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A CONVENIENT METHOD FOR THE PREPARATION OF β-HYDROXY ESTERS

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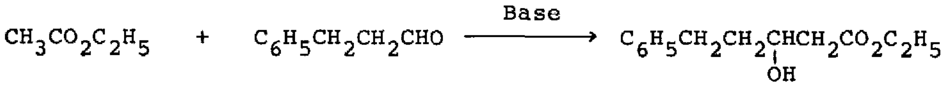
For the preparation of β-hydroxy esters, several bases have been employed to generate the enolate anions from the corresponding esters.[1] In these procedures, it is essential, before treating with appropriate carbonyl compounds, to prepare the ester enolates by using strong bases such as lithium dialkylamides at low temperature in order to avoid the self-condensation reactions of the carbonyl compounds and of esters. Thus, the generation of the enolates can not, in principle, be carried out effectively in the presence of the carbonyl compounds, which makes it difficult to apply these methods to the intramolecular preparation of β-hydroxy esters.

We have recently found that methyl ketone enolates can be generated selectively by treating the corresponding methyl ketones with lithium 1,1-bis(trimethylsilyl)-3-methylbutoxide 1 even in the coexistence of the various aldehydes, which leads to the efficient way to the directed aldol synthesis.[2] In the present, we wish to report that, in spite of the large difference of pK_a values between esters and aldehydes[3], such kind of base is also efficient for the generation of the enolate from ethyl acetate in the coexistence of aldehydes to afford the corresponding β-hydroxy esters in good yield. A typical example is as follows; lithium 1,1-bis(trimethylsilyl)-3-methylbutoxide 1 was prepared by treating the corresponding alcohol[4] (0.255 g, 1.1 mmol) with an equimolar amount of n-butyllithium in 2 ml of tetrahydrofuran (THF). A mixture of 3-phenylpropanal (0.134 g, 1.0 mmol) and ethyl acetate (0.097 g, 1.1 mmol) in 2 ml of THF was added to the resulting solution at -30° under argon atmosphere. After it kept stirring for 8 hr at that temperature, it was worked up with aq NH_4Cl. Removal of the solvent from the ether extracts followed by separation on silica gel chromatography (n-hexane-ether = 3:1) afforded the corresponding adduct, ethyl 3-hydroxy-5-phenylpentanoate (0.171 g, 77%), b.p.

120°/0.07 mmHg; ir (neat) 3420, 1725 cm^{-1}; nmr (CCl_4) δ 1.23 (t, J = 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1.78 (m, 2H, $C_6H_5CH_2C\underline{H}_2CH$), 2.37 (d, J = 6 Hz, 2H, $CH(OH)C\underline{H}_2CO-$), 2.72 (m, 2H, $C_6H_5C\underline{H}_2CH_2CH$), 3.20 (br, 1H, O$\underline{H}$), 3.7-4.2 (m, 1H, C$\underline{H}$OH), 4.10 (Q, J = 7 Hz, 2H, $OC\underline{H}_2CH_3$), 7.12 (s, 5H, aromatic).

In the reaction mixture, only small amounts of self-condensation product of the aldehyde was formed, but the formation of ethyl acetoacetate could not be detected. Efficacy of $\underline{1}$ has been compared with those of several other bases in the reaction of ethyl acetate with 3-phenylpropanal (see Table 1). From the results obtained, stronger base such as lithium diisopropylamide or sterically hindered base such as lithium tri(2-norbornyl)methoxide[5] has been less effective and $\underline{1}$ has proved to be the most efficient base for this type of addition reaction.

Table 1. Comparison of Bases[a]



$$CH_3CO_2C_2H_5 \quad + \quad C_6H_5CH_2CH_2CHO \xrightarrow{\text{Base}} C_6H_5CH_2CH_2\underset{\displaystyle OH}{CH}CH_2CO_2C_2H_5$$

Base	Yield, %	Base	Yield, %
$Me(Me_3Si)_2COLi$	62 (48)^b	t-BuOLi	(27)^b
sec-Bu$(Me_3Si)_2COLi$ ($\underline{1}$)	77 (67)^b	$(2\text{-Norbornyl})_3COLi$	58
c-$C_6H_{11}(Me_3Si)_2COLi$	57	$(iso\text{-}Pr)_2NLi$	47

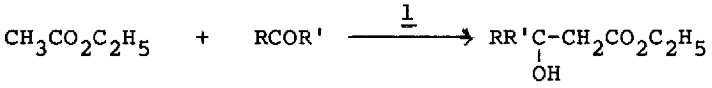
a) Reactions were performed under the similar reaction condition described in the text.
b) Numbers in parentheses were the yields when the reactions were carried out for 3 hr.

Addition reactions of ethyl acetate to the various carbonyl compounds are also examined by employing $\underline{1}$ as the base (see Table 2). As shown in the Table, the corresponding β-hydroxy esters are obtained in good yield under the coexistence of aldehydes as electrophiles, while the adducts are formed in only lower yield in the presence of ketones.

It is also found that the corresponding enolates can be generated much more effectively from γ-butyrolactone and δ-valerolactone which are considered to possess lower pK_a values than ethyl acetate.[6,7] Thus, treatment of the lactones with various carbonyl compounds leads to the formation of the corresponding adducts in excellent yield (see Table 3). Further, contrary to the results with ethyl acetate, the lactone enolates can be trapped effectively by ketones coexistent in the reaction system.

Effects of the bases employed have also been examined for the addition reaction of the lactone enolate to 3-phenylpropanal. On treating γ-butyrolactone with the aldehyde in the presence of $\underline{1}$ or lithium diisopropylamide, the former

Table 2. Reactions of Ethyl Acetate with Carbonyl Compounds in the Presence of $\underline{1}$[a,b)]

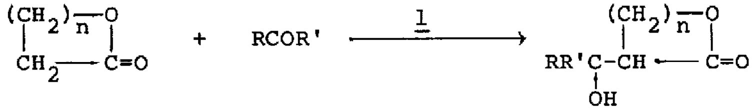


$$CH_3CO_2C_2H_5 \quad + \quad RCOR' \xrightarrow{\underline{1}} RR'\underset{OH}{\underset{|}{C}}-CH_2CO_2C_2H_5$$

RCOR'	Yield,[c]%	RCOR'	Yield,[c]%
$C_6H_5CH_2CH_2CHO$	77	$(n\text{-}C_4H_9)_2CO$	27
$n\text{-}C_5H_{11}CHO$	67	Cyclohexanone	30
$(CH_3)_2CHCHO$	74		
$n\text{-}C_3H_7CH(CH_3)CHO$	85		
$(C_2H_5)_2CHCHO$	87		
$n\text{-}C_3H_7CH{=}CHCHO$	69		
C_6H_5CHO	80		

a) All of the reactions were performed under similar reaction condition described in the text. b) All of the products gave satisfactory spectral and analytical data for the assigned structures. c) Isolated yield.

Table 3. Reactions of γ-Butyrolactone or δ-Valerolactone with Carbonyl Compounds in the Presence of $\underline{1}$.[a,b)]



RCOR'	n	Yield,[c]%	RCOR'	n	Yield,[c]%
$C_6H_5CH_2CH_2CHO$	2	95	$(n\text{-}C_4H_9)_2CO$	2	76
$n\text{-}C_6H_{13}CHO$	2	86	$C_6H_5CH_2CH_2COCH_3$	2	80
$(CH_3)_2CHCHO$	2	89	Cyclohexanone	2	91
$n\text{-}C_3H_7CH{=}CHCHO$	2	92	Cyclohexanone	3	90
C_6H_5CHO	2	95			
$C_6H_5CH_2CH_2CHO$	3	87			

a) All of the reactions were performed under similar reaction condition described in the text. b) All of the products gave satisfactory spectral and analytical data for the assigned structures. c) Isolated yield.

afforded the corresponding adduct in 95% yield, while the yield was decreased to 50% in the presence of the latter.

From the results described above, the alkoxide 1 appears to be a very useful base for selective generation of enolate anions from the corresponding esters.

We are currently investigating the scope and the limitation of this type of the reaction and its application to the intramolecular preparation of β-hydroxy lactones.

References and Foot Notes

1. M. W. Rathke, Org. React., **22**, 423 (1974); P. A. Grieco and K. Hiroi, Chem. Commun., 1317 (1972); P. A. Grieco, C. J. Wang, and S. D. Burke, ibid., 537 (1975).
2. I. Kuwajima, T. Sato, M. Arai, and N. Minami, Tetrahedron Lett., submitted for publication.
3. The pK_a value of methylene or methine group of an aldehyde has not been reported, but it seems to be reasonable to assume that its value is of the same order as that of a ketone.
4. J.-P. Picard, R. Calas, J. Dunogues, and N. Duffaut, J. Organometal. Chem., **26**, 183 (1971). By the modified method, this type of alcohols can be prepared in much higher yield; I. Kuwajima, T. Sato, N. Minami, and T. Abe, Tetrahedron Lett., in press.
5. Potassium tri(2-norbornyl)methoxide has been used as a ramified tertiary alkoxide in a dehydrohalogenation reaction; K. A. Bartsch and D. D. Ingram, J. Org. Chem., **40**, 3138 (1975).
6. To our best knowledge, definite pKa values of γ-butyrolactone and of δ-valerolactone have not been reported, but their more acidic characters have been suggested in several respects.
7. In the reaction with 3-phenylpropanal in the presence of 1, ethyl phenylacetate afforded the corresponding β-hydroxy ester in 98% yield, but ethyl propionate gave the adduct in only 29% yield. These results can also be attributable to the difference of their pKa values.