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The First Diastereoselective Addition of an Organolithium Compound to α-Halocarboxylic Acid Esters

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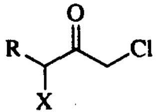
Abstract: Dihalogenated monosilyl ketals 5 have been prepared with high or total diastereoselectivity by reaction of α-halocarboxylic acid esters 3 with chloromethyllithium, generated *in situ*, and further treatment with trimethylchlorosilane.

Ketals have been used mostly for the protection of carbonyl groups of ketones[1]. During the last years, ketals have widely been used in the syntheses of valuable organic compounds[2], since they can undergo carbon-carbon bond-forming reactions by nucleophilic addition in the presence of Lewis acids[3]. On the other hand, we reported the synthesis of α-chloro-α'-haloketones 1 from α-halocarboxylic acid esters 3, chloromethyllithium and further hydrolysis[4].

In this case, we proposed that the reaction proceeded *via* the intermediate 4, which is stable under the reaction conditions, and it does not undergo elimination of the ethoxide group. So, the addition of two molecules of chloromethyllithium to the ester 3 is not possible. We have recently trapped a similar intermediate 2 as the ketal derivative by reaction with trimethylchlorosilane[5].



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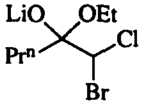

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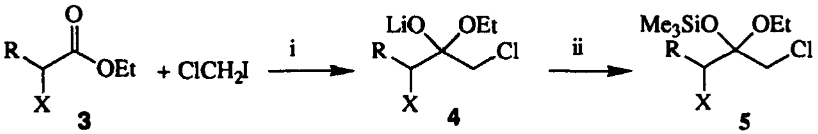
These results stimulated us to study the preparation and the synthetic applications of monosilyl ketals derived from ketones, which are in turn obtained from α-functionalized carboxylic acid esters and chloromethyllithium. It is clear that developing new diastereoselective methods in organic synthesis from 1-chloro-3-functionalized ketals, which are more stable than the easily enolizable 1-chloro-3-functionalized ketones, would be useful.

On the other hand, the first preparation of monosilyl acetals by DIBALH reduction of carboxylic acid esters was quite recently reported[6]. This report prompted us to release in the present paper the preliminary results obtained in the diastereoselective transformation of ethyl α-halocarboxylic acid esters 3 into monosilyl ketals 5 using chloromethyllithium.

The reaction of different ethyl α-chloro or α-bromo carboxylic acid esters 3 with chloromethyllithium, generated *in situ*[7] by treatment of chloroiodomethane with methyllithium at -78°C, gave the corresponding



Scheme. *Reagents and conditions*: i, MeLi, -78°C; ii, Me_3SiCl, -78°C and then 25°C.

Table. Preparation of Monosilyl Ketals **5** from α-Halocarboxylic Acid Esters **3**.

	α-Halocarboxylic Acid Ester				
Entry	R	X	Product[a]	% Yield[b]	Diastereomeric excess[c]
1	Me	Br	**5a**	83[d]	82
2	Me	Br	**5a**	71	67
3	Me	Cl	**5b**	80[d]	87
4	Me	Cl	**5b**	70	67
5	Et	Br	**5c**	78	>99
6	$n\text{-}C_5H_{11}$	Br	**5d**	80	>99
7	$n\text{-}C_6H_{13}$	Cl	**5e**	78	>99

[a] All products were fully characterized by spectroscopic methods (IR, ^1H and ^{13}C NMR, and mass spectrometry). [b] Isolated yield based on the starting α-halocarboxylic acid ester **3**. [c] The diastereomeric excess was determined from the ^1H and ^{13}C NMR data. [d] Reaction temperature -110°C.

intermediate **4**, which reacted with trimethylchlorosilane at -78°C leading to the expected dihalogenated monosilyl ketals **5** (Scheme and Table).

The reaction took place with total diastereoselectivity when R is bulkier than Me (Table, entries 5-7); thus NMR analysis (300 MHz) of the reaction crude showed the presence of only one diastereoisomer, whose stereochemistry was not assigned.

Typical Procedure: To a stirred solution of α-halocarboxylic acid ester (5 mmol), $ClCH_2I$ (8 mmol; 0.58 mL) and LiBr (6 mmol; 0.52 g) in THF (10 mL) at -78°C was dropwise added, under N_2, methyllithium (9 mmol; 6.0 mL of 1.5 M solution in diethyl ether). After 0.5h at -78°C, trimethylchlorosilane (15 mmol; 1.9 mL) was added, and the solution was allowed to reach room temperature. After careful hydrolysis (H_2O, 1mL) of the reaction mixture and extraction with ether (20 mL) the corresponding ketals **5** were isolated in good yields. Ketals **5** were > 95% pure.

In the case of ethyl α-chloro or α-bromopropionate, the synthesis of **5a** and **5b** was highly diastereoselective (Table, entries 1-4) and the temperature appears to be important for achieving high diastereoselectivity in the reaction. We also found that the diastereoselectivity was apparently the same when ethyl α-chloro or α-bromo carboxylic acid esters were used. The reaction was very clean without byproducts formation and the procedure was very simple. Alternatively, the isolation of the ketals **5** can be carried out without hydrolysis and, then the ketals **5** can be stored without decomposition for more than 2 months.

In conclusion, to the best of our knowledge, the results reported here represent the first examples of highly diastereoselective addition of one equivalent of an organolithium compound to α-functionalized carboxylic acid esters [8]. Moreover, the experimental procedure is simple, the starting materials are easily available and the dihalomonosilyl ketals prepared are not accesible by other synthetic methods.

Further studies concerning the reaction of other functionalized monosilyl ketals towards different reagents are currently under investigation.

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8. The ratios of diastereomers obtained in the trapping of the intermediates generated by the DIBALH reduction of carboxylic acid esters[6] were modest.

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