

Easy and General Synthesis of Unsymmetrical α -Halogeno Ketones

José Barluenga,^{a,*} Luján Llavona,^a Miguel Yus^b and José M. Concellón^a

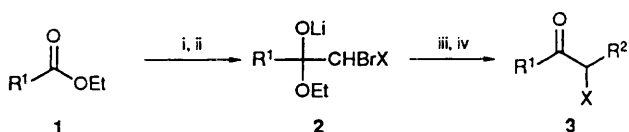
^a Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain

^b Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, 03690 Alicante, Spain

The reaction of carboxylic acid esters **1** with *in situ* generated bromohalomethyl lithium (1:2 molar ratio) at -78°C followed by reaction with lithium dialkylcuprate (1:1 molar ratio) at 0°C , leads, after hydrolysis, to the corresponding α -chloro or α -bromo ketones **3**.

α -Halogeno ketones derivatives are an important class of organic compounds, the chemistry of which occupies a key position in modern organic chemistry, and the literature indeed proves the wide synthetic potential of this class of compounds.¹ However, to our knowledge, the syntheses of unsymmetrical α -halogeno ketones reported are not simple,² or the starting materials are not commercially available,³ or they can only be used for the preparation of halogenomethyl ketones.⁴ Recently we described the synthesis of α,α -dihalogenomethyl ketones,⁵ and α,α,α' -trihalogenomethyl ketones⁶ from *in situ* generated dihalogenomethyl lithium⁷ and carboxylic or α -halogenocarboxylic acid esters respectively. We now report a simple, general and easy one-pot methodology for preparation of unsymmetrical α -halogeno ketones using dihalogenomethyl lithium, carboxylic acid esters and lithium dialkylcuprates.

The reaction of several carboxylic acid esters **1** with bromochloromethyl lithium or dibromomethyl lithium (1:2 molar ratio) at -78°C and further treatment with lithium dialkylcuprate (1:1 molar ratio) at 0°C led, after hydrolysis, to the corresponding α -chloro or α -bromo ketones **3**, respectively (Scheme 1 and Table 1).[†]



Scheme 1 Reagents and conditions: i, 2 mol equiv. BrClCH_2 , Br_2CH_2 ; ii, 2 mol equiv. LDA, -78°C ; iii, R_2CuLi , 0°C ; iv, aq. HCl, 0°C

Bromochloromethyl lithium and dibromomethyl lithium were generated *in situ* by treatment of bromochloromethane or dibromomethane with lithium diisopropylamide. The proposed mechanism proceeds *via* **2** as intermediate, which is stable under the reaction conditions due to the presence of the electronegative halogen substituents.⁵ The alkylation of **2** with

[†] Typical procedure: To a stirred solution of bromochloromethane or dibromomethane (10 mmol) and the starting carboxylic acid ethyl ester **1** (5 mmol) in tetrahydrofuran (THF) (10 cm^3) was added a solution of lithiumdiisopropylamide in THF (20 cm^3) and diethyl ether (10 cm^3) during 10 min at -78°C . The mixture was stirred for 10 min at the same temperature and then was added a solution of lithium dialkylcuprate (5 mmol) [(prepared from CuI (5 mmol) and the corresponding organolithium compound (10 mmol)] in diethyl ether (10 cm^3) at 0°C . After 30 min the mixture was hydrolysed with aq. HCl (6 mol dm^{-3} ; 10 cm^3), the solid was filtered off, the filtrate was extracted with Et_2O , and the ethereal layer was dried (Na_2SO_4). The solvents were removed (15 mmHg) and the resulting residue was distilled to afford the corresponding halogenated ketone **3**.

Table 1 Preparation of α -chloro or α -bromo ketones **3**^a

R ¹	X	R ²	Yield ^b (%)	Selected ¹³ C NMR data of 3 ^c	
				δ_{CHX}	δ_{CO}
Pr	Cl	Me	83	58.0	204.7
Pr	Cl	Bu	87	63.5	205.0
Pr ⁱ	Cl	Bu	84	61.4	208.3
Bu ⁱ	Cl	Bu	78	63.7	204.9
Ph	Cl	Bu	50	57.5	193.4
PhCH=CH	Cl	Me	37	57.7	208.4
PhCH=CH	Cl	Bu	85	62.9	193.6
Pr	Br	Me	68	47.2	203.7
Pr	Br	Bu	78	53.5	203.9
Pr ⁱ	Br	Me	50	45.8	207.9

^a All products **3** were fully characterized by spectroscopic method (IR, ¹H and ¹³C NMR, and mass spectra); purity (>95%) was checked by GLC. ^b Isolated yield based on the starting ester. ^c In CDCl_3 ; recorded in a Bruker AC-300 spectrometer.

lithium dialkylcuprate affords, after hydrolysis, the α -halogenated ketone **3**.

In summary, we believe that the methodology described in this communication represents a simple, rapid and versatile one-pot procedure for the synthesis of unsymmetrical α -bromo or α -chloro ketones **3** starting from commercially available materials.

References

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Paper 1/04089H

Received 6th August 1991

Accepted 9th September 1991