Multistep nucleophilic substitution of the halogen atom in 2-halo-2-alkenals

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ipso-Substitution of the halogen atom in 2-halo-2-alkenals under the action of secondary amines proceeds *via* three consecutive steps: addition, nucleophilic substitution, and β-elimination (the Ad_N—S_N—E mechanism). The main intermediates arising in the reactions of 2-chloropropenal and 2-chloro-2-butenal with piperidine were detected by NMR spectroscopy. A general scheme of the reaction is proposed.

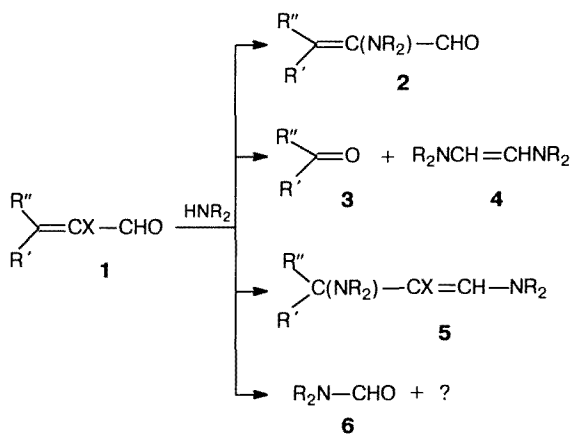
Key words: 2-halo-2-alkenals, secondary amines, nucleophilic vinylic substitution.

For nucleophilic vinylic substitution in olefins in which the leaving group is located in the β-position with respect to the activating group,[1–3] about 30 variants of the mechanism have been suggested.[4] Reactions of the $S_N$vin type in haloolefins in which the activating and leaving groups are attached to the same C atom have been substantially less studied (see Refs. 5 and 6). The most reactive substrates incorporating a formyl group in the *gem*-position with respect to the halogen atom, namely, R″(R′)C=CX—CHO, have been studied only by French researchers[7–9] and by us.[5,10,11] It has been suggested that replacement of the halogen in α-halocrotonaldehydes occurs by an Ad_N—S_N—E mechanism and yields derivatives of α-aminocrotonaldehyde.[11] Taking into account recently published data,[12,13] we studied in detail the reactions of 2-chloro-2-butenal and 2-chloropropenal with piperidine; the results obtained were extended to the whole class of 2-halo-2-alkenals.

Previously we reported[5,10,12] that 2-halo-2-alkenals **1** react with secondary amines, giving, along with the products of *ipso*-substitution of the halogen atom, a number of side products resulting from anhydrocondensation and fragmentation (Scheme 1).

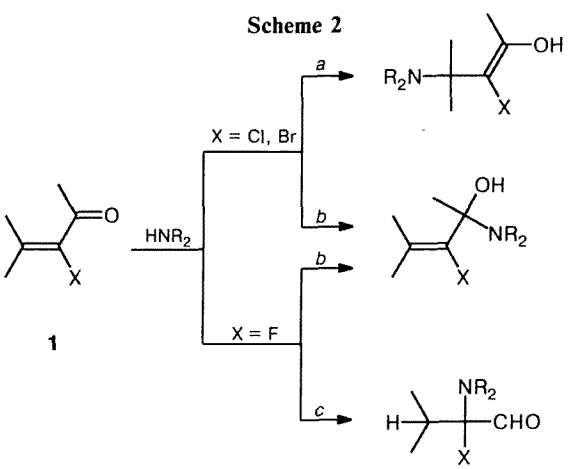
The diversity of the reaction products that were in most cases isolated in a pure state indicates that the *ipso*-substitution of the halogen atom in 2-halo-2-alkenals is a rather complex process. One may assume *a priori* that the primary attack by the amine on 2-chloro- and 2-bromo-2-alkenals **1** (X = Cl or Br) is directed at either of the two electrophilic centers of the substrate, *viz.*, the β-C(sp^2) atom (Scheme 2, pathway *a*) or the C atom of the carbonyl group (Scheme 2, pathway *b*). In the case of 2-fluoro-2-alkenals **1** (X = F) the attack may be directed at the carbon atom of the carbonyl group (pathway *b*) or the olefinic C atom, bound to the leaving group (Scheme 2, pathway *c*).[13]

Scheme 1



a: R″ = R′ = H **d:** R″ = R′ = Me
b: R″ = Me, R′ = H **e:** R″ = Ph, R′ = H
c: R″ = Pr^n, R′ = H **f:** R″ = R′ = Ph
X = F, Cl, Br;
NR_2 = NEt_2, NBu^n_2, $N(CH_2)_4$, $N(CH_2)_5$, $N(CH_2CH_2)_2O$

Scheme 2



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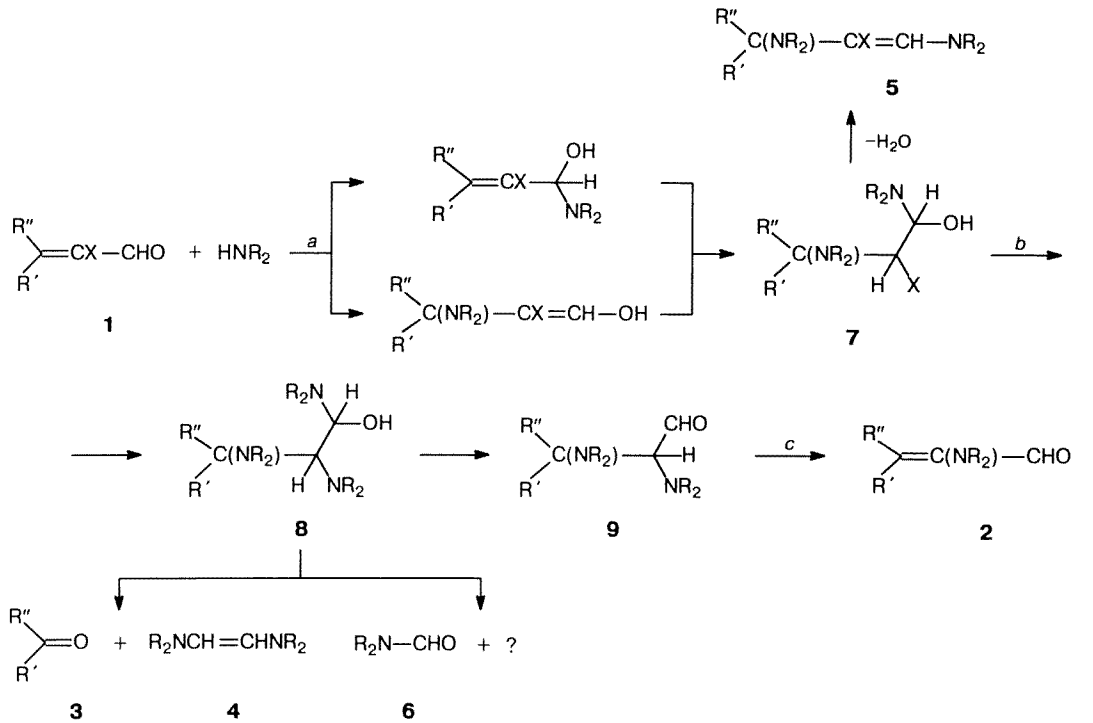
Scheme 3

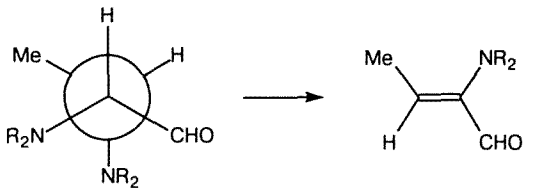


The high reactivity of the formyl group determines the characteristic features of the formation of unsaturated aminoaldehydes **2** and makes it possible to explain the diversity of the side products, which have not been observed with α,β-unsaturated ketones, esters, or nitriles of carboxylic acids.

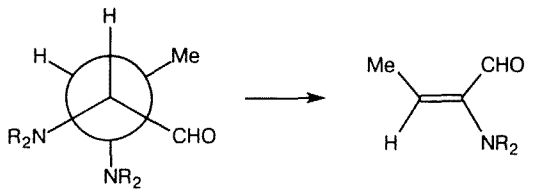
By means of NMR monitoring we detected several main intermediates arising in the reactions of 2-chloropropenal **1a** (X = Cl) and 2-chloro-2-butenal **1b** (X = Cl) with piperidine. Combination of the results of the present and previous studies allowed as to assume a general scheme of nucleophilic substitution of the halogen atom in 2-halo-2-alkenals **1**. A complete interpretation of the reaction mechanism is hampered due to the absence of kinetic data; however, the sequence of transformations is quite obvious. It includes conjugated addition of the amine to the C=C—C=O system of multiple bonds (Scheme 3, *a*), replacement of the halogen at the C(sp^3) atom of the adduct arising in the first step (Scheme 3, *b*), and elimination of amine (Scheme 3, *c*) giving the product of *ipso*-substitution **2**.

The first intermediate of the reaction of compound **1b** (X = Cl) with piperidine that we were able to detect at 5 °C is semiaminal **7b** (X = Cl, NR_2 = $N(CH_2)_5$). Its structure is evidenced by the fact that the doublet corresponding to the methyl group and the quartet of the methine proton are retained in the ^1H NMR spectra and that these signals are substantially shifted upfield (1.04 and 2.82 ppm in semiaminal **7b** and 1.44 and 5.88 ppm in the starting aldehyde **1b**, respectively), as well as by disappearance of the signal of the aldehyde proton and simultaneous appearance of a doublet associated with the proton of the semiaminal group (δ 4.45). The semiaminal **7b** readily undergoes nucleophilic substitution of the Cl atom affording the diamino-substituted analog **8b** (NR_2 = $N(CH_2)_5$). When the temperature is increased to 25 °C, the latter participates in several parallel reactions, among which the removal of the semiaminal protection with regeneration of the aldehyde group predominates. The 2,3-dipiperidinobutanal **9b** (NR_2 = $N(CH_2)_5$) thus formed exists as a mixture of two diastereomers **9A** and **9B**, due to the presence of two chiral centers in the molecule. The chemical shifts of the protons of the aldehyde, methyl, and α-methine groups in the ^1H NMR spectra of isomers **9A** and **9B** differ by 0.03—0.42 ppm. The substantial difference between the chemical shifts of the β-methine protons of the isomers (~1 ppm) can be explained by anisotropic effect of the aldehyde group. Previously we observed an equally essential difference between the chemical shifts of the β-methine protons in the case of *E*- and *Z*-isomers of 2-chloro-3-piperidino-1-trimethylsiloxy-1-butene.[14] By the subsequent β-elimination of the amine molecule diaminoaldehyde **9b** is converted into the final product, 2-piperidino-2-butenal **2b** (NR_2 = $N(CH_2)_5$). The fact that *anti*-elimination is preferred, makes it possible to suggest that diastereomer **9A** yields aminoaldehyde *Z*-**2b**, and **9B** gives *E*-**2b**.

The dynamics of variations and the character of signals in the ^1H NMR spectra indicate that the reaction of 2-chloropropenal **1a** (X = Cl) with piperidine includes a similar sequence of transformations. However in the lat-



9A *Z*-**2b**



9B *E*-**2b**

ter case, unlike the reaction of 2-chloro-2-butenal **1b** (X = Cl), the initially formed semiaminal **7a** (X = Cl) is predominantly dehydrated to give 2-chloro-1,3-dipiperidinopropene **5a** (X = Cl, NR_2 = $N(CH_2)_5$). The formation of α-piperidinoacrolein **2a** (NR_2 = $N(CH_2)_5$) by nucleophilic substitution of the Cl atom followed by amine elimination proves to be a minor process.

In neither of these cases we could elucidate the nature of the product of addition of one equivalent of amine to 2-halo-2-alkenal **1**, because semiaminal **7** is produced almost instantaneously. Nevertheless, some facts indirectly attest to the primary 1,4-addition of the nucleophile. First, when the *N*-trimethylsilyl derivative of secondary amine **10** is used as the nucleophile in the reaction with 2-halo-2-alkenals **1**, the process can be stopped in the stage where the 1,4-adduct, trimethylsilyl ether **11**, is formed (the yields are quantitative).[14,15]

$$\underset{\mathbf{1}}{R'-CH=CX-CHO} + \underset{\mathbf{10}}{Me_3SiNR_2} \longrightarrow \underset{\mathbf{11}}{R'CH(NR_2)-CX=CH-OSiMe_3}$$

R′ = H, Me, Ph; X = Cl, Br; NR_2 = $N(CH_2)_5$, $N(CH_2CH_2)_2O$

Second, in the case of the primary attack by the amine on the carbonyl group, the activity of the double bond should dramatically decrease; accordingly, the subsequent addition of the second equivalent of the amine would be hampered. Special experiments have shown that 2-halo-2-alkenal acetals are only slightly reactive toward secondary amines. For example, acetal of α-bromoacrolein CH_2=CBr—$CH(OEt)_2$ does not react with a fivefold excess of diethylamine in benzene even on prolonged heating in a sealed ampule (130 °C, 20 h).[5] The low mobility of the halogen atom in acetals of α-halo-α,β-unsaturated aldehydes is also indicated by other data.[16]

Third, the inertness of β,β-diphenyl-α-chloroacrolein with respect to piperidine is easily explained by steric factors: the two phenyl groups hamper the attack by the nucleophile on the β-C atom of the double bond. This conclusion is in good agreement with the reported[15] regiospecific 1,2-addition of *N*-trimethylsilylpiperidine **10** (NR_2 = $N(CH_2)_5$) to α-chloro-β,β-diphenylacrolein **1f** (X = Cl).

Some facts that we have found in a study of the reaction of 2-halo-2-alkenals with secondary amines can be accounted for in the framework of the scheme suggested.[12] In all probability, the key intermediates of these reactions are semiaminals of α-halo-β-amino- and α,β-diaminoaldehydes **7** and **8**, whose further transformations depend on both the nature of the β-substituents in the substrate and the type of nucleophile.

Along with the recovery of the aldehyde group from semiaminal **8**, nucleophilic attack on the C(3) and C(1) centers bearing partial positive charges is also possible. It yields fragmentation products: either substituted 1,2-diaminoethene **4** and the corresponding carbonyl compound **3** or formamide **6** (the nature of the second product of this fragmentation reaction is unknown). It is natural to expect that in the case where two methyl groups are present in the β-position, steric hindrance would lead to a change in the ratio between the two fragmentation reactions toward the formation of formamide **6** (see Scheme 1). This assumption was confirmed experimentally: on going from 2-chloro-2-butenal **1b** (X = Cl) to its β-methyl-substituted homolog **1d** (X = Cl), the yield of formamide **6** increases by a factor of 15.[12]

The sequence of transformations suggested makes it possible to interpret the specific behavior of pyrrolidine, which reacts with compounds **1a** (X = Cl) and **1b** (X = Cl) exclusively by a pathway of 1,4-anhydrocondensation yielding 2-chloro-1,3-dipyrrolidinopropene **5a** (X = Cl, NR_2 = $N(CH_2)_4$) and 2-chloro-1,3-dipyrrolidino-1-butene **5b** (X = Cl, NR_2 = $N(CH_2)_4$), respectively.[5,10] Being the most basic and the least sterically hindered among all of the amines used, pyrrolidine acts as an efficient acceptor of the proton from the C atom of semiaminal **7** bound to chlorine. The subsequent elimination of the hydroxyl group gives olefin **5**.

In terms of this scheme, the increase in the yield of α-morpholinocrotonaldehyde **2b** (NR_2 = $N(CH_2CH_2)_2O$) with the appreciably more basic triethylamine being used as the HCl acceptor is readily explained.[17]

Thus, the interaction of 2-halo-2-alkenals **1** with secondary amines is not merely nucleophilic substitution. This is experimentally confirmed by the formation of various reaction products, which is readily explained in terms of the general scheme of transformations suggested by us, which includes the three main steps: Ad_N—S_N—E.

Experimental

The NMR monitoring of the reaction of 2-chloro-2-butenal with piperidine was carried out using a Varian VXR-500S spectrometer (500 MHz). The reaction was carried out with equimolar quantities of the reactants in C_6D_6. The same reaction carried out with a twofold amount of piperidine (in THF-d_8) and the reaction of 2-chloropropenal with piperidine (in C_6D_6 and at a 1 : 2 ratio between the reactants) were monitored on a Bruker WP-200SY instrument (200 MHz). HMDS was used as the internal standard. Signals of the intermediates were assigned using 2D-NMR methods: COSY, RELAY, and TOCSY.

2-Chloropropenal (1a, X = Cl) and 2-chloro-2-butenal (1b, X = Cl) were prepared by chlorination of the corresponding α,β-unsaturated aldehydes with subsequent dehydrochlorination (see Ref. 18).

2-Chloro-2-butenal (1b, X = Cl). ^{1}H NMR, δ: 1.44 (d, Me, J = 6.8 Hz); 5.88 (q, CH=, J = 6.8 Hz); 8.82 (s, CHO).

2-Chloro-1-hydroxy-1,3-dipiperidinobutane (7b, NR_2 = $N(CH_2)_5$, X = Cl). ^{1}H NMR, δ: 1.04 (d, Me, J = 5.6 Hz); 2.82 (dq, MeCH, $J_{H(2),H(3)}$ = 3.7 Hz, $J_{H(3),H(4)}$ = 5.6 Hz); 4.05 (dd, CHCl, $J_{H(2),H(3)}$ = 3.7 Hz, $J_{H(1),H(2)}$ = 7.3 Hz); 4.45 (d, CH(OH)$N(CH_2)_5$, J = 7.3 Hz).

1-Hydroxy-1,2,3-tripiperidinobutane (8b, NR_2 = $N(CH_2)_5$). ^{1}H NMR, δ: 0.98 (d, J = 6.6 Hz); 2.60 (dq, MeCH, $J_{H(2),H(3)}$ = 6.9 Hz, $J_{H(3),H(4)}$ = 6.6 Hz); 3.70 (dd, CH$N(CH_2)_5$, $J_{H(1),H(2)}$ = 8.7 Hz, $J_{H(2),H(3)}$ = 6.9 Hz); 4.48 (d, CH(OH)$N(CH_2)_5$, J = 8.7 Hz).

2,3-Dipiperidinobutanal (9b, NR_2 = $N(CH_2)_5$). ^{1}H NMR, δ: the first diastereomer: 0.89 (d, CH_3, J = 6.6 Hz); 2.95 (dq, MeCH, $J_{H(3),H(4)}$ = 6.6 Hz); 2.58 (dd, CHCHO, $J_{H(1),H(2)}$ = 5.4 Hz); 9.67 (d, CHO, J = 5.4 Hz); the second diastereomer: 1.31 (d, Me, J = 6.6 Hz); 3.98 (dq, MeCH, $J_{H(3),H(4)}$ = 6.6 Hz, $J_{H(3),H(2)}$ = 8.7 Hz); 2.61 (dd, CHCHO, $J_{H(1),H(2)}$ = 3.2 Hz, $J_{H(2),H(3)}$ = 8.7 Hz); 9.57 (d, CHO, J = 3.2 Hz).

2-Piperidino-2-butenal (2b, NR_2 = $N(CH_2)_5$). ^{1}H NMR (THF-d_8), δ: *E*-isomer: 1.59 (m, β-, γ-CH_2); 1.99 (d, Me, J = 7.0 Hz); 3.01 (m, α-CH_2); 6.17 (q, CH=, J = 7.0 Hz); 9.30 (s, CHO); *Z*-isomer: 1.59 (m, β-, γ-CH_2); 2.05 (d, Me, J = 7.8 Hz); 2.75 (m, α-CH_2); 5.60 (q, CH=, J = 7.8 Hz); 9.85 (s, CHO).

2-Chloropropenal (1a, X = Cl). ^{1}H NMR, δ: 5.46 (dd, CH_2=, ^2J = 2.0 Hz, ^3J = 18 Hz); 8.68 (s, CHO).

2-Chloro-1-hydroxy-1,3-dipiperidinopropane (7a, NR_2 = $N(CH_2)_5$, X = Cl). ^{1}H NMR, δ: 2.96 (t, CH_2, J = 5.9 Hz); 3.90 (dt, CHCl, $J_{H(2),H(3)}$ = 5.9 Hz, $J_{H(1),H(2)}$ = 8.8 Hz); 4.37 (d, CH(OH)$N(CH_2)_5$, J = 8.8 Hz).

2-Chloro-1,3-dipiperidinopropene (5a, NR_2 = $N(CH_2)_5$). ^{1}H NMR, δ: 2.96 (s, CH_2); 5.74 (s, CH=).

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