Reactions of α-chloro β-oxo aldehydes with CH-acid anions

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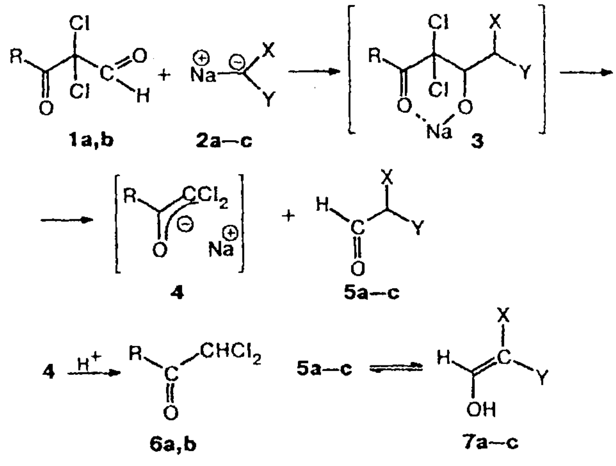
The reactions of α-chloro and α,α-dichloro β-oxo aldehydes with carbanions are accompanied by the cleavage of the carbon—carbon bond in the chloro aldehydes and result in formylation of CH-acids. These electrophiles react with carbanions, which are generated *in situ* from CH-acids in the presence of AcONa in aprotic solvents, to form polyfunctional hydroxy compounds.

Key words: α-chloro β-oxo aldehydes, carbanions, CH-acids.

As part of continuing studies of reactions of α-halogeno-β-dicarbonyl compounds with neutral and anionic nucleophiles,[1—5] in this work we investigated reactions of linear and cyclic α-chloro β-oxo aldehydes with CH-acids.

It was established that the reactions of α,α-dichloro β-oxo aldehydes (**1**) with carbanions (**2**) which were formed as a result of interactions of CH-acids with NaH in aprotic solvents (Et_2O or DMF) afforded (Scheme 1) α,α-dichloromethylcarbonyl compounds (**6**) and formylated CH-acids (**5**).

Scheme 1



1, **6**: R = Ph (**a**), EtO (**b**)
2, **5**, **7**: X = Y = MeCO (**a**), CO_2Et (**b**), X = CN, Y = CO_2Et (**c**)

Apparently, in the first stage of the process, the interaction of nucleophile **2** with the most electrophilic center of dicarbonyl compounds, *viz.*, with the aldehyde group, afforded adduct **3**. The ability of the alkali metal cation (Na^+) to be readily coordinated by the O atom of the carbonyl group to form stable anion **4** is the driving force for decomposition of adduct **3**.

Therefore, the primary products of addition of C-nucleophiles to the aldehyde group of substrates **1a**,**b**, unlike analogous addition products of chloral[6] and other polyhalogenated aldehydes,[7] are unstable and decompose with the cleavage of the carbon—carbon bond of the β-hydroxycarbonyl compounds formed. This fact is attributable to the higher stability of the dichloroacyl anion that was eliminated compared to the trichloromethyl anion, which might be present in the analogous reactions of chloral. According to the ^1H NMR spectral data (and the IR spectral data for **5a**), compounds **5a**—**c** exist as enols **7a**—**c**.

The probable nucleophilic replacement of the Cl atom typical of the majority of α-halogeno-β-dicarbonyl compounds[8] and α-chloro aldehydes[9] did not occur in the reactions of α-chloro-α-formyl-γ-butyrolactone (**8**) with carbanions **2**. These reactions proceeded with the cleavage of the C—C bond to form α-chloro-γ-butyrolactone (**9**) and tricarbonyl compound **5a** according to Scheme 2.

The reactions of carbanions which were generated *in situ* from CH-acids (**10**) under the action of AcONa in aprotic solvents with aldehyde **1a** afforded polyfunctional hydroxy compounds (**12**) (Scheme 3).

Apparently, the nucleophile which was formed under the action of the acetate anion added to the aldehyde group of the initial compound **1a** to give the intermediate alcoholate (**11**), which was stabilized through neutralization of the acetic acid formed.

Substituted butyrolactone **8** reacted analogously (Scheme 4).

Unlike chloral, which reacts in this manner with a wide range of CH-acids,[10] we only succeeded in performing the reactions of α-chloro β-oxo aldehydes with the strongest CH-acids, *viz.*, with acetylacetone ($pK_a \approx 9.00$) and nitromethane ($pK_a \approx 10.20$).

The small difference in the acidity of acetylacetone and nitromethane is actually manifested in the fact that

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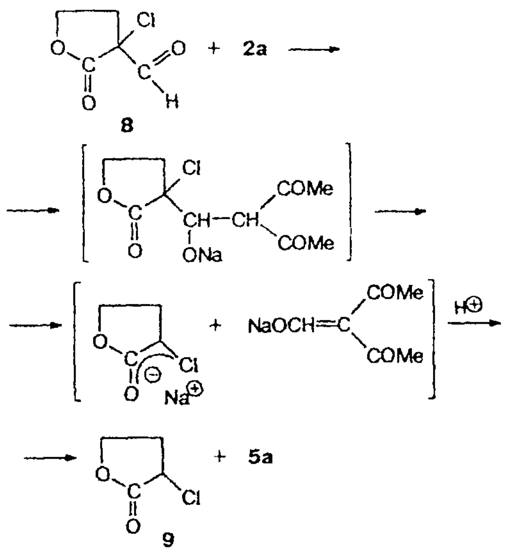
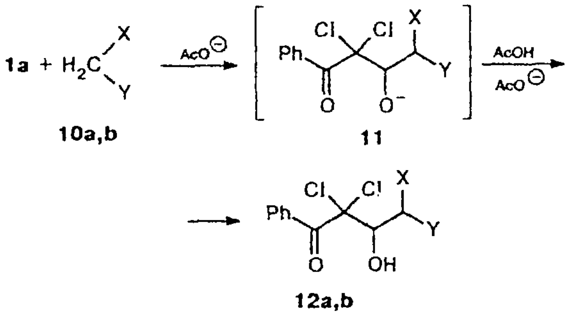
Scheme 2

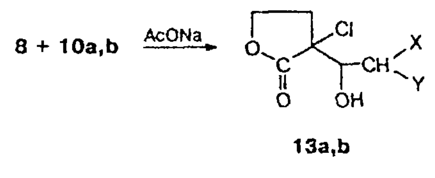


Scheme 3



10, **12**: X = NO_2, Y = H (**a**); X = Y = COMe (**b**)

Scheme 4



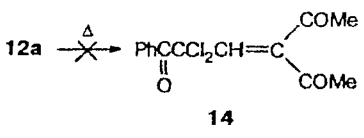
13: X = NO_2, Y = H (**a**); X = Y = COMe (**b**)

the reaction with the former was completed in 1 h, while the reaction with the latter was completed in ~7 days. The course of the reaction was readily monitored by following the disappearance of the signal of the aldehyde group in the ^1H NMR spectra of the initial mixtures.

The compounds obtained are either solid products (**12b** and **13b**) or viscous nondistillable liquids (**12a** and **13a**). Their structures were established by IR and ^1H NMR spectroscopy and confirmed by the data of elemental analysis.

Hydroxy compounds **12** and **13** are rather stable. Thus, boiling of compound **12a** in toluene for 3 h did not result in elimination of water to form an unsaturated compound (**14**) (Scheme 5).

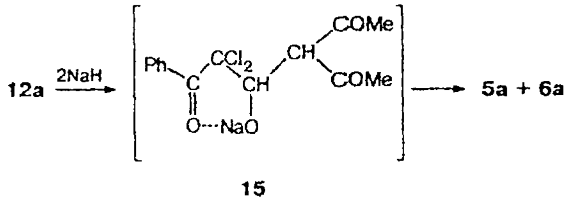
Scheme 5



Attempts to prepare this compound by the Knoevenagel reaction[11] of halogeno aldehydes **1** or **8** with CH-acids in the presence of various catalysts (piperidine, ammonium acetate, or acetic anhydride) also failed. In all the cases, the initial compounds were isolated.

The reaction of NaH with compound **12a** in anhydrous ether afforded dichloroacetophenone and α-formylacetylacetone. Apparently, the reaction proceeded according to Scheme 6.

Scheme 6



The structure of alcoholate (**15**), which is the intermediate reaction product of the base with compound **12a**, is identical with that typical of the intermediate adduct formed in the reaction of sodium derivatives of CH-acids with aldehydes. The identity of the compounds isolated in these two cases supports the suggested scheme of the reaction of β-oxo-substituted aldehydes with enolate anions through an intermediate adduct of type **15**.

To summarize, our studies demonstrated that the reactions of CH-acid anions with the α-chloro β-oxo aldehydes under study proceed exclusively at one reaction center, *viz.*, at the most electrophilic carbonyl C atom of the aldehyde group.

Experimental

The IR spectra were recorded on a UR-20 spectrometer in thin films or as Nujol mulls. The ^1H NMR spectra were obtained on a Tesla BW-567 instrument (100 MHz) with HMDS as the internal standard (δ 0.055).

Reactions of α-chloro aldehydes (1a,b; 8) with CH-acid anions (general procedure). A solution of a CH-acid (**2a—c**)

(0.1 mol) in Et_2O (50 mL) was slowly added with stirring to a suspension of NaH (0.2 mol) in anhydrous Et_2O (150 mL). Then the reaction mixture was refluxed for 1 h and cooled to 0 °C. A solution of aldehyde **1a**,**b** or **8** (0.1 mol) in Et_2O (20 mL) was added. The mixture was stirred at ~20 °C for 6 h and kept for ~24 h. Then water (100 mL) and concentrated HCl (50 mL) were successively slowly added to the mixture. The ethereal layer was separated and the aqueous layer was extracted with ether (2×50 mL). The combined ethereal extracts were washed with a saturated NaCl solution and dried with $MgSO_4$. The solvent was distilled off and the corresponding reaction products, **6a**,**b** and **5a**—**c** or **9** and **5a**, were isolated by fractionation.

2-Acetyl-3-oxobutanal (5a). The yield was 34% (41% in the case of the reaction of **8** with **2a**), b.p. 105—107 °C (15 Torr). Found (%): C, 56.12; H, 6.28. $C_6H_8O_3$. Calculated (%): C, 56.25; H, 6.29. IR, ν/cm^{-1}: 3200 (OH); 1680 (C=O); 1590 (C=C). ^{1}H NMR ($CDCl_3$), δ: 2.01 (s, 6 H, 2 MeCO); 8.00 (s, 1 H, CH=); 10.50 (br.s, 1 H, OH).

α,α-Dichloroacetophenone (6a). The yield was 34%, b.p. 130—132 °C (15 Torr), n_D^{20} 1.5682 (*cf.* Ref. 12: b.p. 143 °C (25 Torr), n_D^{20} 1.5686). ^{1}H NMR ($(CD_3)_2CO$), δ: 6.87 (s, 1 H, $CHCl_2$); 7.50 (m, 3 H, Ph); 8.12 (m, 2 H, Ph).

Diethyl α-formylmalonate (5b) and dichloroacetophenone (6a) were isolated as a mixture with b.p. of 95—120 °C (15 Torr). The yield was 70%. ^{1}H NMR ($(CD_3)_2CO$), δ: for **5b**, 1.25 (m, 6 H, 2 Me); 4.14 (m, 4 H, 2 OCH_2); 8.34 (s, 1 H, CH=); 13.40 (br.s, 1 H, OH); for **6a**, 6.85 (s, 1 H, $CHCl_2$); 7.65 (m, 3 H, Ph); 8.10 (m, 2 H, Ph).

Ethyl α-formylcyanoacetate (5c): an amorphous compound which is sublimed on heating. The yield was 36%. Found (%): C, 49.84; H, 4.81; N, 9.72. $C_6H_7NO_3$. Calculated (%): C, 51.06; H, 4.96; N, 9.93. ^{1}H NMR ($CDCl_3$), δ: 1.20 (m, 3 H, Me); 4.20 (m, 2 H, OCH_2); 8.20 (s, 1 H, CH=); 14.00 (br.s, 1 H, OH).

Ethyl dichloroacetate (6b). The yield was 38%, b.p. 62—64 °C (13 Torr) (*cf.* Ref. 13: b.p. 56 °C (10 Torr)). ^{1}H NMR ($CDCl_3$), δ: 1.22 (t, 3 H, Me); 4.25 (q, 2 H, OCH_2); 6.80 (s, 1 H, $CHCl_2$).

α-Chloro-γ-butyrolactone (9). The yield was 42%, b.p. 104—106 °C (2 Torr). ^{1}H NMR ($CDCl_3$), δ: 2.25 and 3.00 (both m, 2 H, CH_2); 4.50 (m, 3 H, OCH_2, $CHCl_2$).

Reactions of aldehydes (1a and 8) with $MeNO_2$ in the presence of AcONa (general procedure). Aldehyde **1a** or **8** (0.1 mol) was added with stirring to a suspension of AcONa (0.1 mol) in $MeNO_2$ (0.1 mol) and ether or benzene (10 mL) at 20 °C. The reaction was accompanied by an exothermic effect. The mixture was stirred for 7 days. The resulting viscous mixture was dissolved in Et_2O (100 mL) and filtered. The solvent was distilled off under reduced pressure. Products **12a** and **13a** are viscous nondistillable liquids.

2,2-Dichloro-3-hydroxy-4-nitro-1-phenylbutan-1-one (12a). The yield was 91%. Found (%): Cl, 25.41; N, 4.95. $C_{10}H_9Cl_2NO_4$. Calculated (%): Cl, 25.49; N, 5.04. IR, ν/cm^{-1}: 3480 (OH); 1730 (C=O); 1580 (NO_2). ^{1}H NMR ($CDCl_3$), δ: 2.20 (d, 2 H, CH_2NO_2, J = 7.50 Hz); 4.30 (br.s, 1 H, OH); 4.60 (t, 1 H, CH, J = 7.50 Hz); 7.65 (m, 3 H, Ph); 8.20 (m, 2 H, Ph).

2-Chloro-2-(1-hydroxy-2-nitro)ethyl-4-butanolide (13a). The yield was 84%. Found (%): Cl, 17.21; N, 6.80. $C_6H_8ClNO_5$. Calculated (%): Cl, 16.91; N, 6.68. IR, ν/cm^{-1}: 3450 (OH); 1780 (OC=O); 1570 (NO_2). ^{1}H NMR ($CDCl_3$), δ: 2.10 (d, 2 H, CH_2NO_2, J = 7.50 Hz); 2.35, 3.10 (both m, 2 H, CH_2); 4.50 (m, 3 H, OCH_2, OH); 4.55 (t, 1 H, CH, J = 7.50 Hz).

Reactions of aldehydes 1a and 8 with acetylacetone in the presence of AcONa (general procedure). Aldehyde **1a** or **8** (0.1 mol) was slowly added with stirring to a suspension of AcONa (0.1 mol) in acetylacetone (0.1 mol) and ether (10 mL) at ~20 °C. After heat evolution ceased, the reaction mixture was stirred for 0.5 h. The crystalline compound that formed (**12b** or **13b**) was filtered off, washed with water and Et_2O, and dried *in vacuo*.

4-Acetyl-2,2-dichloro-3-hydroxy-1-phenylhexane-1,5-dione (12b). The yield was 74%, m.p. 63—66 °C. Found (%): Cl, 22.34. $C_{14}H_{14}Cl_2O_4$. Calculated (%): Cl, 22.40. IR, ν/cm^{-1}: 3510 (OH); 1735 (MeC=O); 1680 (PhC=O). ^{1}H NMR ($CDCl_3$), δ: 7.60 (m, 3 H, Ph); 8.25 (m, 2 H, Ph); the keto form: 2.15 and 2.25 (both s, 3 H, 2 Me); 4.25 (br.s, 1 H, OH); 4.50 (d, 1 H, $\underline{\mathrm{CH}}$—OH, J = 7.50 Hz); 5.50 (d, 1 H, C$\underline{\mathrm{H}}$COMe, J = 7.50 Hz); the enol form (a mixture of *cis* and *trans* isomers): 1.94 and 1.96 (both s, 3 H, MeCO); 2.05 and 2.15 (both s, 3 H, MeC=); 5.50 (m, 2 H, CH and OH).

2-(2-Acetyl-1-hydroxy-3-oxobutyl)-2-chloro-4-butanolide (13b). The yield was 68%, m.p. 82—84 °C. Found (%): Cl, 14.60. $C_{10}H_{13}ClO_5$. Calculated (%): Cl, 14.46. IR, ν/cm^{-1}: 3480 (OH); 1780 (OC=O); 1730 (C=O). ^{1}H NMR ($CDCl_3$), δ: 2.30 and 3.00 (both m, 2 H, CH_2); 4.60 (m, 2 H, OCH_2); the keto form: 2.15 and 2.25 (both s, 3 H, 2 Me); 4.20 (br.s, 1 H, OH); 4.40 (d, 1 H, $\underline{\mathrm{CH}}$—OH, J = 7.50 Hz); 5.55 (d, 1 H, $\underline{\mathrm{CH}}$COMe, J = 7.50 Hz); the enol form (a mixture of *cis* and *trans* isomers): 1.99 and 2.01 (both s, 3 H, MeCO); 2.10 and 2.20 (both s, 3 H, MeC=); 5.55 (m, 2 H, CH and OH).

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