in 98% yield. Under certain conditions, the latter undergoes intramolecular substitution of chlorine and subsequent rearrangement being thus converted into β-aminocyclobutenecarboxylate or an isoquinoline derivative.[52–54]



23a (70% – 92%) (53%)

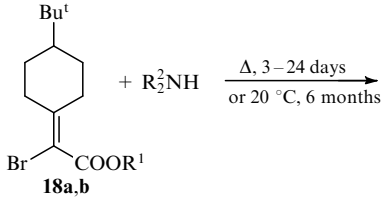
B is base.

The addition of N-nucleophiles to the double bonds of the compounds **23** or their analogues containing substituents other than methyl is usually highly diastereoselective. The nucleophilic attack occurs at the *trans*-position in relation to the bulkiest substituent in the cyclopropane ring.[51,55,56]

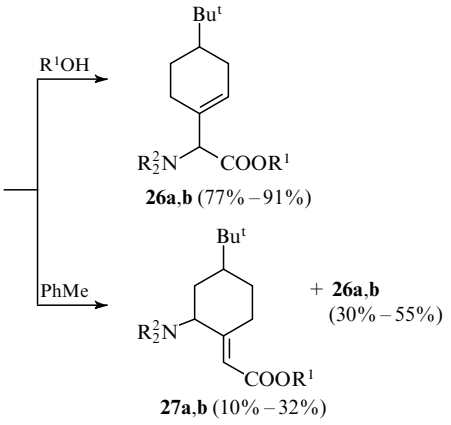


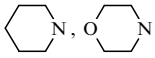
R^1 = Me, Bn; R^2 = Me, Et, CH_2OMe, CH_2OBn, SMe.

On passing from the chloro(or bromo)(cyclopropyl-idene)acetates **23** to alkyl bromo(cyclohexylidene)acetates **18a**,**b**, the reaction route changes sharply. Thus prolonged (3 – 24 days) refluxing of methyl (**18a**) or ethyl (**18b**) bromo(4-*tert*-butylcyclohexylidene)acetate with acyclic or heterocyclic secondary amines affords either one product of bromine substitution or a mixture of two products, depending on the solvent used. When the reaction is carried out in the corresponding alcohol (methanol or ethanol), methyl or ethyl amino(4-*tert*-butylcyclohex-1-enyl)acetate **26a**,**b** is formed as the only product in a good yield. Conversely, the reaction in toluene always yields a mixture of the amino ester **26a**,**b** and its isomer **27a**,**b**.[38] No Michael adduct of type **2b** or product of halogen *ipso*-substitution like **6b** was detected. Sterically hindered secondary amines (for example, 2,2,6,6-tetramethylpiperidine) do not react with the esters **18a**,**b**.

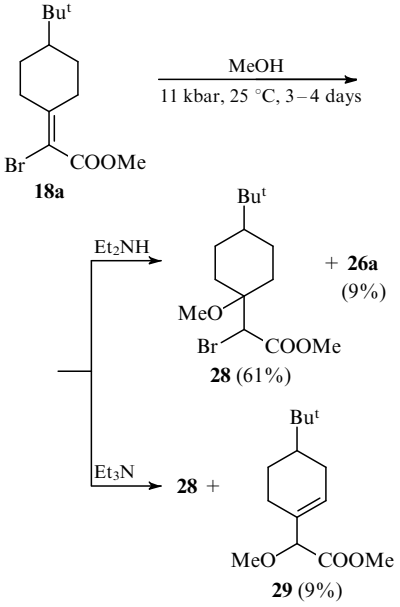


18a,**b**

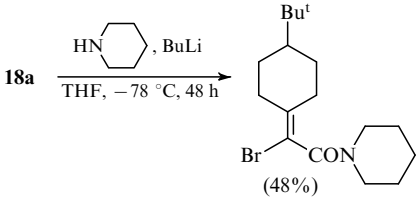


R^1 = Me (**a**), Et (**b**); R^2_2N = , Et_2N, Bn_2N.

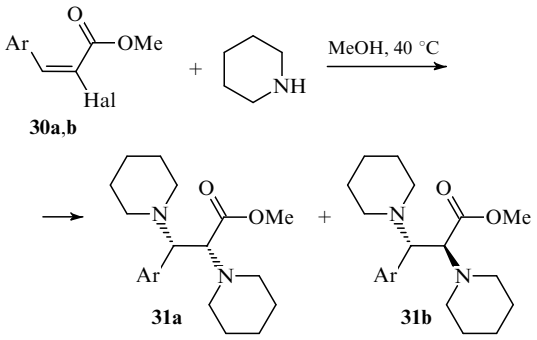
The reaction of amines with the same substrate **18a** at elevated pressures leads to absolutely different results.[37,38] In this case, the solvent (methanol) acts as a reactant, and adduct **28** is formed in 60%–70% yield together with a small (up to 9%) amount of the amino ester **26a** (R^2 = Et) or compound **29** (for reactions in the presence of di- and triethylamine, respectively). It is noteworthy that, as in the case of benzylamine, the nucleophilic attack of methanol results in predominant (up to 90%) formation of the isomer of **28** in which the methoxy group is equatorial. In the absence of amines or when dichloromethane is used as the solvent, the initial substrate **18a** remains unchanged under the same conditions (11 kbar, 25 °C).



Finally, the reaction of lithium piperidide with **18a** involves unexpectedly only the ester group, which is converted into an amide group. The double bond and the halogen atom remain intact.



The reaction of piperidine with methyl 3-aryl-2-haloacrylates **30a**,**b** occurs according to the classical addition–substitution pattern and yields a mixture of isomeric 2,3-dipiperidino-derivatives **31a** and **31b**, the *threo*-isomers **31b** being the predominant products.[57]



Hal = Cl (**a**), Br (**b**); Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$.

Kinetic studies showed [57] that the rate of this reaction depends on the nature of substituent in the benzene ring, configuration of the alkene, and the nature of the halogen. For example, methyl (*E*)-2-bromo-3-phenylacrylate **30b** (Ar = Ph) reacts at 40 °C with piperidine 1200 times faster than the corresponding *Z*-isomer. Replacement of bromine in the substrate **30b** (Ar = 4-$O_2NC_6H_4$) by chlorine decreases the reaction rate constant by a factor of ~6. Based on the kinetic measurements, it was concluded [57] that the nucleophilic attack at the β-carbon atom of the alkenes **30a**,**b** is the rate-determining step of the process.

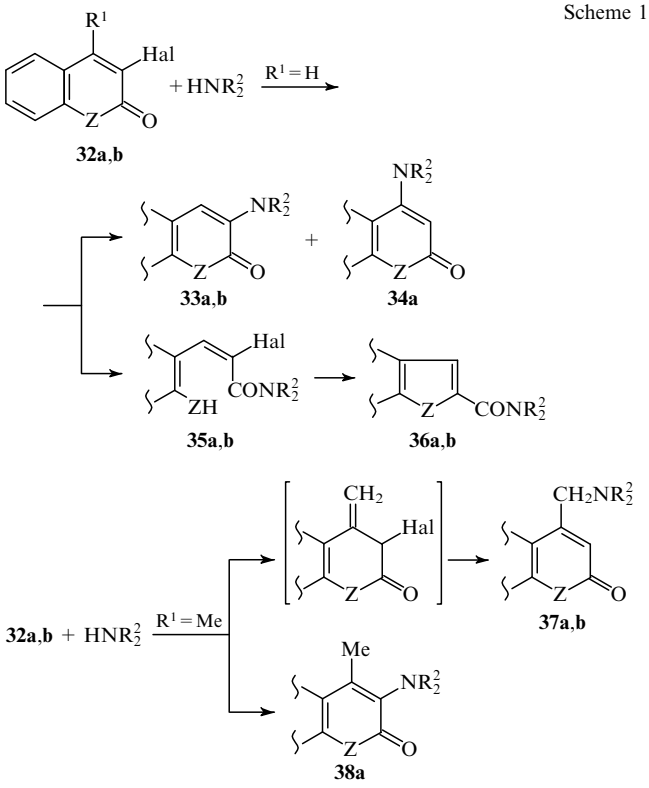
A large series of studies [58–68] have been devoted to 3-halocoumarins **32a** and 3-halothiocoumarins **32b**, which can be regarded as cyclic esters. The discussion about the routes for their transformation induced by N-nucleophiles is still being continued. In principle, nucleophilic attack can be directed at any of the three electrophilic centres — at positions 2, 3, or 4.

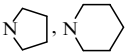
In fact, the interaction of highly basic amines with 3-halocoumarins **32a** containing a hydrogen atom at the 4-position (R^1 = H) gives rise to complex mixtures of products (Scheme 1) in which the *ipso*- and *syn*-substitution products **33a** and **34a** are the major components.[58,59,67] However, in some cases, the reaction is accompanied by pyrone ring contraction and yields benzofuran derivatives **36a**.[60,63] In the series of thio-derivatives **32b**, benzothiophene **36b** is, as a rule, the only reaction product.[62,63]

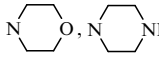
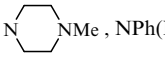
It is quite probable that the ring contraction reaction follows a domino transformation pattern. First, the ring is cleaved giving amides **35a**,**b**, which can be isolated in some cases.[60,64] The resulting hydroxy (or thiol) group participates in the substitution of bromine, and this gives furan (**36a**) or thiophene (**36b**) derivatives. The driving force of these transformations is the creation of an aromatic system. This pathway is realised more easily in the case of thio-derivatives **32b** owing to the higher nucleophilicity of the thiol group in the intermediate amide **35b**.[62,63]

The transformation of halo-coumarins **32a** and -thiocoumarins **32b** containing a methyl group at the 4-position includes initial 1,3-shift of the methyl proton. The subsequent substitution of the allylic halogen yields either the corresponding aminomethyl derivatives **37a**,**b** [65] or their mixtures with the products of nucleophilic vinylic substitution **38a**,[66–68] depending on the nature of the amine.

Scheme 1



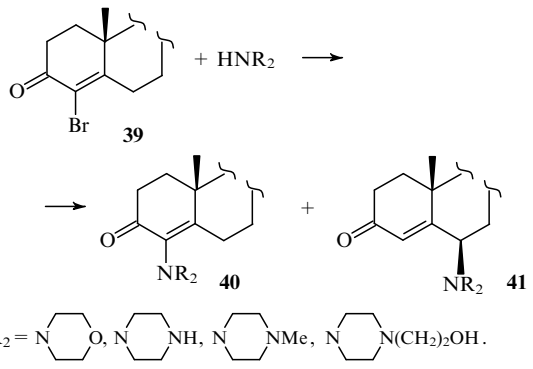
Z = O (**a**), S (**b**); Hal = Cl, Br, I; NR^2_2 = NEt_2, NPr_2, , ,

, , NPh(Me), NPh(Et).

3. Haloalkenes activated by a carbonyl group

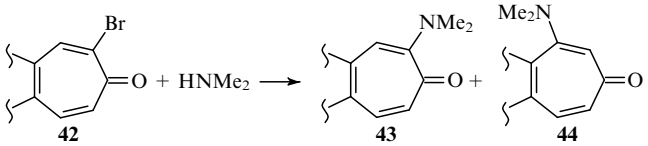
The haloalkenes **1c** and **1d** with a geminal acyl or formyl group are the most reactive towards N-nucleophiles. The possibility of condensation at the keto and especially formyl group extends the spectrum of the transformations observed.

Similarly to esters and nitriles, α-halo α,β-unsaturated aldehydes and ketones react with secondary amines giving rise to α-, β-, or γ-amino-derivatives of α,β-unsaturated carbonyl compounds.[16,69–83] Thus reaction of 4-bromocholest-4-en-3-one **39** with heterocyclic amines affords a mixture of 4- and 6-amino-substituted cholestenones, **40** and **41**, respectively, the isomer **41** being the major product in all cases.[77,78]



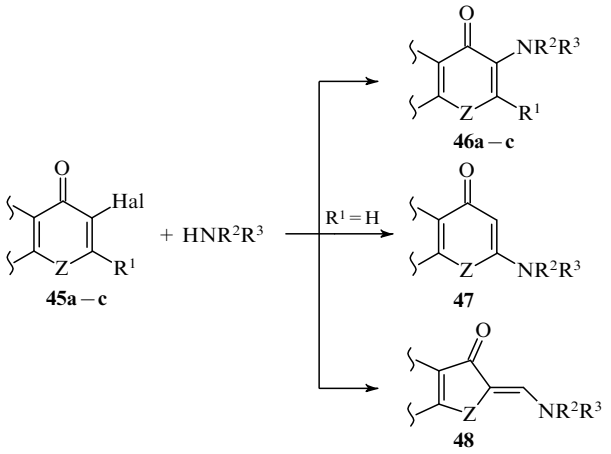
NR_2 = , , , .

Impressive results have been obtained in a study of the temperature dependence of the regioselectivity of the amination of bromobenzotropone **42** with dimethylamine.[81] An increase in the temperature is favourable for the formation of the *ipso*-substitution product **43**. At 0 °C, β-amino-derivative **44** is formed specifically, whereas the reaction at 120 °C yields amino ketone **43** as the only product.



T /°C	0	60	120
43 : **44** (%)	0 : 100	66 : 33	100 : 0

The reactions of 3-halochromanones **45b**,**c** with amines yield in all cases only 3-aminochromanones **46b**,**c**. However, when **45a** is introduced in this reaction, both the *ipso*-substitution products **46a** and compounds **47** are formed. In some cases, the reaction is accompanied by the γ-pyrone ring contraction and gives derivatives **48**.[70–74,82,83] This difference between the behaviours of these compounds has not yet received any plausible explanation.

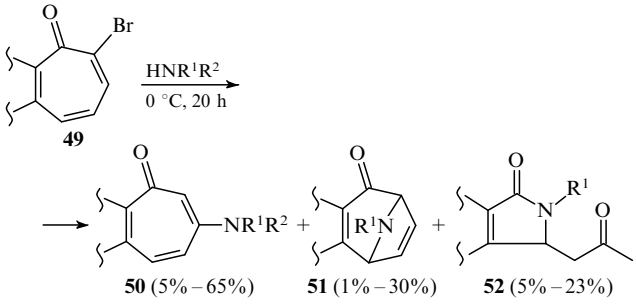


Z = O, S; Hal = Cl, Br; R^1 = H (**a**), Me (**b**), Ph (**c**);

NR^2R^3 = NMeEt, NEt_2, , , , BnNH,

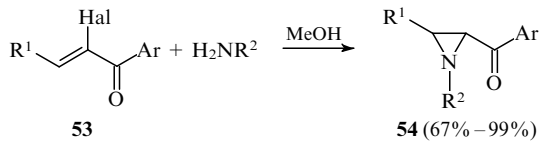
cyclo-$C_6H_{11}NH$.

Complex mixtures containing *syn*-substitution products **50**, bridged compounds **51**, and lactams **52** are formed under mild conditions when α-bromo ketone **49** is made to react with primary amines. Secondary amines react with the same substrate giving rise to the corresponding β-enamino ketones **50**.[80]



R^2 = H: R^1 = H, Me, Et, Pr^i, $(CH_2)_nNMe_2$, where n = 2, 3; R^1 = R^2 = Me; R^1, R^2 = $(CH_2CH_2)_2O$.

Nevertheless, in most cases, the reaction of 2-haloalk-2-enones **53** with ammonia and primary amines, like the reactions in the series of nitriles and esters, proved to be a versatile and efficient method for the synthesis of aziridinyl ketones **54**[84,85] including those containing polyfluoroalkyl substituents.[86,87]

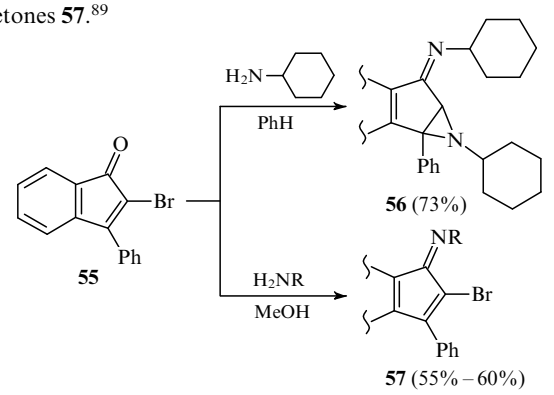


53 **54** (67% – 99%)

Hal = Cl, Br; R^1 = Me, Ph, CF_3; R^2 = Me, Bn, cyclo-C_6H_{11}, C_6H_{13}; Ar = Ph, 4-PhC_6H_4.

The main limitation in the synthesis of the aziridines **54** is the steric accessibility of the nitrogen atom. The carbon atom attached to the amino group should not be tertiary.[85] Thus *tert*-butylamine does not form the corresponding aziridines **54** with α-bromochalcones,[85] although some nitriles of type **1a** and some aldehydes of type **1d** can be converted into aziridine derivatives with a *tert*-butyl group.[24, 88]

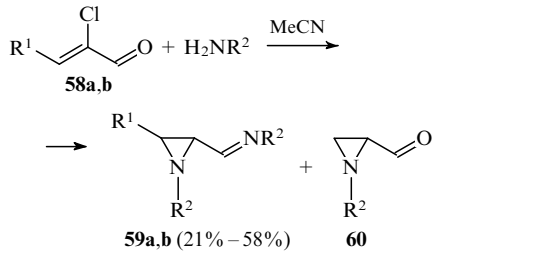
At the same time, the reaction often involves a carbonyl group. For instance, 2-bromo-3-phenylinden-1-one **55** reacts with N-nucleophiles containing a primary amino group to give ketimine derivatives of aziridines **56**[75] or of the initial bromo ketones **57**.[89]



55 **56** (73%) **57** (55% – 60%)

R = OH, NHPh.

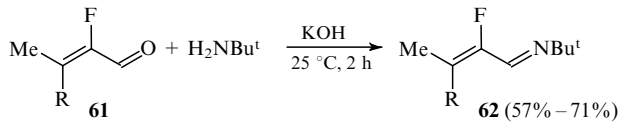
A similar situation has been observed for 2-haloalk-2-enals **1d**.[88, 90, 91] Thus 2-chloropropenal **58a** and 2-chlorobut-2-enal **58b** react with three equivalents of a primary amine giving rise to azomethine derivatives of aziridines **59a**,**b**.[88] Interestingly, the reaction of the aldehyde **58a** with a twofold excess of amine affords a small amount of aziridine derivative **60** together with the azomethine **59a**.[88]



58a,**b** **59a**,**b** (21% – 58%) **60**

R^1 = H (**a**), Me (**b**); R^2 = Et, Pr^i, Bu^t.

The condensation of 3-alkyl-2-fluorobut-2-enals **61** with *tert*-butylamine involves only the aldehyde group and results in the formation of aldimines **62**.[91] Neither the double bond nor the fluorine atom participate in the process.



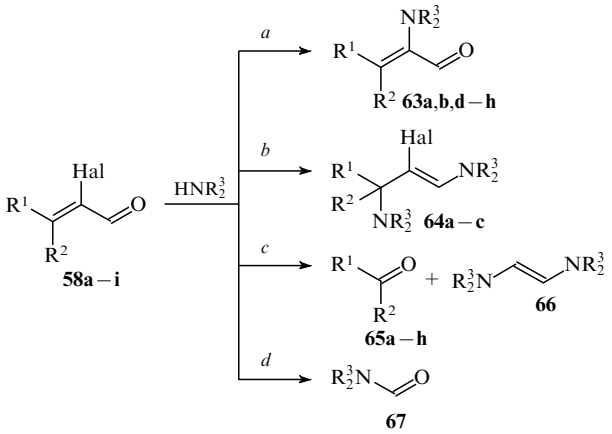
61 **62** (57% – 71%)

R = Me, Et, Bu^t.

The reactions of secondary amines with 2-haloalk-2-enals **58a** – **i** follow an unusual pathway and give an array of polyfunctional unsaturated compounds.[9, 92 – 95]

The predominant route of transformations is mostly determined by the structure of the initial substrate. Thus the interaction of 2-chloropropenal **58a** with secondary amines gives mostly 1,3-diamino-2-chloropropenes **64a** [Scheme 2, pathway (*b*)]. The same reaction route is observed for 2-fluorobut-2-enal **58c**. Conversely, the reactions of 3-alkyl(or aryl)-2-chloro(or bromo)alk-2-enals **58b**,**d** – **g** with highly basic secondary amines normally yield *ipso*-substitution products **63b**,**d** – **g** as the major products [pathway (*a*)]. This route competes with fragmentation [pathway (*c*)], which results in the formation of carbonyl compounds **65b** – **h** and unsaturated diamines **66**. When the initial substrate contains a second alkyl substituent at the β-position (aldehyde **58h**), the *N*-formyl derivative of the initial amine **67** [pathway (*d*)] is produced, in addition to the substitution product **63h**, in a comparable amount. The presence of two phenyl groups in the substrate (**58i**) makes it completely inert towards secondary amines.

Scheme 2



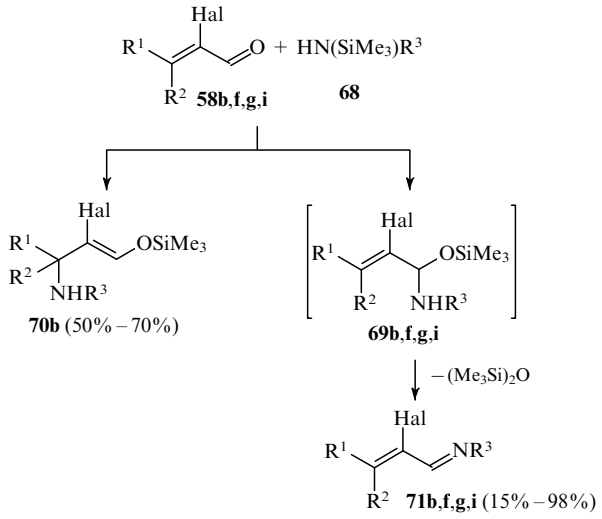
58a – **i** **63a**,**b**,**d** – **h** **64a** – **c** **65a** – **h** **66** **67**

R^1 = R^2 = H, Hal = Cl (**a**); R^1 = Me, R^2 = H, Hal = Cl (**b**), F (**c**), Br (**d**); R^1 = Pr, R^2 = H, Hal = Cl (**e**); R^1 = Ph, R^2 = H, Hal = Cl (**f**), Br (**g**); R^1 = R^2 = Me, Hal = Cl (**h**); R^1 = R^2 = Ph, Hal = Cl (**i**);

NR_2^3 = NEt_2, NBu_2, , , .

The selectivity of the reaction does not correlate with the basicity of the nucleophile. Indeed, piperidine, pyrrolidine, and diethylamine in which the nitrogen atoms are close in basicity and steric accessibility react with the same substrate **58b** according to pathways (*a*), (*b*), and (*c*), respectively.[94] Aprotic solvents (benzene, THF, pyridine) facilitate the *ipso*-substitution reaction [pathway (*a*)], whereas in protic solvents, pathway (*c*) prevails.[94, 95]

Considerable interest was aroused by the reaction of 2-haloalk-2-enals with alkylaminotrimethylsilanes **68** containing an N – H bond. These nucleophiles could behave like secondary amines being involved in, for example, *ipso*-substitution of halogen or like aminosilanes with a tertiary amino group, which would result in the formation of 1,2- or 1,4-addition products.[96] It turned out that the aldehydes **58b**,**f**,**g**,**i** readily react with one equivalent of the alkylaminotrimethylsilane **68** giving rise to the products of 1,2-addition (**69b**,**f**,**g**,**i**) and/or 1,4-addition (**70b**). The adducts **69b**,**f**,**g**,**i** are unstable; they eliminate siloxane to give aldimines **71b**,**f**,**g**,**i**. This is a facile and efficient method for preparing valuable azomethine derivatives of 2-haloalk-2-enals.[97]



R^1 = Me, R^2 = H, Hal = Cl (**b**), R^1 = Ph, R^2 = H, Hal = Cl (**f**); R^1 = Ph, R^2 = H, Hal = Br (**g**); $R^1 = R^2$ = Ph, Hal = Cl (**i**); R^3 = cyclo-C_6H_{11}, Bn, Ph.

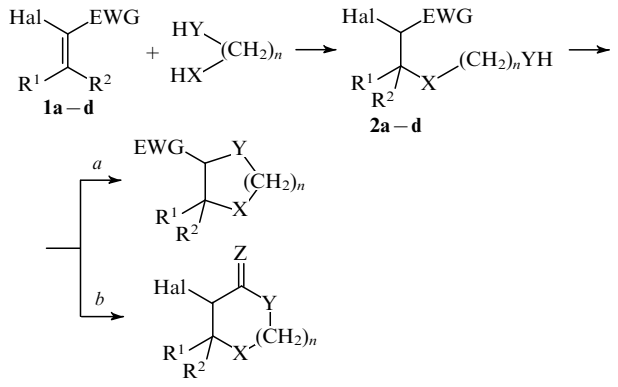
To summarise the foregoing, it should be emphasised that although most of these transformations are described by a common scheme, it is often difficult to predict the outcome of reactions of haloalkenes, activated by geminal substitution, with N-nucleophiles. Nevertheless, the regularities discovered promote the intense use of haloalkenes **1a–d** in the synthesis of various heterocyclic compounds.

III. Reactions of haloalkenes activated by geminal groups with binucleophiles

Reactions of haloalkenes **1** with bidentate nucleophiles of various types (from α,α to α,ω) have resulted in the synthesis of a wide range of N-, S-, or O-containing heterocyclic derivatives. It is significant that these reactions are usually highly chemo- and regio-selective.

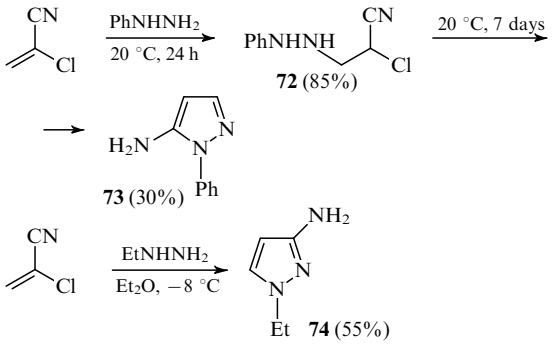
A possible route for interaction of the alkenes **1a–d** with binucleophiles is conjugated addition at the double bond. Depending on the activity of the electron-withdrawing substituent, the process is either terminated at the stage of formation of the Michael adduct **2a–d** or proceeds further as subsequent transformations of the adduct; these include nucleophilic substitution of the halogen atom [Scheme 3, pathway (*a*)] or nucleophilic attack at the activating group giving rise to a halo-containing heterocyclic derivative, which often undergoes subsequent transformations [pathway (*b*)]. The process can be directed at one or another route by varying the type of the activating group, the nature of the nucleophile, or experimental conditions.

Scheme 3

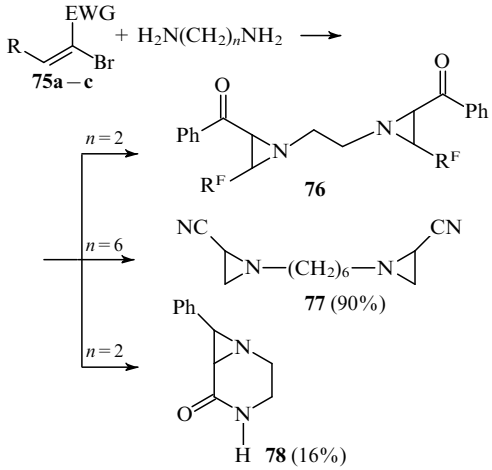


n = 0–6; X = Y = NR^3; X = NR^3, Y = O; X = S, Y = NR^3; R^3 = H, Alk, Ar; Z = O, NH.

Thus phenylhydrazine readily adds to the double bond of 2-chloroacrylonitrile to give 2-chloro-3-phenylhydrazinopropionitrile **72** in a high yield; this product cyclises to give 1,5-disubstituted pyrazole **73**. In the case of more basic ethylhydrazine, the addition at the double bond involves the secondary amino group of the hydrazine, and this results in the formation of 1,3-disubstituted pyrazole **74**.[28]

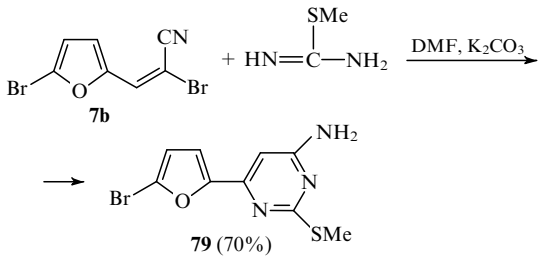


Despite the fact that unimolecular reactions are favourable from the entropy viewpoint, reactions of haloalkenes **1a–d** with N,N-binucleophiles can give rise to both intra- and inter-molecular cyclisation products. For instance, reaction of α-bromo α,β-unsaturated ketone **75a** with ethylenediamine affords derivative **76**.[98] 2-Bromoacrylonitrile **75b** reacts with hexamethylenediamine in a similar way and gives bis-aziridine **77** in a high yield.[24] Conversely, the reaction of ethyl α-bromoacrylate **75c** with ethylenediamine initially proceeds by a usual pathway but then an amide ring is closed, and 5-oxo-7-phenyl-1,4-diazanorcaran **78** is formed as the final product.[99]



EWG = COPh, R = R^F (**75a**); EWG = CN, R = H (**75b**); EWG = COOEt, R = Ph (**75c**).

The reaction of substituted 2-bromoacrylonitrile **7b** with *S*-methylisothiourea leads to pyrimidine **79**.[100]

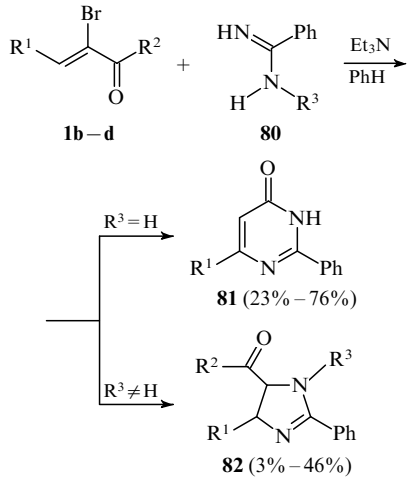


Pyrimidine derivatives have also been obtained in reactions of urea and thiourea with β-substituted α-haloacrylates.[101–104]

The influence of the steric accessibility of the nitrogen atom in the nucleophile on the direction of the attack has been demon-

strated in a number of studies.[103–105] Thus benzamidine **80** (R^3 = H) with a primary amino group converts haloalkenes **1b–d** into pyrimidinones **81**. Mono-*N*-substituted amidines react with the same substrates under the same conditions giving rise to 2-imidazoline derivatives **82** (Scheme 4).

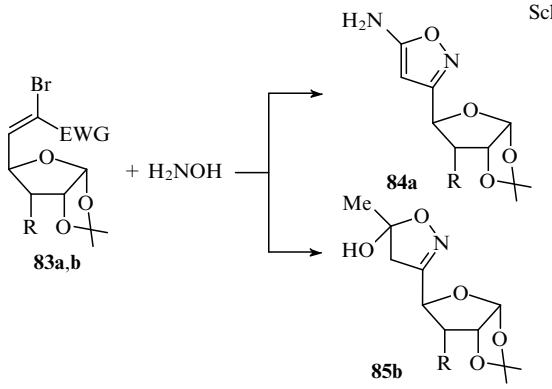
Scheme 4



R^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4; R^2 = H, Me, Bu^t, Ph, OMe, OEt; R^3 = H, Me, Pr^i, Bn.

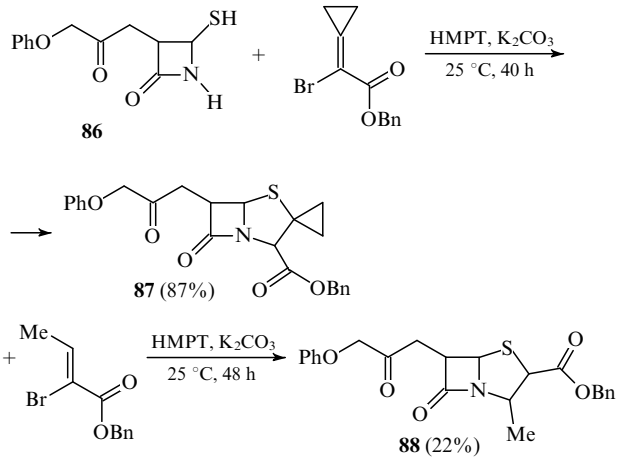
Hydroxylamine reacts with α-bromo-β-glycosyl α,β-unsaturated nitriles **83a** and ketones **83b** as an N,O-binucleophile affording isoxazole derivatives **84a** and isoxazoline derivatives **85b**, respectively (Scheme 5).[20, 106, 107] The positions of substituents in the N,O-heterocycle make it possible to draw conclusions about the direction of the primary nucleophilic attack. As a rule, the nitrogen atom in N,O-binucleophiles proves to be more nucleophilic. However, rare examples of formation of isoxazoles in which the β-carbon atom of an alkene is bound to the oxygen have also been reported.[20, 108]

Scheme 5



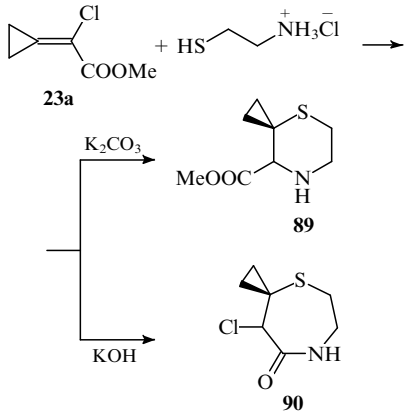
EWG = CN (**a**), Ac (**b**); R = H, OMe, OBn, CF_3CONH.

Conversely, in the case of N,S-binucleophiles, the sulfur atom is more nucleophilic and adds at the double bond. The resulting Michael adduct with a free amino group participates in cyclocondensation involving either the α-carbon atom or the activating group.[52, 109–113] Thus the reaction of 4-sulfanylazetidinone **86** with benzyl 2-bromo(cyclopropylidene)acetate yields a mixture of epimeric cyclopropanespiro-2-bisnorpenicillanates **87**.[113] The formation of the ester **88** from benzyl α-bromocrotonate and the same binucleophile **86** was interpreted[112] by assuming isomerisation of the intermediate product of S-addition of the nucleophile.

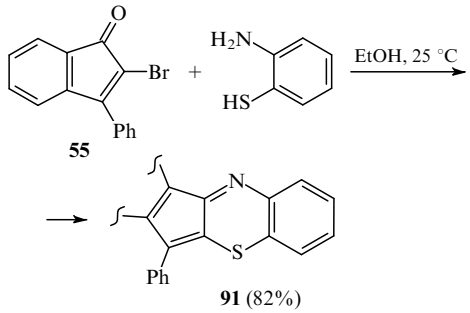


HMPT is hexamethylphosphotriamide.

A clear illustration of the influence of the nature of the base used on the direction of cyclisation has been reported by Wessjohann and de Meijere.[52] Treatment of α-chloroacrylate **23a** with 2-aminoethanethiol in the presence of K_2CO_3 gives rise to 1,4-thiazine derivative **89**, whereas the use of KOH under the same conditions results in the formation of seven-membered heterocycle **90**.



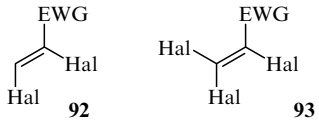
Reactions of N,N-, N,C-, and N,S-binucleophiles with α-halo α,β-unsaturated ketones **1c** begin with halogen substitution, which is followed by intramolecular interaction of the free amino group with the carbonyl carbon atom leading to cyclisation.[89, 114–118] This route is realised, for example, when *o*-aminobenzenethiol is made to react with 2-bromo-3-phenylindenone **55**; this reaction results in the formation of compound **91** with a 1,4-benzothiazine ring.[89, 115]



As a rule, reactions of haloalkenes **1** with binucleophiles afford heterocyclic compounds. However, in some cases,[18, 29, 80, 119] β-aminoalkenes of type **4** have been obtained as the reaction products. This cannot be always explained by steric hindrance at the electrophilic centre of the substrate or by steric inaccessibility of a particular heteroatom in the nucleophile.

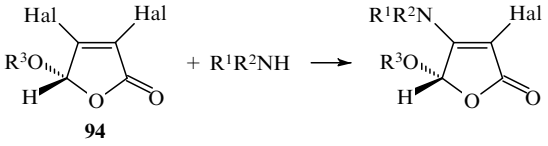
IV. Reactions of polyhaloalkenes with N-nucleophiles

Di- and tri-haloalkenes **92** and **93** are even more reactive and are widely used in organic synthesis. The presence of a halogen atom at the β-carbon atom sharply changes the general pattern of interaction of haloalkenes **1a**–**d** with N-nucleophiles. It is known that a halogen atom located in the β-position in relation to an activating group can be readily substituted. Therefore, compounds of this type have served as the basis for the preparation of various β-functionally substituted α,β-unsaturated carbonyl compounds and their analogues.[120, 121]



92 **93**

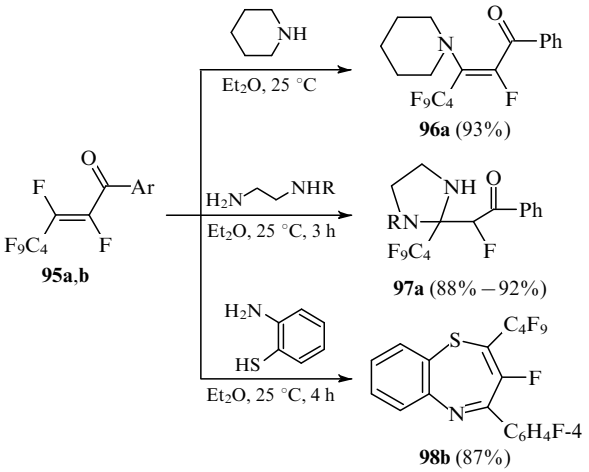
The difference between the reactivities of halogen atoms occupying different positions with respect to an activating group is so great that reactions of N-nucleophiles with α,β-di- (**92**) and α,β,β-tri-haloalkenes **93** involve almost in all cases the β-halogen atom, whereas α-halogen remains absolutely inert. Thus primary and secondary amines enter into a tandem addition–elimination reaction with chiral dihalo(menthyloxy)furanone **94** to replace the β-halogen atom with high enantioselectivity.[122–124]



94

Hal = Cl, Br; $R^1R^2N = (CH_2)_4N$, $O(CH_2CH_2)_2N$, BnNH, PhCH(Me)NH; R^3 = 1-menthyl.

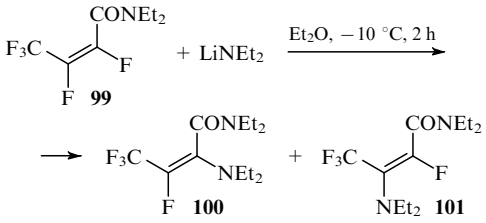
Secondary amines replace only the β-halogen atom in trifluoroacrylonitrile under mild conditions.[125] Of all possible paths of interaction of unsaturated perfluoro ketones **95a**,**b** with amines or binucleophiles, only chemoselective substitution of the vicinal fluorine atom does occur. The reaction with piperidine results in the formation of product **96a**. In the case of binucleophiles, this is followed by Michael cyclisation yielding imidazolidines **97a**.[126, 127] The reaction of ketone **95b** with *o*-aminobenzenethiol gives substituted benzothiazepine **98b**. The primary attack by the thiol group in this reaction was confirmed by NMR monitoring.[127]



95a,**b** **96a** (93%) **97a** (88%–92%) **98b** (87%)

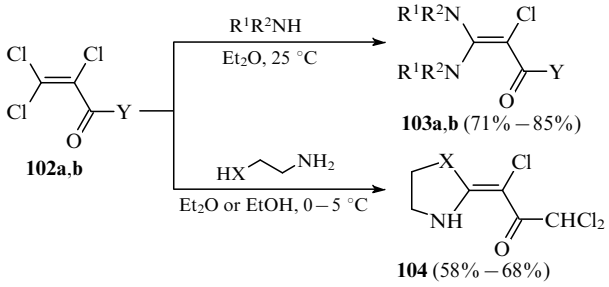
R = H, Me; Ar = Ph (**a**), 4-FC_6H_4 (**b**).

At first glance, these data seem to be at variance with the results obtained by Nguyen *et al.*[128] The reaction of *N*,*N*-diethylperfluorocrotonamide **99** with lithium diethylamide under mild conditions gave a mixture of isomeric α- (**100**) and β- (**101**) diethylamino-derivatives in ~3 : 1 ratio. It is clear that in this case, the regioselectivity of nucleophilic substitution is influenced by the highly electron-withdrawing trifluoromethyl group.



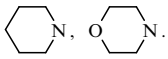
99 **100** **101**

The reactions of primary and secondary amines and also N,N- and N,O-bidentate nucleophiles with α,β,β-trichloro-substituted unsaturated ketones **102a**,**b** involve exclusively the β-chlorine atoms and give polyfunctional compounds **103a**,**b** and **104**.[129, 130] No trisubstituted products or products of reaction at the carbonyl group are formed even with excess nucleophile. When the nucleophile : substrate ratio is decreased to 1 : 2, some of the initial ketone is recovered unchanged, but no monosubstituted products arise.[130]



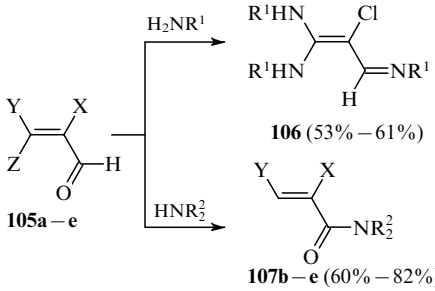
102a,**b** **103a**,**b** (71%–85%) **104** (58%–68%)

Y = $CHCl_2$ (**a**), CF_3 (**b**); X = NH, O; R^1R^2N = PhMeN, PhNH, Bu^{t}NH,



When β-bromo-α,β-dichloroacrolein **105a** is treated with primary amines, the replacement of the β-halogen atoms is accompanied by condensation at the aldehyde group resulting in the formation of 1,1-diamino-2-chloro-3-iminoprop-1-enes **106**.[131] Neither an increase in the excess of amine nor raising the temperature lead to substitution of the α-chlorine atom.

On treatment with secondary amines, trihaloacroleins **105b**–**e** are unexpectedly converted into dihaloacrylamides **107b**–**e**;[132, 133] it was found [133] that halogen was eliminated from the β-carbon atom. Based on this conclusion, a possible reaction mechanism was proposed that included primary nucleophilic attack on the carbonyl group of the substrate.



105a–**e** **106** (53%–61%) **107b**–**e** (60%–82%)

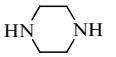
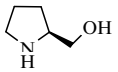
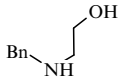
X = Y = Cl, Z = Br (**a**); X = Y = Z = Cl (**b**); X = Br, Y = Z = Cl (**c**); X = Cl, Y = Z = Br (**d**); X = Y = Z = Br (**e**); R^1 = Ph, Bn, 2,4-$Me_2C_6H_3$;

$NR^2_2 = NEt_2$,

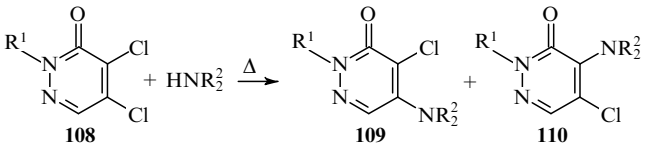


The α-halogen atom in α,β-dihaloalkenes of type **92** can be involved in the reaction only in rare cases. For instance, reaction of 4,5-dichloro-3(2*H*)-pyridazinones **108** with N-nucleophiles affords either the product of substitution of only the β-halogen

Table 1. Reactions of pyridazinones **108** with N-nucleophiles.

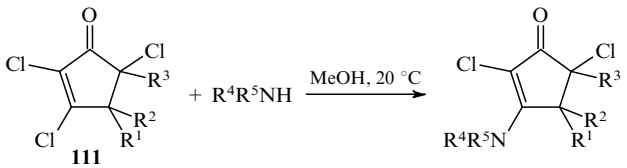
HNR^2_2	R^1	Solvent	*t* /h	Yield (%)		Ref.
				109	**110**	
	H	EtOH, Et_3N	4	40	–	134
	Me			50	–	134
	Ph			50	–	134
	H	BuOH	4	60	0	135
	Me	EtOH	4	73	7	135
	$BnOCH_2$	H_2O	11	41	4	136
		PhMe	11	21	13	136

atom **109** [134] or a mixture of isomeric α- and β-amino-derivatives **110** and **109**, the latter being formed in substantially (up to 10 : 1) larger amounts (Table 1).[135, 136]



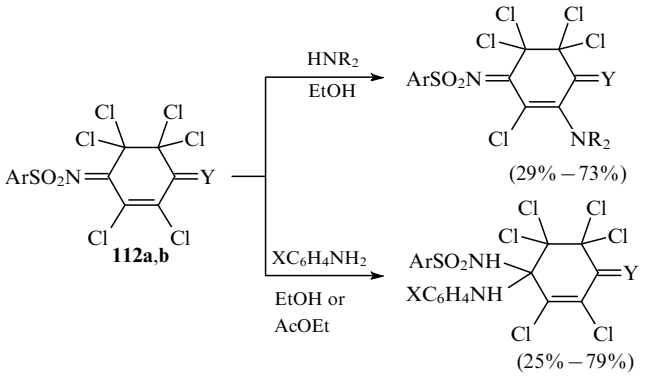
When 5,6-dihalopyrimidines are treated with N-nucleophiles as well as with N,N-, N,O-, and N,S-binucleophiles, both halogen atoms are substituted.[137–139]

Halogen atoms at a double bond may also remain intact during the reaction of haloalkenes of type **1** with nucleophiles; this is the case when the molecule of the initial substrate contains other, more electrophilic, sites.[140, 141] It is of interest to consider molecules that contain halogen atoms attached to an sp^3 hybridised carbon atom in addition to halogen atoms at a double bond. As a rule, the former are replaced much more easily.[142, 143] Substitution at the vinylic centre requires more drastic conditions. Hence, these two processes can be carried out separately, and different amine fragments can be introduced into the molecule.[144] In some cases, β-halogen atoms can be easily substituted, other centres remaining intact (see, for example, Refs 145–150). Thus the reaction of substituted 2,3,5-trichloro-2-cyclopentenones **111** with various amines occurs smoothly and regiospecifically in accordance with the expected *N*-oxovinylation scheme, the α-chlorine atom at the double bond being inert.

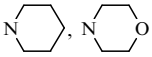


$R^1 = R^2 = OMe$; $R^1 = OH$, $R^2 = Me$; $R^3 = CH_2CH{=}CH_2$, $CH{=}C{=}CH_2$; $R^4 = Me$, $R^5 = H$; $R^4 = HO(CH_2)_2$, $R^5 = H$; $R^4 = R^5 = Me$, Et; R^4, $R^5 = MeN(CH_2CH_2)_2$; R^4, $R^5 = O(CH_2CH_2)_2$; R^4, $R^5 = (CH_2)_5$.

When polychloro-derivatives **112a**,**b** are made to react with heterocyclic amines (piperidine, morpholine), the chlorine atom at the double bond undergoes nucleophilic substitution.[151] The reaction of **112b** with pyridine follows a similar route.[152] Aniline and its derivatives do not form substitution products; instead, they unexpectedly add to the C = N bond.[151, 153]

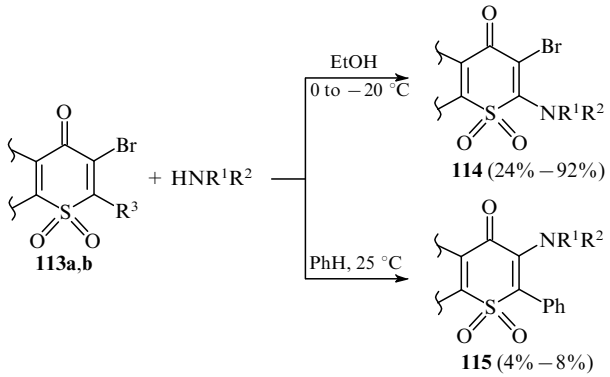


Y = O (**a**), NSO_2Ar (**b**); Ar = 4-MeC_6H_4, 4-ClC_6H_4;

X = H, 4-Me, 3-Me; NR_2 = .

The reactions of 2,3-dibromo-4*H*-1-benzothiopyran-4-one 1,1-dioxide **113a** with alkylamines, dialkylamines, aniline, and its derivatives afford only products **114** resulting from substitution of bromine that occupies the β-position with respect to the carbonyl group.[154, 155]

The substitution of bromine in the substrate **113b** results in the formation of compound **115** in a low yield.[156]



R^3 = Br (**a**), Ph (**b**); $R^1 = R^2 = Me$; $R^1 = H$, $R^2 = Me$; Ph, C_6H_4OMe-4.

V. The mechanism of nucleophilic substitution of halogen atoms in *gem*-activated haloalkanes

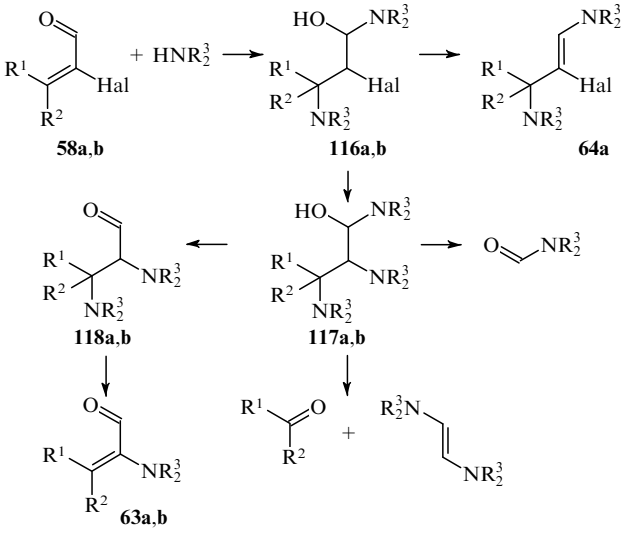
The mechanism of vinylic nucleophilic substitution (S_NVin) in alkenes in which the leaving group is in the β-position in relation to the activating group has been studied fairly comprehensively.[157] About 30 different variants of this reaction have been proposed. However, the mechanism of this reaction for the alkenes in which the leaving and activating groups are attached to the same carbon atom has been much less studied. The diversity of the products of reactions of the haloalkenes **1a**–**d** with amines indicates unambiguously that it is not a one-step process. The scheme now generally accepted, which permits interpretation of the overwhelming majority of the results obtained, is quite obvious. An amine adds to the double bond of the haloalkene **1a**–**d** to give the adduct **2a**–**d** the structure of which is responsible for the direction of subsequent transformations. When primary amines are used, the adducts usually undergo intramolecular substitution of the halogen atom giving rise to aziridines **3a**–**d**. In the case of secondary amines, the transformations in question occur either as halogen substitution yielding α,β-diamino-derivatives **5a**–**d** or as dehydrohalogenation to give β-aminoalkenes

4a–d. This scheme was first proposed by Cromwell [7] as the most probable hypothesis. Subsequently, it was confirmed experimentally and further developed. Strong evidence supporting this scheme has been provided by detection and, in some cases, isolation of the main intermediates. The Michael adducts **2** were isolated for the nitriles **1a**, esters **1b**, and ketones **1c**.[158–160] The attractive hypothesis of the intermediate formation of an aziridinium salt has been confirmed only after isolation and full spectroscopic identification of this intermediate.[160, 161] The transformation of the diamino-derivative **5** into the corresponding unsaturated compound **6**, discovered in a number of studies,[95, 162] has provided final evidence for the reaction mechanism consisting of three successive steps, Ad–S_N–E.

The general scheme of transformations has been recently extended to the most reactive series of substrates **1d**.[162] These compounds differ from all the other haloalkenes activated by geminal substitution in that their activating group does not remain unchanged during the transformations.

The sequence of transformations of 2-chloroacrolein **58a** and 2-chlorobut-2-enal **58b** on treatment with piperidine has been monitored by NMR spectroscopy. At low temperatures, several main intermediates were detected; they accounted for the formation of all the reaction products. Although the nature of the product resulting from the addition of one equivalent of the amine was not elucidated, some findings as well as the electronic structures of the starting compounds [163] suggest that the process starts with the 1,4-addition of the nucleophile.

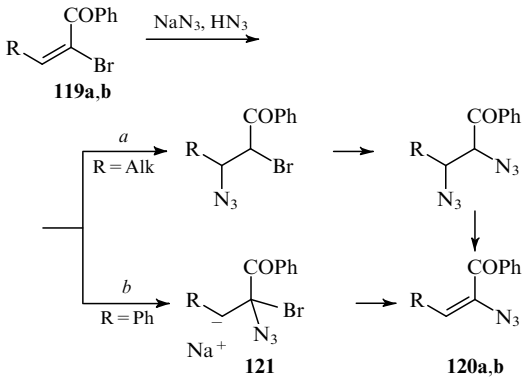
The first intermediate that could be detected in the reaction of the substrate **58b** with piperidine at 5 °C was hemiaminal **116b**. In the presence of excess amine, **116b** readily undergoes bimolecular nucleophilic substitution of the halogen atom being thus converted into triamino-derivative **117b**. When the temperature is increased to 25 °C, the latter participates in several competing reactions, the removal of the hemiaminal protection with regeneration of the aldehyde group being the predominant route. The resulting 2,3-diamino aldehyde **118b** undergoes β-elimination of an amine molecule and is thus converted into the final product **63b**. A similar sequence of transformations is observed when **58a** is used as the substrate in this reaction. However, in this case, the hemiaminal **116a** formed initially is mostly dehydrated yielding the alkene **64a**. The sequence of transformations **116a** → **117a** → **118a** → **63a** is not the prevailing route. In general, the proposed scheme accounts for the diversity of the products obtained from haloalkenes activated by a formyl group. It also explains why transformations of this type do not occur in the series of substrates **1a–c**.



$R^1 = R^2 = H$ (**a**); $R^1 = H$, $R^2 = Me$ (**b**).

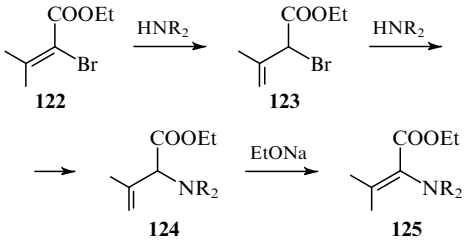
Despite the fact that the multistep scheme of nucleophilic vinylic substitution in these systems is currently generally accepted, in some cases, the possibility of direct substitution also cannot be dismissed.[164, 165] For example, it is believed that the substitution of bromine in the alkene **119a** by the azide ion occurs as the Ad–S_N–E sequence of steps [Scheme 6, pathway (*a*)]. However, introduction of a phenyl group into the β-position of the substrate (compound **119b**) enables stabilisation of the negative charge in the β-position of the adduct **121**. Therefore, apart from the multistep substitution [pathway (*a*)], direct α-addition of the azide ion to the double bond [pathway (*b*)] resulting in the formation of the same substitution product **120b** also becomes possible.

Scheme 6



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

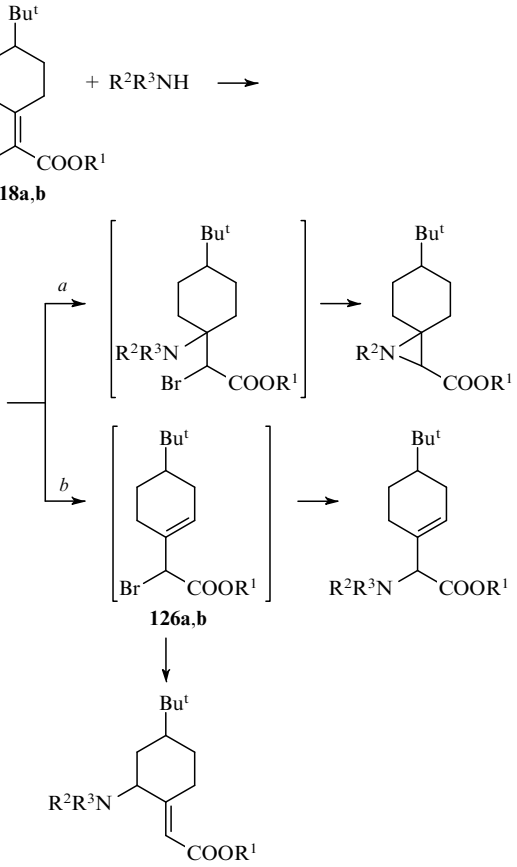
The question arises as to whether nucleophilic substitution in *gem*-activated haloalkenes always includes the step of conjugated addition, or whether another reaction route is also possible in those cases where the β-carbon atom proves to be inaccessible for some reason (mostly steric). The first attempt to answer this question was undertaken as early as the middle 1950s by a group of French chemists.[166] They studied reactions of ethyl 2-bromo-3-methylcrotonate **122** with secondary amines and suggested that the first step of the process is prototropic transformation of the initial α,β-unsaturated carbonyl compound **122** into its β,γ-isomer **123**. The subsequent bimolecular substitution of the allylic halogen atom gives rise to the amino-derivative **124** isomerisation of which induced by a strong base affords the final product **125**.



However, thorough studies [167] made it possible to give preference to the classical Ad–S_N–E mechanism, which includes formation of the ethyleneimmonium intermediate. This is the only possibility that provides a plausible explanation of the migration of the amine fragment from the β-carbon atom, where it is detected initially, to the α-position.

The idea [166] that the reaction might start with the 1,3-shift has later been confirmed for other examples.[38, 65–68] Thus the diversity of products formed upon interaction of the esters **18a,b** with primary and secondary amines, and also the fact that the spiroaziridine derivative **19a,b** is not transformed into the isomeric ester **20** have led Rulev *et al*[38] to the conclusion that the process can occur by different mechanisms, depending on the type of the nucleophile and experimental conditions. The reactions with primary amines carried out at room temperature under an elevated or atmospheric pressure follow the classical Ad–S_N–E

pattern [pathway (*a*)]. Conversely, for the reactions with secondary amines and also for those with primary amines carried out under reflux, the key stages are isomerisation of the initial ester **18a**,**b** giving ester **126a**,**b** with an endocyclic double bond and the subsequent easy substitution of the allylic halogen atom by the amine [pathway (*b*)]. Examples of such isomerisation in the series of α-halo α,β-unsaturated acids, induced by amines under very mild conditions, have been reported.[168]



VI. Conclusion

The high and diverse reactivity of haloalkenes containing an electron-withdrawing group in the α-position is based on the phenomenon, which has been called by Louis Henry 'functional solidarity'.[169] The essence of this phenomenon is the following. When several functional groups are bound to the same carbon atom in a molecule, their mutual influence results in some cases in substantially changed chemical properties, not typical of the same functional groups occurring separately.

Easily accessible *gem*-activated haloalkenes, which are used as polyfunctional building blocks, occupy a prominent place in modern organic synthesis. Analysis of the available data indicates that nucleophilic vinylic substitution in haloalkenes activated by a geminal group differs substantially from related reactions in the series of alkenes with vicinal leaving and activating groups. These reactions have specific features, and it is not always possible to predict the outcome of a particular transformation.

Despite the fact that such polydentate systems are widely used in synthesis, their potential is far from being exhausted. We believe that the synthetic and theoretical aspects of the chemistry of *gem*-activated haloalkenes would remain the focus of the attention of researchers as a part of the chemistry of unsaturated heteroatomic derivatives with a geminal electron-withdrawing group.

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