Reactions of α-monochloro- and α,α-dichloro-β-oxoaldehyde acetals with bases

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α,α-Dichloro-β-oxoaldehyde diethyl acetals decompose under the action of bases (NaOH, MeONa) with cleavage of the carbon—carbon bond and formation of carboxylic acids or their esters and the dichloroacetaldehyde diethyl acetal carbanion. The latter reacts *in situ* with benzaldehyde to form stable α-chloro-α,β-epoxyacetal. α-Chloro-α-formyl-γ-butyrolactone diethyl acetal is transformed into α-chloro-α-diethoxymethyl-γ-hydroxybutyric acid under the action of an alkali.

Key words: α,α-dichloro-β-oxoaldehyde acetals, base, carbanion, benzaldehyde, intramolecular nucleophilic reaction.

Reactions of α,α-dichloroaldehydes and α,α-dichloroketones with MeONa are known to occur mainly with retention of the C—C bond resulting in the formation of β-oxoacetals[1] and β-oxoketals,[2] respectively. It was supposed[1,2] that the intermediate formed initially by the addition of the alcoholate at the carbonyl group of the substrate is transformed due to the intramolecular nucleophilic reaction into α-alkoxy-β-chlorooxirane, whose subsequent reactions with nucleophiles result in the corresponding products.

We have previously shown[3] that the reactions of α,α-dichloro-β-oxoaldehydes with anionic nucleophiles (MeONa, PhONa) proceed *via* two directions with cleavage of the C—C bond in the $-C(O)-CCl_2$ and CCl_2-CHO groups.

All the above does not allow one to predict unambiguously the behavior of diethyl acetals of α-monochloro- and α,α-dichloro-β-oxoaldehydes in reactions with bases. Therefore, we studied reactions of representatives of these compounds with bases.

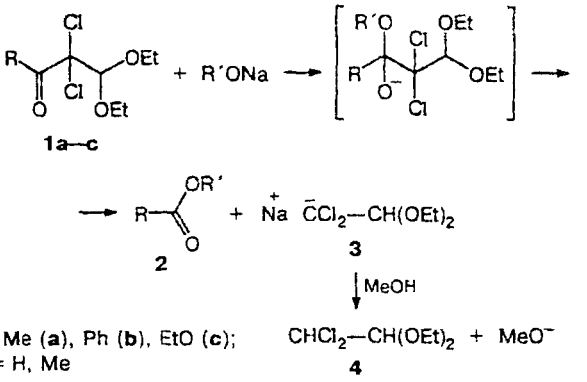
We have shown that carboxylic acids or their esters (**2**) and dichloroacetaldehyde diethyl acetal (**4**) are the products of the reactions (Scheme 1) of α,α-dichloro-β-oxoaldehyde acetals (**1a—c**) with NaOH or MeONa. Compound **4** is formed in protic solvents due to solvolysis of the sodium salt (**3**) that formed. The process evidently occurs according to Scheme 1.

The formation of products **2** and **4** is evidence that the acetal group, as well as carbonyl and nitrile groups,[4] favors the generation of a stable anion of salt **3** and thus facilitates the cleavage of the $C(O)-CCl_2$ bonds in the acetals **1**. When the reaction is carried out in MeOH, sodium methoxide can be used in catalytic amounts.

It is known that α-halogenated organic derivatives of alkali metals even at low temperatures undergo α-elimination to form carbenes.[5] The data on the synthesis and existence of α-bromolithium organic compounds are documented. For example, cyclic *endo*-7-bromo-7-lithionorcarane was shown[6] to be unstable in THF at −90°C, while its 2-oxa-analog, *endo*-7-bromo-7-lithio-2-oxanorcarane, which can form a relatively stable intramolecular coordination O—Li bond due to convergence of the O and Li atoms, does not decompose in ether at −20°C. *endo*-7-Bromo-7-litho-3-oxanorcarane is even more stable.[7] The synthesis and reactions of relatively stable 3-litho-3,3-dichloroprop-1-ene are also described.[8] In this case, the stability of the dichlorolithium organic compound is the result of coordination of the metal to the electron-rich π-system of the double bond.

Taking into account the published data mentioned above, we can suggest that intermediate **3** exists at

Scheme 1



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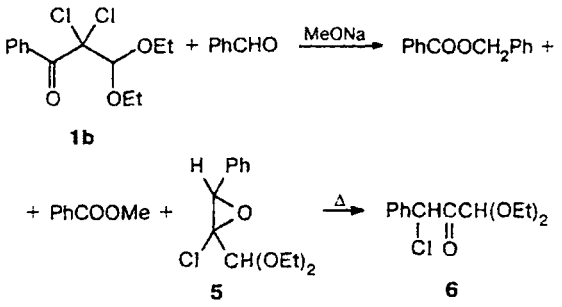
relatively high temperature (0—20 °C) and the generation of carbene is prevented due to binding of the sodium ion as the result of the chelating effect of the acetal group or formation of the stable coordination bond between the metal ion and the O atom of one of the acetal groups.

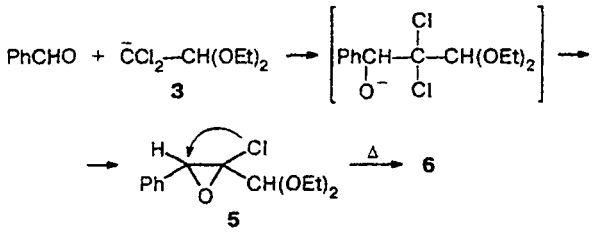
Assuming that the reaction of dichloroanion **3** with electrophilic reagents can lead to interesting transformations, we studied its reaction with benzaldehyde. The reaction of acetal **1b** with MeONa in the presence of benzaldehyde (0—20 °C, 24 h) resulted in the formation of a mixture of chlorooxirane **5** and benzyl and methyl benzoates in the 3 : 1 : 2 ratio (NMR data) in the overall yield of 80% (Scheme 2).

Scheme 2

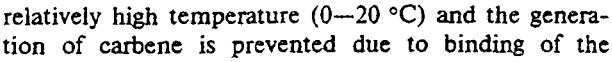


Distillation of the reaction mixture results in the transformation of chlorooxirane **5** into chloroketone (**6**) due to thermal rearrangement. The structure of compound **6** was established on the basis of physicochemical and spectral parameters, which were identical to those of the sample obtained previously.[9] The formation of this product is explained by the reaction of anion **3** that formed with benzaldehyde followed by intramolecular cyclization resulting in stable α-chloroepoxide **5**.[8] The latter isomerizes into chloroketone **6** at 160—180 °C (Scheme 3).

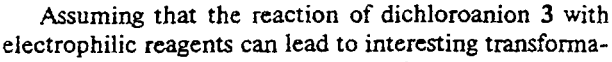
Scheme 3



The formation of benzyl benzoate is most likely due to the fact that MeONa, along with the participation in the fragmentation of acetal **1**, reacts competitively with benzaldehyde according to the Cannizzaro condensation[10] to give methyl benzoate and sodium benzoxide:



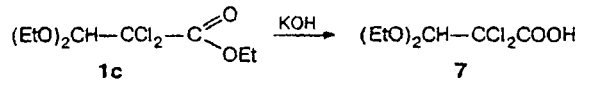
The synthesis of the by-product, benzyl benzoate, occurs *via* the fragmentation of the starting acetal **1b** under the action of the benzyloxide anion:



The possibility of the formation of the benzyloxide anion in the reaction of benzaldehyde with sodium methylooxide was proved experimentally: this reaction affords methyl benzoate and sodium benzyloxide identified as benzyl alcohol after acidification of the reaction mixture.

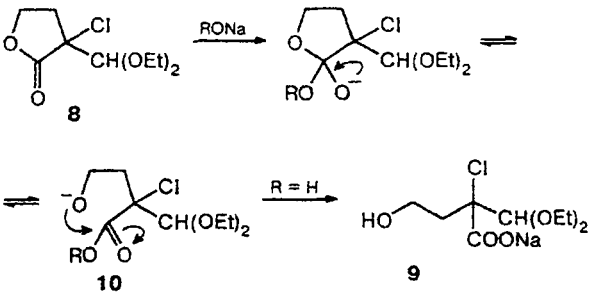
The reactions of acetal **1b** with MeONa and *p*-bromobenzaldehyde and substituted nitrobenzaldehydes results in a unidentified mixture of products.

The reaction of compound **1c** with an aqueous solution of KOH gives the product of alkaline hydrolysis of the ester group, *viz.*, acid **7**.



α-Chloro-α-formyl-γ-butyrolactone diethyl acetal (**8**) in reactions with nucleophiles (RONa) in MeOH undergoes no changes even for a long time; however, the action of an aqueous solution of NaOH results in the formation of the sodium salt of acid (**9**) in 88% yield (Scheme 4).

Scheme 4



The structure of product **9** was proved by IR and ^{1}H NMR spectroscopy.

Evidently, the fact that MeONa and NaOH behave in different manners with respect to lactone **8** is related to the nature of intermediate **10** (see Scheme 4), which is transformed again into the starting lactone by the intramolecular nucleophilic attack of the O anion at the ester C atom. In the case of NaOH, the anion **10** that formed is transformed into the stable product **9** due to intramolecular neutralization.

Table 1. Products of reactions of α,α-dichloro-β-oxo acetals (**1a—c**) with bases

Compound	Base/solvent	Reaction products	B.p./°C (*p*/Torr)	n_D^{20}* (Ref. 9)
1a	MeONa/ether	$MeCOOMe$		(1.3619)
		$CHCl_2CH(OEt)_2$	184 (760)	1.4354 (1.4360)
	$NaOH/H_2O$	MeCOOH	115—120 (760)	1.3721 (1.3715)
		$CHCl_2CH(OEt)_2$	184 (760)	1.4358
1b	MeONa/ether	PhCOOMe		1.5163 (1.5170)
		$CHCl_2CH(OEt)_2$	184 (760)	1.4363
	MeONa/MeOH	PhCOOMe		1.5166 (1.5170)
		$CHCl_2CH(OEt)_2$	184 (760)	1.4354
	$NaOH/H_2O$	PhCOOH	123.5—124 (122.5)	—
		$CHCl_2CH(OEt)_2$	184 (760)	1.4361
1c	MeONa/ether	EtOCOOMe	32—36 (14)	—
		$CHCl_2CH(OEt)_2$	184 (760)	1.4365

* This work.

Experimental

IR spectra were recorded on a UR-20 spectrometer in a solution of CCl_4 or in Nujol. ^1H and ^{13}C NMR spectra were recorded on a Tesla BW-567 instrument (100 MHz) using HDMS as the internal standard.

Compounds were separated by column chromatography on silica gel (80—120 mesh) using hexane as the eluent.

The starting diethyl acetals of α-monochloro- (**8**) and α,α-dichloro-β-oxoaldehydes (**1a—c**) were obtained by the previously described procedure.[11]

Reactions of α,α-dichloro-β-oxoaldehyde diethyl acetals (1a—c) with bases (general procedure). Acetal **1** (0.05 mol) was added to a suspension or a solution of a base (0.05 mol) in an anhydrous solvent (50 mL) at 0 °C with stirring. Then cooling was discontinued, the reaction mixture was stirred for 4 h at ~20 °C and treated with 10% HCl (50 mL), and the aqueous solution was extracted with ether (2×25 mL). The combined ethereal extracts were dried with $MgSO_4$. After removal of the solvent, the residue was fractionated to give the corresponding reaction products, whose physicochemical parameters and the ^1H NMR spectral data are presented in Table 1.

1,1-Diethoxy-3-phenyl-3-chloropropan-2-one (6). Powdered MeONa (2.16 g, 0.04 mol) was added to a solution of acetal **1c** (11.64 g, 0.04 mol) and PhCHO (4.28 g, 0.04 mol) in anhydrous ether (50 mL) at 20—−25 °C with stirring. The reaction mixture was stirred for 3 h, kept for ~8 h, and worked up as described above. After fractionation of the residue, methyl benzoate (3.6 g, 64%) and a mixture of chloroketone **6** and benzyl benzoate was obtained. The mixture was separated by column chromatography to yield compound **6** (6.15 g, 60%), b.p. 165—167 °C (12 Torr), n_D^{20} 1.6364 (*cf.* Ref. 9). Found (%): Cl, 13.84. $C_{13}H_{17}ClO_3$. Calculated (%): Cl, 14.01. ^1H NMR ($CDCl_3$), δ: 1.00 (m, 6 H, 2 Me); 3.50 (m, 4 H, 2 OCH_2); 4.75 (s, 1 H, OCHO); 6.00 (s, 1 H, CHCl); 7.35 (s, 5 H, Ph). IR, ν/cm^{-1}: 1750 (C=O). ^{13}C NMR (Me_2SO), δ: 15.1 (d.q, Me); 62.1 (d, CHCl); 65.0 (d.t, CH_2O); 102.0 (d, CHO_2); 135.0, 130.8, 127.6, 127.1 (Ph); 198 (s, C=O).

Reaction of benzaldehyde with sodium methoxide. PhCOOMe (5 g, 70%, b.p. 76—79 °C (14 Torr), n_D^{20} 1.5167) and $PhCH_2OH$ (3.2 g, 60%, b.p. 102—103 °C (14 Torr), n_D^{20} 1.5402) were obtained from MeONa (2.7 g, 0.05 mol) and freshly distilled PhCHO (10.6 g, 0.1 mol) according to the general procedure.

2,2-Dichloro-3,3-diethoxypropionic acid (7). Acetal **1c** (5.18 g, 0.02 mol) was added to a solution of KOH (1.12 g, 0.02 mol) in water (20 mL). The reaction mixture was heated to 60 °C and then stirred at ~20 °C for 5 h. Concentrated HCl (80 mL) was added to the mixture, which was extracted with ether (2×30 mL). The residue after removal of the solvent was recrystallized from hexane to yield compound **7** (4.8 g, 78%), m.p. 62—64 °C. Found (%): Cl, 30.68. $C_7H_{12}Cl_2O_4$. Calculated (%): Cl, 30.74. IR (CCl_4), ν/cm^{-1}: 3510 (OH); 1760 (C=O). ^1H NMR ($CDCl_3$), δ: 1.25 (t, 3 H, 2 Me); 3.88 (m, 4 H, 2 OCH_2); 5.00 (s, 1 H, CH); 12.48 (br.s, 1 H, OH).

Sodium 2-chloro-2-diethoxymethyl-4-hydroxybutyrate (9). Compound **9** (4.2 g, 88%, m.p. > 300 °C) was obtained from lactone **8** (4.46 g, 0.02 mol) and NaOH (0.8 g, 0.02 mol) according to the procedure described above. Found (%): Cl, 14.05. $C_9H_{17}ClO_4Na$. Calculated (%): Cl, 14.31. IR, ν/cm^{-1}: 3350 (OH); 1620, 1380 (O=CONa). ^1H NMR ($(CD_3)_2SO$), δ: 1.28 (m, 6 H, 2 Me); 2.14 (t, 2 H, CH_2); 3.84 (m, 6 H, 3 OCH_2); 5.09 (s, 1 H, CH); 5.95 (br.s, 1 H, OH).

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