An Easy Synthesis of α-Chloro-α'-bromo or α,α'-Dichloro Ketones

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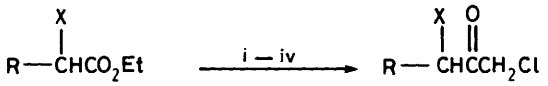
The reaction of α-chloro or α-bromo carboxylic acid esters (**1**) with *in situ*-generated chloromethyl-lithium (1:1.5 molar ratio) at −78 °C in the presence of lithium bromide leads, after hydrolysis, to the corresponding α,α'-dichloro or α-chloro-α'-bromo ketones (**2**), respectively.

The α,α'-dihalo ketones are interesting precursors in organic chemistry because they are highly functionalized compounds, and have, for instance, been used in the Favorskii rearrangement.[1,2] However, to our knowledge, there is not a general method for the preparation of these compounds.[2] Recently we described the use of chloromethyl-lithium, generated *in situ*, for the preparation of olefins,[3a] cyclopropanols,[3b] bifunctionalized organic compounds,[3c] allyl alcohols,[3d] and epichlorohydrins.[3e] We now report a simple and facile methodology for the synthesis of α,α'-dihalo ketones using chloromethyl-lithium and ethyl α-halo carboxylates.



(1) (2)

Scheme 1. *Reagents and conditions:* i, LiBr–$ClCH_2I$ (1;1.5), −78 °C; ii, 1.6 equiv. MeLi, −78 °C; iii, HCl–Et_2O; iv, HCl–water.

Treatment of several α-chloro or α-bromo carboxylic acid esters (**1**) with chloroiodomethane (1 : 1.5 molar ratio) at −78 °C in the presence of lithium bromide and then with methyl-lithium (1 : 1.6 molar ratio) at −78 °C led, after hydrolysis, to the corresponding α-chloro-α'-bromo or α,α'-dichloro ketones (**2**), respectively (Scheme 1, Table).†

The reaction proceeds *via* the intermediate (**3**) which is formed by addition of chloromethyl-lithium to the α-halogenated ester (**1**). This intermediate is stable under the reaction conditions due to the presence of the electronegative halogen substituents and it does not undergo elimination of the ethoxide group.[4] Thus, the addition of two molecules of chloromethyl-lithium to the ester (**1**) is not possible. However, reaction of chloromethyl-lithium with 3-bromo-1-chloropentan-2-one gave the corresponding alcohol (**4**), which supports the proposed mechanism.

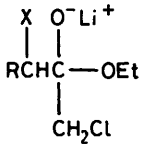
In conclusion, we believe that the methodology described in this communication represents a simple, rapid, and versatile procedure for the synthesis of unsymmetrical α,α'-dichloro and α-chloro-α'-bromo ketones (**2**), in which the halogen atoms are attached to primary and secondary carbon atoms, respectively.

† Typical procedure: to a stirred solution of chloroiodomethane (6 mmol), the α-halo carboxylic acid ethyl ester (**1**) (4 mmol), and lithium bromide (4 mmol) in tetrahydrofuran (THF) (10 ml) was added methyl-lithium (1.5 M, 6.4 mmol) in diethyl ether, over 5 min at −78 °C under nitrogen. Stirring was continued for 10 min at this temperature, then the mixture was hydrolysed successively with a diethyl ether solution of HCl (5 M, 2 ml) and aqueous HCl, and extracted with diethyl ether. The ethereal layer was dried (Na_2SO_4), the solvents were removed (15 mmHg), and the resulting residue distilled to afford the ketone (**2**).

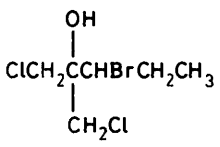
Table. Preparation of α-chloro-α'-bromo or α,α'-dichloro ketones (**2**)[a]

R	X	Yield[b]/%	Selected ^{13}C NMR data of (**2**)[c] δ_{CH_2Cl}	δ_{CHX}
Me	Br	64	45.1	46.8
Et	Br	95	45.5	51.1
C_5H_{11}	Br	75	45.2	49.4
H	Cl	60	47.0	47.0
Cl	Cl	50	42.9	67.6
Me	Cl	80	45.6	55.5
C_6H_{13}	Cl	80	45.8	60.7

[a] All products (**2**) were fully characterized by spectroscopic methods (IR, ^1H and ^{13}C NMR, and mass spectra); purity (>95%) was checked by g.l.c. [b] Isolated yield based on the starting ester. [c] In $CDCl_3$; recorded in a Brucker AC-300 spectrometer.



(3)



(4)

These compounds are difficult to prepare selectively by other methods.[5]

References

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Paper 9/03970H
Received 28*th July* 1989
Accepted 28*th September* 1989