Dichloroacetic Acid Dianion; Preparation, Alkylation, and Darzens Reaction with Carbonyl Compounds

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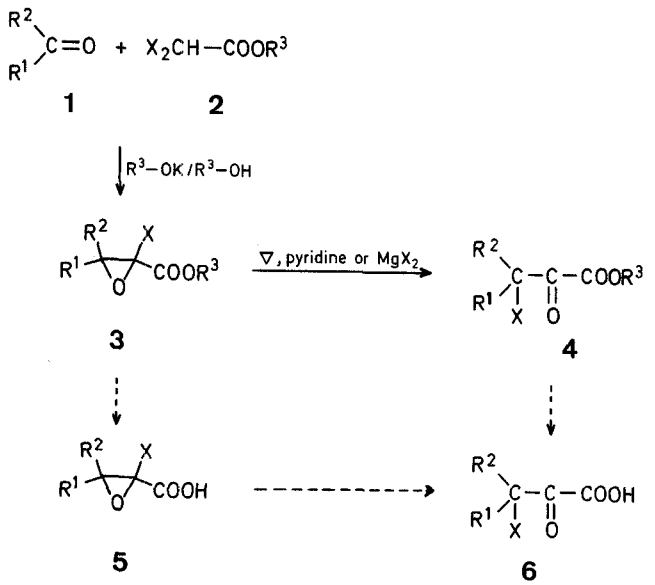
In previous communications it was shown that the α-carbanions of trivalent functions containing two α-halogen atoms react with carbonyl compounds giving α-haloglycidic acid derivatives *via* a Darzens type reaction[1-4]. These latter compounds can be easily converted into α-bromocarboxylic esters[5], α-oxocarboxylic esters, or unsymmetrical 1,2-diketones[6] halogenated or not halogenated in the α-position.

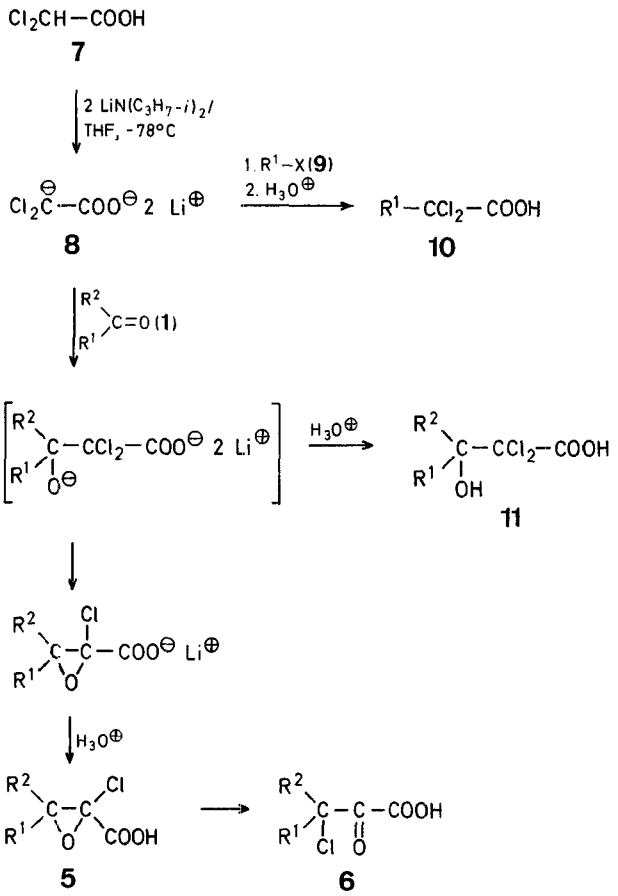
Alkyl dihaloacetates **(2)** are particularly useful reagents for the conversion of carbonyl compounds **(1)** into 3-halo-2-oxoalkanoic esters **(4)** via introduction of a C_2 unit[1].



Since the above-mentioned reactions lead to esters **(3, 4)** and hydrolysis of the esters **3** and **4** affords only poor yields of the corresponding acids **5** and **6**, respectively, we tried to find a more efficient method for the synthesis of acids of the types **5** and **6**. In order to circumvent the unsatisfactory hydrolysis step, we investigated the Darzens reaction of a dihaloacetic acid dianion, namely lithium lithiodichloroacetate **(8)**. There seems to be no report in the literature on dianions of the type **8** and their use in synthesis[7] and only recent publications deal with the analogous chloroacetic acid dianion[8,9].

Dianion **8** (more correctly: its dilithium salt) was generated in aprotic medium by treatment of dichloroacetic acid **(7)** with lithium diisopropylamide in tetrahydrofuran at −78°C. At higher temperatures, the dianion **8** partially decomposes: Thus, after one hour at −78°C, then warming the mixture to room temperature, and quenching it with water, only 50% of dichloroacetic acid was recovered, the other 50% being tarry products.

Five minutes after the generation of the dianion **8** at −78°C, the carbonyl compound **(1)** or another electrophile **(9)** is added and the mixture (Method A) allowed to warm to room temperature and quenched with water or (Method B) stirred at −78°C and quenched with water at −78°C.



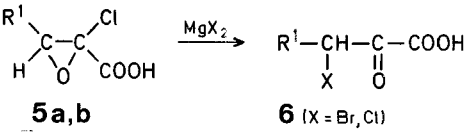
Dianion **8** *exhibits only moderate nucleophilic reactivity towards alkyl halides* **(9)** (which are known for their SN_2 reactivity) and it was not possible to obtain more than 52% of products **10** under various reaction conditions (variation of the mode of addition, prolonged reaction time at −78°C, or addition of HMPT). Dianion **8** seems to react better with alkyl bromides than with alkyl chlorides or iodides; thus, it does not react with iodomethane and only 10% of 2,2-dichloro-3-phenylpropanoic acid **(10a)** is obtained with benzyl chloride. Poor yields of products **10** are also obtained with chloromethyl methyl ether, chlorotrimethylsilane, and diphenyl disulfide.

The reactivity of dianion **8** is considerably higher towards carbonyl compounds and the yields of products **5** and **11** reach 85% (Table 1). The reaction with ketones at −78°C (Method B) leads to 2,2-dichloro-3-hydroxyalkanoic acids **(11)**, the first intermediates of the Darzens reaction, whereas the reaction with aldehydes affords the expected 2-chloro-2,3-epoxyalkanoic acids **(5)** which are often accompanied by the isomeric 3-chloro-2-oxoalkanoic acids **(6)**.

For ketones, only the results obtained with Method B are given in Table 1 because this Method leads to solid products which can be easily isolated and purified by crystallization and then analyzed. The microanalyses permit to distinguish clearly between the structures **11** and **5** (or **6**) whereas differentiation between these structures by ^{1}H-N.M.R. spectrometry is less easy. Performance of the reaction with ketones according to Method A leads to the formation of syrupy products which are difficult if not impossible to purify and to characterize.

The reaction of aldehydes with dianion **8** proceeds with varying degrees of efficiency. With 2-methylpropanal or 2,2-dimethylpropanal, Method A affords high yields of the corresponding acids **5** whereas Method B works only with 2-methylpropanal; when Method B is applied to 2,2-dimethylpropanal the starting material is recovered, probably due to steric hindrance. The reaction with the mentioned aldehydes is highly stereoselective and leads only to the (*Z*)-isomer of **5**.

2-Chloro-2,3-epoxyalkanoic acids **(5)** are very sensitive to heat; gentle warming is sufficient to effect their quantitative isomerization to 3-chloro-2-oxoalkanoic acids **(6)**. Acids **5** obviously are less stable than the corresponding esters **(3)**. Treatment of the epoxyacids **5** with Lewis acids such as magnesium halides also leads to ring cleavage of give 3-halo-2-oxoalkanoic acids **(5)**.



5a,b **6** (X = Br, Cl)

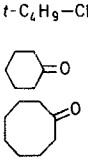
These reactions unambiguously prove the oxirane structure of compounds **5**.

Reaction of Dichloroacetic Acid Dianion (8) with Electrophiles (1, 9); General Procedure:

To a solution of lithium diisopropylamide (5.06 g, 50 mmol) in tetrahydrofuran (100 ml) under nitrogen at −78°C, a 1.6 molar solution of butyllithium in hexane (33 ml, 53 mmol) is added dropwise, with stirring. The mixture is stirred for 20 min at −78°C and then a solution of dichloroacetic acid (**7**; 3.2 g, 25 mmol) in tetrahydrofuran (10 ml) is added dropwise at −78°C. Stirring is continued for 5 min at −78°C whereupon a solution of the electrophile (**1** or **9**; 25 mmol) in tetrahydrofuran (10 ml) is added.

Method A: The mixture is allowed to warm to room temperature and is stirred for 1 h. Then, water (40 ml) is added with stirring.

Table 1. Reaction of Dianion **8** with Alkylating Agents **(9)** or Carbonyl Compounds **(1)**

Electrophile 9 or 1	Product[a] No.	R^1	R^2	Method	Yield [%]	b.p./torr or m.p. [°C] (Lit. data)	Molecular Formula[b]	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ [ppm]
$C_6H_5-CH_2-Br$	**10a**	$C_6H_5-CH_2$	–	A	51[c]	b.p. 130°/0.8	$C_9H_8Cl_2O_2$ (219.1)	3.67 (s, 2H); 7.28 (s, 5H); 11.4 (s, 1H)
$H_2C=CH-CH_2-Br$	**10b**	$H_2C=CH-CH_2$	–	A	52[c]	b.p. 70°/0.8	$C_5H_6Cl_2O_2$ (169.0)	3.18 (d, 2H); 5.04–6.29 (m, 3H); 11.0 (s, 1H)
$(H_3CO)_2SO_2$	**10c**	H_3C-	–	A	52[c]	b.p. 55°/0.8 (b.p. 90–92°/14)[10]	$C_3H_4Cl_2O_2$ (143.0)	2.31 (s, 3H); 10.5 (s, 1H)
i-C_3H_7-CHO	**5a**	*i*-C_3H_7	H	A	80[d]			1.11 (t, 6H); 1.38–2.18 (m, 1H);
t-C_4H_9-CHO	**5b**	*t*-C_4H_9	H	B	85[d]			3.04 (d, 1H); 10.5 (s, 1H)
				A	85[d]			1.15 (s, 9H); 3.11 (s, 1H)
	**11a**	$-(CH_2)_5-$		B	82[d], 68[e]	m.p. 102°	$C_8H_{12}Cl_2O_3$ (227.1)	1.0–1.5 (m, 10H); 8.4 (s, 2H)
	**11b**	$-(CH_2)_7-$		B	84[d], 70[e]	m.p. 104°	$C_{10}H_{16}Cl_2O_3$ (255.1)	1.0–1.6 (m, 14H); 8.7 (s, 2H)

[a] The I.R. spectra were in good accord with the proposed structures.
[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.28; H, ±0.17; Cl, ±0.28. Exceptions: **10c**, Cl, −0.50; **11b**, C, +0.73.
[c] Yield of distilled product.
[d] Yield of crude product.
[e] Yield of recrystallized (CCl_4) product.

Table 2. 3-Halo-2-oxoalkanoic Acids (**6**, R^2 = H) from 2-Chloro-2,3-epoxyalkanoic Acids **(5)** and Magnesium Halides

6	R^1	X	Yield [%]	b.p./torr [°C]	Molecular Formula[a] or b.p./torr [°C] reported	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ [ppm]
a	*i*-C_3H_7	Cl	90	77°/0.1	$C_6H_9ClO_3$ (164.6)	1.07 (dd, 6H); 2.04–2.75 (m, 1H); 4.80 (d, 1H); 11.3 (s, 1H)
b	*i*-C_3H_7	Br	80	95°/0.2	$C_6H_9BrO_3$ (209.05)	1.04 (d, 3H); 1.13 (d, 3H); 1.94–2.75 (m, 1H); 4.89 (d, 1H); 10.6 (s, 1H)
c	*t*-C_4H_9	Cl	90	90°/0.2	$C_7H_{11}ClO_3$ (178.6)	1.11 (s, 9H); 4.99 (s, 1H); 10.7 (s, 1H)
d	*t*-C_4H_9	Br	80	105°/0.1	$C_7H_{11}BrO_3$ (223.1)	1.19 (s, 9H); 5.10 (s, 1H); 10.4 (s, 1H)

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.59; H, ±0.47; Hal, ±0.59. Contrary to the analyses, the I.R. spectra of compounds **6a–d** were in good accord with the proposed structures. The unsatisfactory results of the analyses are due to partial decomposition of products on distillation.

Method B: The mixture is stirred for 3 h at −78°C and then water (40 ml) is added at this temperature.

For product isolation, the layers are separated, the organic layer is washed with water (40 ml) and with saturated aqueous sodium chloride (40 ml), the aqueous layers are combined, and washed with ether (2 × 50 ml). The aqueous layer is acidified to pH 2 with 2.5 molar sulfuric acid and extracted with dichloromethane (3 × 40 ml). The organic layer is dried with magnesium sulfate, the solvent removed, and the residual crude product **5**, **10**, or **11** purified (if sufficiently stable) by distillation or recrystallization from tetrachloromethane.

3-Halo-2-oxoalkanoic Acids (6, X = Br, Cl, R^2 = H) from 2-Chloro-2,3-epoxyalkanoic Acids (5) and Magnesium Halides:

A solution of magnesium bromide in ether or magnesium chloride in tetrahydrofuran is obtained by addition of dibromethane (3.8 g, 20 mmol) or dichloroethane (2 g, 20 mmol), respectively, to magnesium turnings (0.5 g, 20 mmol) in ether (30 ml) or tetrahydrofuran (50 ml). To this is added, dropwise at room temperature and with stirring, a solution of the 2-chloro-2,3-epoxyalkanoic acid (**5**, R^2 = H; 20 mmol) in ether (10 ml) or tetrahydrofuran (10 ml). Stirring is continued for 1 h at room temperature whereupon water (40 ml) is added. The aqueous layer is extracted with ether (2 × 50 ml) and the organic extract dried with magnesium sulfate. The solvent is removed to leave product **5** as a syrupy oil which may be purified by distillation in vacuo.

Received: July 4, 1983

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