α-Haloenolates of Esters; III.—A Novel High-Yield Preparation of α,α-Dichloroesters

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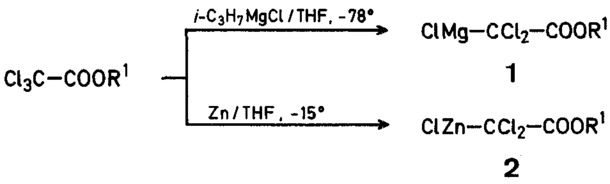
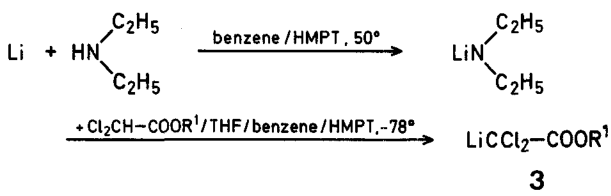
The Reformatsky reagents derived from alkyl trichloroacetates (**1**, **2**) have been prepared both through chlorine-magnesium exchange, and direct attack of zinc metal.



1 **2**

The nucleophilicity of **1** and **2** in reactions with aldehydes, ketones, and carboxylic anhydrides has been utilized[1,2,3] for synthetic purposes. However, alkylation reactions of **1** have been limited to very reactive alkyl halides (fair to good yields).

We report here a new preparation of the lithio analog **3** of **1** and **2** by metallation of alkyl dichloroacetates by means of lithium diethylamide[4] in tetrahydrofuran/hexamethylphosphoric triamide (HMPT) at −78°.



3

Although methyl dichloroacetate can be metalled to methyl α-lithiodichloroacetate in only fair yields (due to concomitant Claisen self-condensation), the analogous metallation of ethyl- and isopropyl dichloroacetate proceeds with high yields.

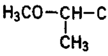
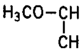
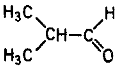
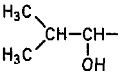
The role of HMPT is twofold: it renders metallation possible and it enhances the nucleophilicity of **3** towards alkylating agents (the analogous activation of non-chlorinated α-lithiocarboxylic esters has been reported[5]). The alkylation can be performed even with *prim*-alkyl bromides at −40° (nearly quantitative yields).

$$\underset{}{R^2-X} + \underset{\mathbf{3}}{LiCCl_2-COOR^1} \longrightarrow \underset{\mathbf{4}}{R^2-CCl_2-COOR^1}$$

The reaction with secondary alkyl bromides can be performed at 0°; however, competitive decomposition of **3** then occurs. Representative examples of the alkylation reaction are listed in the Table. A large-scale run is described in the following.

Isopropyl 2,2-Dichlorobutanoate (4, $R^1 = i$-C_3H_7, $R^2 = C_2H_5$):
In a 2000-ml four-necked flask equipped with a mechanical stirrer, a thermometer (−80° to +60°), an addition funnel, and a gas-inlet tube are placed, under a nitrogen atmosphere, freshly distilled HMPT (300 g), dry benzene (300 g), and diethylamine (140 g, freshly distilled from sodium hydride). Lithium wire (Merck; 11.6 g, 1.65 g-atom) is introduced in 2-cm pieces. With the beginning of stirring, a blood-red colour appears. The temperature rises rapidly and should be maintained at 50°. Five hours later, all lithium is consumed and the lithium diethylamide is ready for use. The reaction mixture is then cooled to 20° and tetrahydrofuran (distilled from naphthalene-sodium; 1000 ml) is added. The red solution is cooled to −80° (liquid-nitrogen bath) and pure isopropyl dichloroacetate (257 g, 1.5 mol) is added dropwise with stirring over a 1 h period. Stirring is continued for another 30 min; ethyl bromide (200 g, ~20% excess) is then added rapidly (10 min) at −80° and the reaction mixture subsequently allowed to warm slowly to −20° (2°/min). Stirring is continued for 30 min at this temperature and the mixture poured onto crushed ice (1 kg) and pure sulfuric acid (200 g) with vigorous shaking. The organic phase is separated by decantation and the aqueous phase extracted with pentane (2 × 300 ml). The organic phases are combined, washed twice with

Table. Alkyl 2,2-Dichloroalkanoates (**4**) from Alkyl Dichloroacetates via Lithiation and Alkylation

R^1	R^2-X	R^2 in **4**	Yield[a] %	b.p./torr	n_D^{20}	Brutto formula	Elemental Analyses			
$i\text{-}C_3H_7$	H_3C-Br	H_3C-	85	54°/13	1.429	$C_6H_{10}Cl_2O_2$	calc.	C 38.94	H 5.44	Cl 38.3
						(185.1)	found	38.9	5.5	38.4
$i\text{-}C_3H_7$	C_2H_5-Br	C_2H_5-	90	68°/12	1.436	$C_7H_{12}Cl_2O_2$	calc.	C 42.23	H 6.07	Cl 35.61
						(199.1)	found	42.1	6.2	35.5
CH_3	$n\text{-}C_4H_9-Br$	$n\text{-}C_4H_9-$	44	91°/18	1.447	$C_7H_{12}Cl_2O_2$	calc.	C 42.23	H 6.07	Cl 35.61
						(199.1)	found	42.2	6.1	35.7
C_2H_5	$n\text{-}C_4H_9-Br$	$n\text{-}C_4H_9-$	75	94°/12	1.446	[b]				
$i\text{-}C_3H_7$	$n\text{-}C_4H_9-Br$	$n\text{-}C_4H_9-$	92	58°/1.15	1.442	$C_9H_{16}Cl_2O_2$	calc.	C 47.59	H 7.1	Cl 31.21
						(227.1)	found	47.4	7.1	31.4
$i\text{-}C_3H_7$	$n\text{-}C_6H_{13}-Br$	$n\text{-}C_6H_{13}-$	88	63°/0.1	1.445	$C_{11}H_{20}Cl_2O_2$	calc.	C 51.77	H 8.46	Cl 27.78
						(255.2)	found	51.6	8.6	27.9
$i\text{-}C_3H_7$	$i\text{-}C_3H_7-Br$[c]	$i\text{-}C_3H_7-$	51	86°/13	1.442	$C_8H_{14}Cl_2O_2$	calc.	C 45.09	H 6.62	Cl 33.27
						(213.1)	found	45.1	6.5	33.3
$i\text{-}C_3H_7$	$H_2C=CH-CH_2-Br$	$H_2C=CH-CH_2-$	95	82°/14	1.450	$C_8H_{12}Cl_2O_2$	calc.	C 45.5	5.73	Cl 33.59
						(211.1)	found	45.4	5.8	33.7
$i\text{-}C_3H_7$	$HC\equiv C-CH_2-Br$	$HC\equiv C-CH_2-$	83	87°/14	1.456	$C_8H_{10}Cl_2O_2$	calc.	C 45.95	H 4.82	Cl 33.91
						(209.1)	found	45.8	4.7	34.0
$i\text{-}C_3H_7$	H_3CO-CH_2-Cl	H_3CO-CH_2-	86	92°/15	1.441	$C_7H_{12}Cl_2O_3$	calc.	C 39.09	H 5.62	Cl 32.96
						(215.1)	found	39.2	5.7	33.01
$i\text{-}C_3H_7$	 $H_3CO-CH(CH_3)-Cl$	 $H_3CO-CH(CH_3)-$	89	102°/12	1.445	$C_8H_{14}Cl_2O_3$	calc.	C 41.94	H 6.16	Cl 30.95
						(229.1)	found	41.7	6.2	30.8
$i\text{-}C_3H_7$	 [d]		71	68°/0.15	1.459	[e]				

[a] Yields refer to isolated product and are based on alkyl dichloroacetate.
[b] Ref.[1], b.p. 93–95°/14 torr.
[c] After the addition of isopropyl bromide, the reaction mixture is allowed to warm slowly to 0° (2°/min).
[d] The hydroxyalkylation is complete after 10 min at −80°.
[e] Ref.[3], b.p. 74°/0.2 torr; $n_D^{21} = 1.4583$.

saturated sodium chloride solution, and dried with magnesium sulfate. The solvents are evaporated and the residue distilled under reduced pressure; yield: 270 g (90%); b.p. 68°/12 torr; n_D^{20}: 1.436.

The purity of the products was examined by I.R.- and N.M.R. spectrometry and by G.L.C.

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