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REARRANGEMENT OF α-ACYLOXYACETATES INTO 2-HYDROXY-3-KETOESTERS

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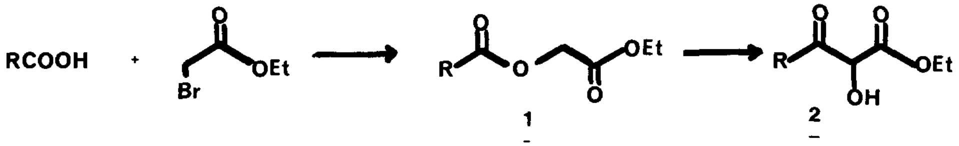
Abstract: α-Acyloxyacetates rearrange under LDA conditions to give 2-hydroxy-3-ketoesters. The corresponding trimethylsilyl- or acetyl derivatives can be obtained by quenching the reaction mixture with Me_3SiCl or Ac_2O.

The Darzens reaction[1,2] is the condensation of an halo ester with an aldehyde (or ketone) in the presence of base to give glycidic ester. We wish to report the condensation of an halo ester with a carboxylic acid, followed by rearrangement of the resultant α-acyloxyacetate under basic conditions to give a 2-hydroxy-3-ketoester or its derivatives, as illustrated in scheme 1. The overall scheme provides a method for the formation of C-C bond from carboxylic acid, as well as a general method for the synthesis of 2-functionalized β-ketoesters.

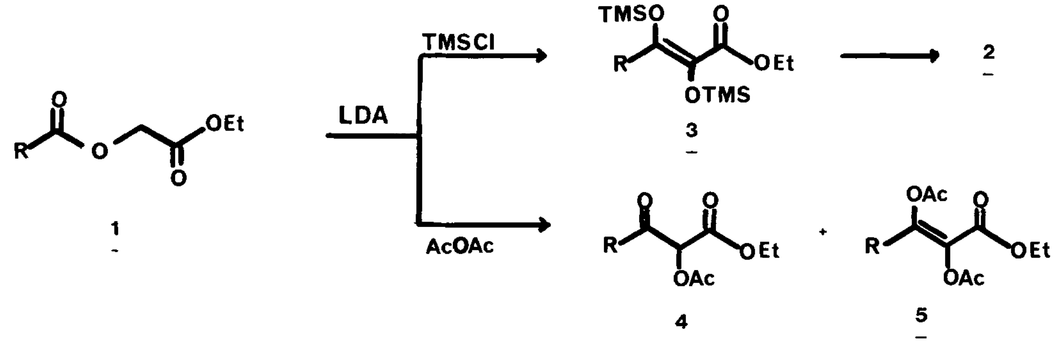


a: R=C_2H_5, b: R=C_5H_{11}-, e: R=Ph- Scheme 1
c: R=c-C_6H_{11}- d: R=$C_3H_7\underset{CH_3}{CH}$-

The first step in Scheme 1 is readily achieved by the treatment of carboxylic acid with ethyl bromoacetate and anhydrous potassium carbonate in refluxing acetone[3]. A number of ethyl α-acyloxyacetates (1) have been prepared[4] (Table 1) in good yields.

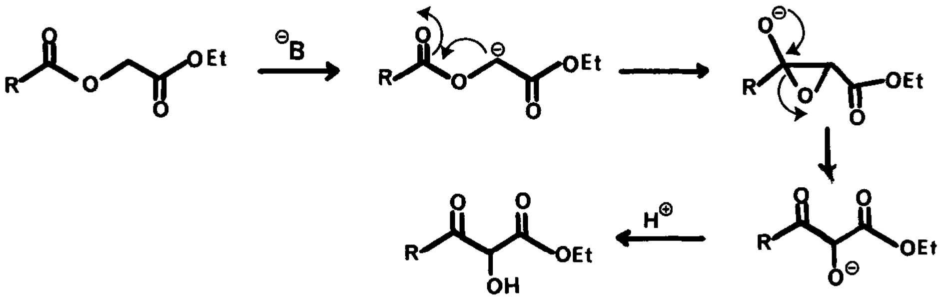
When compound 1 was treated with 2 equivalents of lithium diisopropylamide (LDA) in THF at 0° for 30 mins. and the mixture was quenched with 0.1N HCl,[5] the product was found to be ethyl 2-hydroxy-3-ketoesters (2) in 52-65% isolated yield after flash chromatography.[6] The structure of 2 was evident from the spectroscopic data. The presence of OH was deduced from the exchangeable H in ^{1}H nmr and the broad bands between ~3620, and ~3250 cm^{-1} in the ir. Absorption bands at 1725 as well as ~1750 cm^{-1} indicate the presence of both keto and ester carbonyl groups.

If the reaction mixture, after treatment with LDA at 0°, was quenched with trimethylchlorosilane, the 2,3-bis-(trimethylsiloxy)-α,β-unsaturated ester 3 was obtained. The structure of 3 has been confirmed by desilylation to 2 upon treatment with dilute HCl solution in THF.[7]



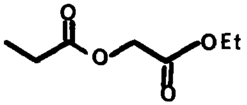
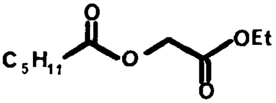
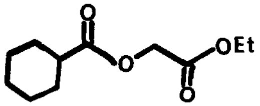
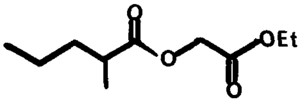
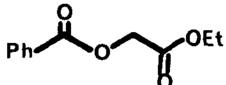
When the mixture was quenched with acetic anhydride, the correspond 2-acetoxy-ketoester (4) or the 2,3-diacetoxy-α,β-unsaturated ester (5) were obtained, depending on the amount of acetic anhydride used.[8]

From the above investigation, one might postulate the mechanism of the rearrangement process to be as follows:



The overall result of scheme 1 is equivalent to the acylation of the carbanion of α-hydroxyester[9] by a carboxylic acid, a transformation otherwise difficult to achieve.

Table 1: Rearrangement of α-acyloxyacetate to 2-substituted-3-ketoesters

α-Acyloxyacetate	Reaction Conditions Used	Product Structure	% yield isolated
 **1a**	LDA/0°/H+	**2a**	57%
	LDA/0°/TMSCl	**3a**	87%
	LDA/0°/1Ac$_2$O	**4a**	35%
 **1b**	LDA/0°/H+	**2b**	52%
	LDA/0°/TMSCl	**3b**	65%
	LDA/0°/Ac$_2$O	**4b**	45%
 **1c**	LDA/0°/H+	**2c**	65%
	LDA/0°/TMSCl	**3c**	50%
	LDA/0°/Ac$_2$O	**4c**	67%
	LDA/0°/2Ac$_2$O	**5c**	59%
 **1d**	LDA/0°/H+	**2d**	65%
	LDA/0°/TMSCl	**3d**	62%
	LDA/0°/1Ac$_2$O	**4d**	65%
	LDA/0°/2Ac$_2$O	**5d**	62%
 **1e**	LHMDS/0°/2Ac$_2$O	**5e**	63%

References and Footnotes

1. G. Darzens, Compt. Rend., 139, 1214 (1904).
2. M.S. Newman and B.J. Magerlein, "Organic Reactions", Vol. 5, John Wiley and Sons, New York, N.Y. (1949), p. 413.
3. R.E. Ireland, D.A. Evans, D. Glover, G.M. Rubottom and H. Young, J. Org. Chem., 34, 3717 (1969); S.C. Welch and R.Y. Wong, Tetrahedron Letters, 1853 (1972).
4. A typical experimental procedure is as follows: To a solution of acid (0.15 mol) in 120 mL of acetone was added anhydrous K_2CO_3 (0.23 mol), followed by ethyl α-bromoacetate (0.1 mol) under N_2 atmosphere. After refluxed overnight, the mixture was cooled to r.t. and evaporated in vacuo. The residue was partitioned between ether and 10% aq. K_2CO_3 solution. The organic layer was washed with water until neutral pH and finally with brine solution, dried, filtered and concentrated to give ester product.
5. A typical experimental procedure is as follows: Under N_2 at 0°C, to a solution of diisopropylamine (48 mmol) in dry THF (100 mL) was added n-BuLi (30 mL of 1.6M in hexane) and followed by 1 (20 mmol) in THF (20 mL). After 30 mins., the reaction mixture was cooled to -78°C and quenched with 0.1 N HCl. The mixture was allowed to warm to r.t. and concentrated. It was diluted with ether. The ether solution was dried, filtered and concentrated. The product was purified by flash column chromatography.
6. W.C. Still, M. Khan and A. Mitra, J. Org. Chem., 43, 2923 (1978).
7. Desilylation reaction condition is as follows: To a solution of 3 (0.5 mmol) in THF (2 mL) was added 2 drops of dilute hydrochloric acid. Stirring was continued overnight at r.t. The reaction mixture was concentrated and then extracted with ether. The ether extract was dried, filtered and concentrated. The product was purified by flash column chromatography.
8. The same reaction conditions as footnote 5 except that the reaction mixture was treated with 1 equiv. each of acetic anhydride and LDA for 2-acetoxy-3-ketoester and with 2 equiv. each of acetic anhydride and LDA for 2,3-diacetoxy-α,β-unsaturated ester.
9. For other equivalents of carbanion of α-hydroxyester, see T.R. Kelly and A. Arvanitis, Tetrahedron Letters 25, 39 (1984), and J. d'Angelo, O. Pages, J. Maddaluno, F. Dumas and G. Revial, ibid, 24, 5869 (1983).

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