BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 1844—1847 (1973)

Chemistry of α-Haloaldehydes. II.[1] Base-catalyzed Condensation of α-Haloaldehydes with Methyl Chloroacetate

Akira Takeda, Sadao Tsuboi, and Tōru Hongo
Department of Synthetics Chemistry, School of Engineering, Okayama University, Tsushima, Okayama 700

(Received December 15, 1972)

The Darzens-type condensation of α-haloaldehyde (**2**) with methyl chloroacetate has been studied. The reaction of aliphatic α-chloroaldehydes afforded 4-chloro-2,3-epoxyalkanoates (**4**). The reaction of 2-bromo-2-methylpropanal (**2d**) with methyl chloroacetate gave α-chloro-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (**7**) as a major product. α-Bromo-*n*-alkanal gave a mixture of many minor products.

Two diastereomeric isomers of 4,5-dihydroxyhexanoic acid gamma lactone (**1**) have been isolated as major constituents of the aroma extracts of flour sherries.[2] In order to carry out the attempted synthesis of **1** and their derivatives we needed 4-halo-2,3-epoxys alkanoates (**4**) as starting materials. The Darzen-condensation of aldehydes and ketones may be the most convenient and common procedure for the one-step synthesis of 2,3-epoxyalkanoates, but there have been few reports on the title reaction of α-haloaldehydes (**2**).

We have been studying the reactions of α-haloaldehydes with active hydrogen compounds and reported on the Darzens-type condensation of **2** with dichloroacetate[1] giving 2,4-dichloro-2,3-epoxyalkanoates. As an extension of the previous work[1] we carried out the reaction of **2** with monochloroacetate in the presence of sodium alkoxide to prepare 4-halo-2,3-epoxyalkanoates. Ether or THF was used as solvent to prevent **2** from being transformed into α-hydroxy acetal.[3] In this paper the results of the reaction and a discussion of the reaction mechanism are given. The yields, boiling points and the analytical data are summarized in Table 1.

The cyclization of the possible intermediate (**3**) to an epoxyalkanoate may occur in such a way that the α- and γ-halogen atoms compete with each other as a leaving group to produce either 4-halo-2,3-epoxyalkanoate (**4**) (route 1) or 2-halo-3,4-epoxyalkanoate (**5**) (route 2). In the reaction of α-chloroaldehydes only 2,3-epoxyalkanoate (**4**) was obtained[4] in a 9—40% yield indicating that the oxyanion of **3** attacked more readily its α-carbon atom which was made more electron-deficient by the electron-withdrawing effect of the carboxyl group. The reaction sequence is given

---

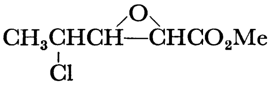
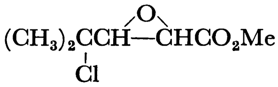
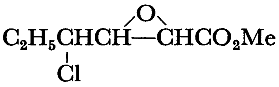
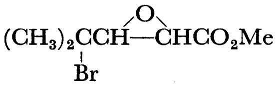
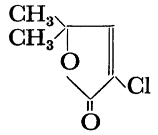
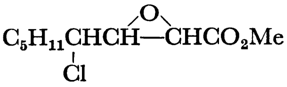
[1] The first paper of this series: A. Takeda, S. Tsuboi, S. Wada, and H. Kato, This Bulletin, **45**, 1217 (1972).

[2] C. J. Muller, L. Maggiora, R. E. Kepner, and A. D. Webb, *J. Agr. Food Chem.*, **17**, 1373 (1969).

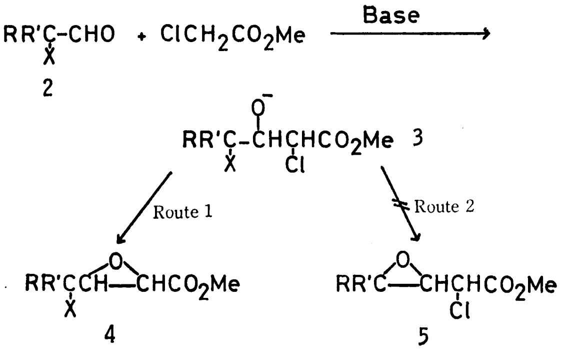
[3] C. L. Stevens, E. Farkas, and B. Gillis, *J. Amer. Chem. Soc.*, **76**, 2695 (1954).

[4] A moderate amount of resinous material was produced.

Table 1. Products from the reaction of α-haloaldehydes with methyl chloroacetate

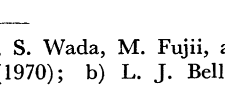
α-Haloaldehyde $RR'\underset{X}{C}\text{-CHO}$ Code	R	R′	X	Products[a)] Code	Structure	Yield, %	Bp, °C/mmHg (Mp)	Found, % C	H	Calcd, % C	H
2a	CH_3	H	Cl	**4a**	 $CH_3\underset{Cl}{CH}\overset{O}{CH—CH}CO_2Me$	15	56—60/16	43.61	5.38	43.79	5.51
2b	CH_3	CH_3	Cl	**4b**	 $(CH_3)_2\underset{Cl}{C}\overset{O}{CH—CH}CO_2Me$	40	100—103/12	46.90	6.30	47.07	6.21
2c	C_2H_5	H	Cl	**4c**	 $C_2H_5\underset{Cl}{CH}\overset{O}{CH—CH}CO_2Me$	10	90—94/5	47.44	5.91	47.07	6.21
2d	CH_3	CH_3	Br	**4d**	 $(CH_3)_2\underset{Br}{C}\overset{O}{CH—CH}CO_2Me$	9	93—125/3	37.90	5.25	37.69	4.97
					and						
				7		14	(94—95)	49.18	4.50	49.15	4.78
2e	C_5H_{11}	H	Cl	**4e**	 $C_5H_{11}\underset{Cl}{CH}\overset{O}{CH—CH}CO_2Me$	25	130—133/5	54.13	7.87	54.42	7.77

a) All the compounds are new.



Scheme 1.

in Scheme 1. The structure of **4** was confirmed by IR spectra, NMR spectra, MS, and microanalyses. The IR bands of **4** at 1750—1755, 900—910, and 820—825 cm^{-1} [1,5a,b)] are characteristic of the epoxyester. The singlets or doublets at δ 3.28—3.24 (J=0—2.3 Hz) in the NMR spectrum of **4** represent the signal from the C_2-proton. The geometry of **4** can be estimated to be *trans* from the small value of the coupling constants due to epoxy-ring protons.



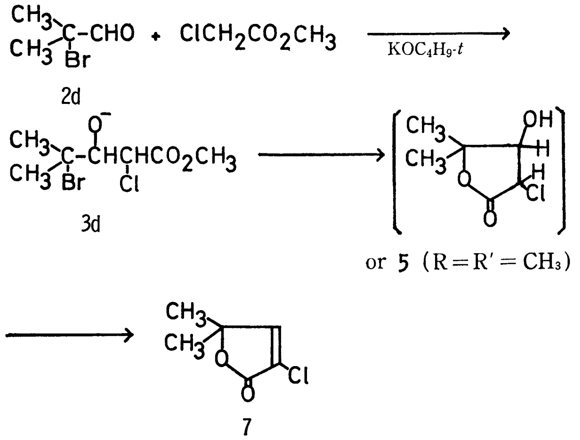
On account of a higher reactivity toward nucleophiles than their chlorine homologs α-bromoaldehydes tend to react in different ways. In contrast with α-chloroaldehydes, it is expected that in the reaction of α-bromoaldehydes the bromine atom attached to the γ-carbon of the intermediate **3** becomes a better leaving group as in the base-catalyzed condensation of α-bromoheptanal with methyl dichloroacetate.[1)] As expected, the reaction of 2-bromo-2-methylpropanal (**2d**) with methyl chloroacetate gave α-chloro-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (**7**) in a 14% yield, together with a small amount (9% yield) of methyl 4-bromo-4-methyl-2,3-epoxypentanoate (**4d**). α-Bromoheptanal (**2f**) only underwent displacement to yield α-hydroxyheptanal dimethyl acetal (**8**) and not the desired product, when methanol was used as solvent. It is not likely that acetal **8** was derived from acetal (**9**) of α-bromoaldehyde (**2f**) since α-bromoaldehyde acetal appears inactive toward nucleophiles such as sodium methoxide and sodium ethoxide as suggested by the reaction of α-bromopropanal acetal. It is reasonable to consider that the transformation of **2f** into **8** involves epoxy-ring intermediate.[3)]

The $\Delta^{\alpha,\beta}$-butenolide structure of **7** is supported by IR and NMR spectra. The IR band of **7** at 1730 cm^{-1} is characteristic of the conjugated lactone carbonyl,[6)] two singlets at δ 1.50 (methyl proton) and 7.35 (olefinic proton) in the NMR spectrum of **7** being indicative of butenolide structure. A possible pathway of the formation of **7** is shown in Scheme 2.

---

5) a) A. Takeda, S. Wada, M. Fujii, and H. Tanaka, This Bulletin, **43**, 2997 (1970); b) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen & Co. Ltd., London, U. K. (1958), p. 118.

6) A. Takeda, K. Takahashi, S. Torii, and T. Moriwake, *J. Org. Chem.*, **31**, 316 (1966).



Scheme 2.

Experimental

All the boiling points and the melting points are uncorrected. α-Haloaldehydes were prepared by the method described previously.[1] The analytical determinations by glpc were performed on a Hitachi K-53 model gas chromatograph (3 mm o.d. × 1 m, 10% Apiezon Grease L on Chromosorb W column); carrier gas, N_2 (0.5 kg/cm^2, 42 ml/min); detector, FID. The preparative glpc was performed on a Yanagimoto GCG-550T model gas chromatograph (3 mm o.d. × 2.25 m, 10% Apiezon Grease L on Chromosorb W). Mass spectra were measured with a Hitachi RMS-4 model mass spectrometer and NMR spectra on a Hitachi R-24 NMR model spectrometer. Liquid samples were purified by glpc or tlc for analyses and spectral measurements.[7] The following experiments are shown as an example.

*Methyl 4-Chloro-2,3-epoxypentanoate (**4a**).* Powdered sodium methoxide (5.9 g, 0.11 mol) was added in several portions to a mixture of α-chloropropanal (9.3 g, 0.1 mol) and methyl chloroacetate (12.2 g, 0.1 mol) in dry ether (50 ml), at −30 °C.[8] After the mixture was stirred for 2 hr, it was allowed to cool to room temperature, stirring being continued for 4 hr. The reaction mixture was allowed to stand overnight and then treated with water. The ethereal layer was separated, washed several times with water and dried over $MgSO_4$. After removal of the solvent it was distilled giving 1.6 g (10%) of **4a**: bp 87—97 °C/8 mmHg; IR (cm^{-1}, liquid) 1755 (ester C=O), 900 and 825 (epoxide ring); NMR (CCl_4) δ 1.57 (d, 3H, J=6.5 Hz, $C\underline{H}_3CHCl-$), *ca.* 3.19 (q, 1H, J=1 Hz, $-C\underline{H}\overset{O}{\text{——}}CHCO_2CH_3$), 3.30 (s, 1H, $-CH\overset{O}{\text{——}}C\underline{H}CO_2CH_3$), 3.65 (m, 1H, $>CHCl$), and 3.75 (s, 3H, CO_2CH_3).

*Methyl 4-Chloro-4-methyl-2,3-epoxypentanoate (**4b**).* Powdered sodium methoxide (5.4 g, 0.1 mol) was added gradually to a solution of freshly-distilled 2-chloro-2-methylpropanal (10.6 g, 0.1 mol) and methyl chloroacetate (12.2 g, 0.1 mol) in dry ether (60 ml), at 0—3 °C. After the mixture was stirred at room temperature for 12 hr and then refluxed for 1 hr, it was treated with water. The ethereal layer was separated, washed several times with water and dried over Na_2SO_4. After removal of the solvent it was distilled to give 7.2 g (40%) of **4b**: bp 100—103 °C/12 mmHg; IR (cm^{-1}, liquid) 1750 (ester C=O), 910 and 828 (epoxide ring); NMR (CCl_4) δ 1.53 (s, 3H, $>C<^{C\underline{H}_3}_{CH_3}$), 1.59 (s, 3H, $>C<^{CH_3}_{C\underline{H}_3}$), 3.33 (d, 1H, J=1.7 Hz, $-CH\overset{O}{\text{——}}C\underline{H}-$), 3.40 (d, 1H, J=1.7 Hz, $-C\underline{H}\overset{O}{\text{——}}CH-$), and 3.74 (s, 3H, CO_2CH_3).

*Methyl 4-Chloro-2,3-epoxyhexanoate (**4c**).* Powdered sodium methoxide (5.4 g, 0.1 mol) was added in several portions to a mixed solution of freshly-distilled α-chloro-*n*-butanal (10.6 g, 0.1 mol) and methyl chloroacetate (10.9 g, 0.1 mol) in dry ether (30 ml) at 0—3 °C. The mixture was allowed to warm up to room temperature and then refluxed for 4 hr. The ethereal extract was worked up as usual and distilled to give 3.3 g (10% yield[9]) of the liquid, which was collected at 90—94 °C/5 mmHg. Glpc analysis showed it to consist of five components. The peaks, retention times (min), and integrated percentages[10] were: 1, 4.6, 55; 2, 6.6, 31; 3, 7.7, 5; 4, 8.3, 5; 5, 9.4, 4. Component 1 was collected by preparative glpc and identified as **4c**: IR (cm^{-1}, liquid) 1750 (ester C=O), 900 and 820 (epoxide ring); NMR (CCl_4) δ 1.10 (t, 3H, J=7.5 Hz, $C\underline{H}_3CH_2-$), 1.91 (m, 2H, $CH_3C\underline{H}_2-$), 3.19 (q, 1H, J=1 Hz, $-C\underline{H}\overset{O}{\text{——}}CHCO_2CH_3$), 3.33 (d, 1H, J=1 Hz, $-CH\overset{O}{\text{——}}C\underline{H}CO_2CH_3$), 3.40 (m, 1H, $>CHCl$), and 3.77 (s, 3H, CO_2CH_3).

Reaction of 2-Bromo-2-methylpropanal with Methyl Chloroacetate. Powdered potassium *tert*-butoxide (29.6 g, 0.26 mol) was added to a solution of freshly distilled 2-bromo-2-methylpropanal (19 g, 0.13 mol) and methyl chloroacetate (28.6 g, 0.26 mol) in dry THF (50 ml) at −5—0 °C. After addition was completed, stirring was continued for 1 hr. The reaction mixture was stirred for 5 hr at room temperature. It was allowed to stand overnight, refluxed for 1 hr and then treated with water. After the mixture was acidified with 10% HCl, the organic layer was extracted with ether, and the ethereal extract was washed several times with water and dried over Na_2SO_4. After removal of the solvent the residue was distilled to give 7 g of a liquid boiling at bp 93—125 °C/6 mmHg. The solidified material (0.9 g) was separated from the liquid, and recrystallized from *n*-hexane to give lactone **7**: mp 94—95 °C; IR (cm^{-1}, Nujol) 1730 (conjugated C=O), 1605 (conjugated C=C); NMR ($CDCl_3$) δ 1.50 (s, 6H, $(CH_3)_2C\langle$), and 7.35 (s, 1H, $=\dot{C}-H$); MS (70 eV) *m/e* (relative intensity) 146 (13, M$^+$, 1Cl), 131 (100, M$^+$–CH$_3$), 111 (43, M$^+$–Cl), 103 (61), 68 (48), and 43 (73). Glpc analysis of the filtrate showed the presence of two major and six minor components. The peaks, retention times, and integrated percentages[11] were: 1, 6.0, 21%; 2, 10.6, 49%. Component 1 was collected by preparative glpc and identified as **7** by comparison of the retention times (min) and the IR spectrum with those of an authentic sample.

Component 2 was collected similarly and identified as **4d**: IR (cm^{-1}, liquid) 1750 (ester C=O), 905 and 820 (epoxide ring); NMR (CCl_4) δ 1.68 (s, 3H, $-CH_3$), 1.79 (s, 3H, $-CH_3$), 3.36 (d, 1H, J=2.3 Hz, $-CH\overset{O}{\text{——}}C\underline{H}-$), 3.42 (d, 1H, J=2.3 Hz, $-C\underline{H}\overset{O}{\text{——}}CH-$), and 3.76 (s, 3H, CO_2CH_3): MS (70 eV) *m/e* (relative intensity) 190 (1, M$^+$–CH$_3$OH), 164 (25), 162 (20), 142 (100, M$^+$–HBr), 135 (82), 133 (82), 104 (85), 88 (79), 54 (82), and 38 (80).

*Methyl 4-Chloro-2,3-epoxynonanoate (**4e**).* Into a solution

---

[7] Microanalyses were carried out by Mr. Eiichiro Amano.

[8] When the reaction was carried out at 0 °C, glycidate **4a** was obtained only in a poor yield, many unknown substances being obtained.

[9] Estimated as compound **4c**.

[10] Column temp., 150 °C.

[11] Column temp., 120 °C.

of α-chloroheptanal (14.8 g, 0.1 mol) and methyl chloroacetate (12.2 g, 0.1 mol) in dry ether (60 ml), sodium methoxide (5.4 g, 0.1 mol) was added in several portions at 0—3 °C. The mixture was worked up as in the preparation of **4b** and 5.6 g (25%) of **4e** was obtained: bp 130—133 °C/5 mmHg; IR (cm^{-1}, liquid) 1755 (ester C=O), 900 and 825 (epoxide ring); NMR (CCl_4) δ 0.93 (t, 3H, J=5 Hz, $C\underline{H}_3(CH_2)_4$-), 1.15—2.15 (m, 8H, $CH_3(C\underline{H}_2)_4$-), 3.28 (s, 1H,-$\text{-CH}\overset{\text{O}}{\text{——}}\text{C}\underline{\text{H}}\text{CO}_2\text{CH}_3$), 3.15—3.50 (m, 1H, $\text{-C}\underline{\text{H}}\overset{\text{O}}{\text{——}}\text{CH-CO}_2\text{CH}_3$), 3.50 (m, 1H, $\rangle$CHCl), and 3.75 (s, 3H, CO_2CH_3).

Reaction of α-Bromoheptanal (2f) with Methyl Chloroacetate in Methanol. To a mixed solution of α-bromoheptanal (15.7 g, 0.081 mol) and sodium methoxide (4.4 g,0.081 mol) in 60 ml of methanol was added 8.7 g (0.081 mol) of methyl chloroacetate with stirring, at −4 °C. Stirring was continued for 2 hr at room temperature and 0.5 hr at reflux temperature. The reaction mixture was diluted with 200 ml of water and then extracted with ether. The ethereal layer was washed several times with water, dried with $MgSO_4$ and the solvent was evaporated. The residual oil was distilled to give 10.9 g of a fraction boiling at 45—109 °C/17 mmHg. Glpc analysis of this fraction showed one major peak (58%)[12] and six minor (42% in total) peaks. The major constituent with the retention time of 8 min was collected by preparative glpc and identified as α-hydroxyheptanal dimethyl acetal (**9**) on the basis of the IR spectrum and analysis: IR (cm^{-1}, liquid) 3450 (OH), 1200, 1125, and 1070 (acetal C-O-C-O-C). Found: C, 61.06; H, 11.03%. Calcd for $C_9H_{20}O_3$: C, 61.32; H, 11.44%. Other minor products were not investigated further.

Treatment of α-bromopropanal diethyl acetal with sodium methoxide or sodium ethoxide in absolute alcohols only resulted in the recovery of starting materials.

---

12) Calculation based on peak area.