Tetrahedron Letters No. 39, pp 3753 - 3756.
0040-4039/78/0922-3753$02.00/0

DEACYLATIVE CONDENSATION I. A NEW FACILE METHOD FOR THE DIRECT α-METHYLENATION OF ESTER OR LACTONE STARTING FROM MONOSUBSTITUTED ACTIVE METHYLENE COMPOUNDS

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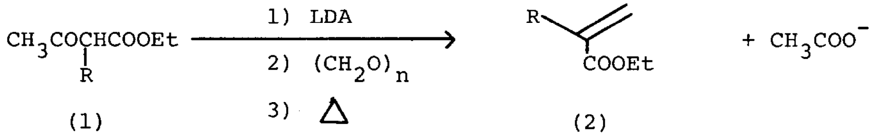
The α-methylenation of esters, especially of lactones has been currently studied as a key synthetic reaction, since the various kinds of α-methylene lactone structures have been found in many naturally occurring products.[1a)]

In general, α-methylene esters or lactones have been prepared by multistep procedures, for example, by the formation of the Mannich base followed by the quarternarization and elimination of amines, or the introduction of sulfenyl (selenyl) groups followed by the sulfoxide (selenoxide) elimination.[1b)]

Meanwhile, despite the comprehensive works on the condensation of various active methylene compounds with carbonyl compounds,[2)] very few works[3)] have been reported on the condensation of monosubstituted active methylene compounds, in which one cannot expect the normal dehydrative condensation.

We wish to report herein a new type of deacylative condensation of monosubstituted active methylene compounds with carbonyl compounds. Thus, we found the reaction mixture of the carbanion of α-monoalkylated β-ketoesters (1) and paraformaldehyde was easily thermolized under mild conditions (THF refluxing) to afford the α-methylenated esters (2) with liberation of acetate anion as formulated in the equation [1].



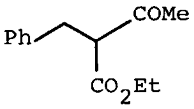
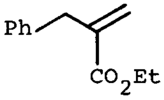
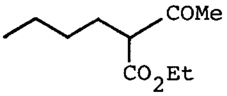
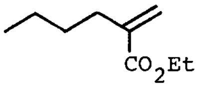
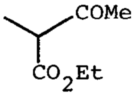
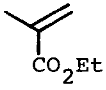
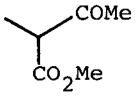
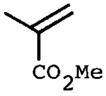
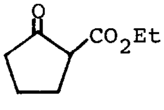
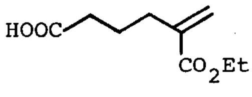
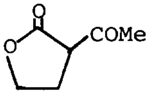
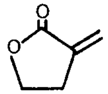
(1) (2) ----[1]

This type of deacylative condensation seems to occur quite generally in both acyclic and cyclic esters (lactone) as summarized in TABLE I.

In every case studied here, no isomerization of double bond has been observed. In the case of α-acethyl-γ-butyrolactone, α-methylenated γ-butyrolactone was obtained in 74% yield without endo-olefin isomer, which has been obtained as an undesirable by-product in the sulfoxide elimination procedure.

The present reaction provides a facial method for the α-methylenation of esters or lactones, and seems to be superior to the known methods in the following aspects: (1) the simplicity, (2) one pot reaction, and (3) the process without special reagents.

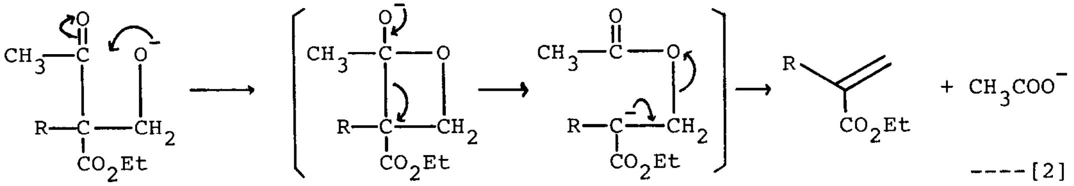
TABLE I. α-Methylenated Esters

β-Ketoester	Product[4]	Yield (%)	Olefinic protons H' NMR (δppm)
		96	5.35, 6.16
		94	5.45, 6.06
		45[*a]	5.45, 6.00
		59[*a]	5.50, 6.12
		53	5.27, 5.87
		74	5.63, 6.06

a) Low yield due to the partial polymerization.

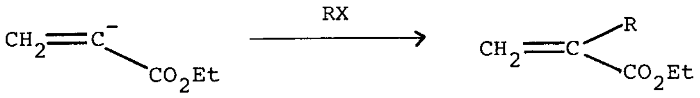
The general procedure is as follows: The reaction was carried out under nitrogen atmosphere. Lithiumdiisopropylamide (LDA) (5.5 mmol) was prepared in THF (15 ml) at -78°c by the known method. To this solution was added β-ketoesters (5 mmol) in THF (1 ml) and stirred for 10 min. To the resulting solution was added excess paraformaldehyde (700 mg) at room temperature. After stirring for 1 hr the mixture refluxed for 4 hr. Excess paraformaldehyde was removed by filtration and the filtrate was concentrated. The residue was treated with saturated aqueous potassium bicarbonate for 30 min. and extracted with methylene chloride. After usual work-up the oily product (2) was obtained, which was purified by chromatography (alumina, eluted by chloroform or n-hexane-diethyl ether).

The reaction scheme may be best explained by the acyl transfer from carbon to oxygen atom followed by elimination of carboxylate anion.



----[2]

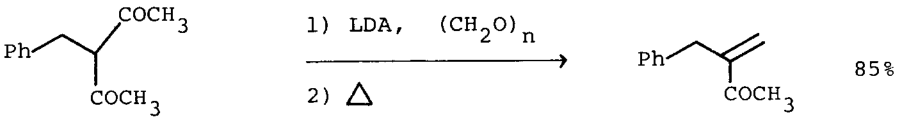
Since the substituents R in the products are originally derived from alkyl halides (RX), the overall transformation shown in the equation [1] also represents the synthetic synthon of α-vinyl carbanion of acrylic acid esters (3).

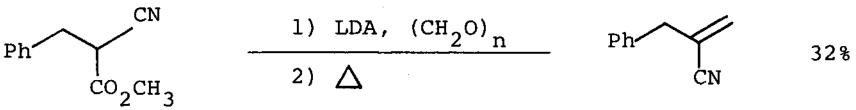


(3)

The schematic consideration shown in the equation [2] suggests us the general applicability of the present method to the various kinds of monosubstituted active methylene compounds activated by keto, formyl, nitro, or cyano groups.

Thus we have recently found that α-methylenated ketone and nitrile were obtained in similar fashions from 3-benzyl-2,4-pentan-dione and methyl 2-cyano-3-phenylpropionate, respectively.





In summary, the methodology reported herein offers several advantages over existing methods on the α-methylenation of esters, lactones, ketones or nitriles in several aspects described above.

We are currently investigating the application of the present method to the various kinds of monosubsituted active methylene compounds and we will report the full details in near future.

References

1a) For review see P. A. Grieco, Synthesis, 1975, 67.

1b) E. E. van Tamelen, S. R. Bach, J. Am, Chem. Soc., 77, 4683 (1955).
B. M. Trost, T. N. Salzman, J. Am. Chem. Soc., 90, 6840 (1973).

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3) G. Ferdinand, K. Schank, Synthesis, 1976, 404.
G. M. Ksander, J. E. McMurry, and M. Jhonson, J. Org. Chem., 42, 1180 (1977)

4) All compounds obtained here had satisfactory physical and spectral data.

(Received in Japan 19 June 1978; received in UK for publication 1 August 1978)