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A CONVENIENT SYNTHESIS OF KETONES

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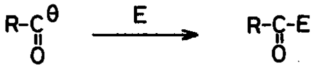
In the recent years, the synthetic utilization of nucleophilic acylation (Equation 1) has been extensively investigated,[1∿8] which involves the direct method with acyl metal compounds[2∿4] and the indirect method proceeding via " *masked* " acyl anions.[1,5∿8]

(Equation 1)

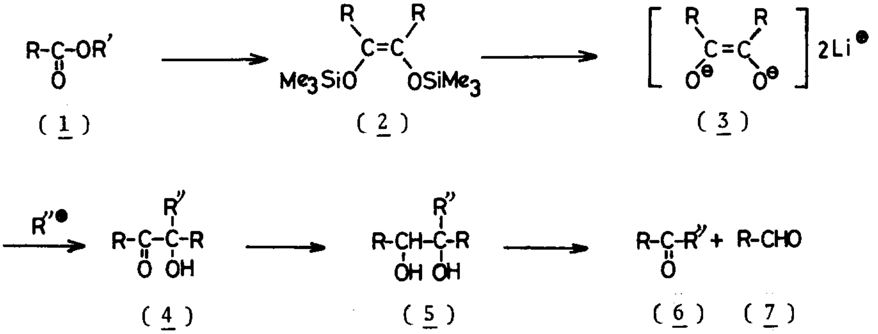


$$\underset{\overset{\|}{O}}{R\text{-}C^{\ominus}} \xrightarrow{E} \underset{\overset{\|}{O}}{R\text{-}C\text{-}E}$$

It is known that the acyloins are subject to alkylation in the presence of various bases, taking place usually at the carbon carrying the hydroxyl group.[9,10]

We wish to report a novel simplified procedure of alkylation of lithium acyloin enediolates (3) easily obtained from the enediol-bis-trimethylsilyl ethers (2) with methyllithium, which is combined with the subsequent reduction followed by the oxidative cleavage, providing the ketones [(6) RCOR''] with the aldehydes [(7) RCHO] in excellent overall yields. This method constitutes " *a detour but a facile way* " to the synthesis of ketones, corresponding to the acyl anion synthesis which starts from the esters (1). The processes are demonstrated in Scheme 1.

(Scheme 1)



The enediol-bis-trimethylsilyl ethers (2)[11] readily prepared in high yields by the acyloin condensation of the esters (1) in the presence of trimethylchlorosilane were converted by addition of 2 equiv. of methyllithium in monoglyme into its enediolates (3),[12] which were immediately subjected to alkylation with alkyl halides to produce exclusively the α-hydroxy ketones (4) in good yields.

The typical procedure with R = *n*-propyl is described and the results are compiled in Table 1 and 2.

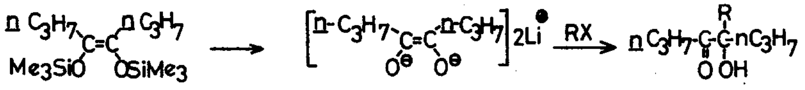
A. *Acyloin condensation* [(1) → (2)]: Ethyl butyrate is submitted to the acyloin condensation using trimethylchlorosilane according to the modified procedure.[11] The enediol-bis-trimethylsilyl ether (2) is purified by distillation.

B. *Alkylation* [(2) → (3) → (4)]: To a solution of (2)(0.01 mol) in 10 ml of dry monoglyme is added a solution of 0.022 mol of methyllithium in ether dropwise with vigorous stirring. The whole mixture is stirred at room temperature for 30 min. After replacement of the solvent by tetrahydrofuran, a solution of the halide (0.011 mol) in 5ml of tetrahydrofuran is added, and the mixture is stirred overnight (*ca.* 15 hrs). Removal of the solvent, addition of water, and extraction with ether or methylene chloride are followed by drying over $MgSO_4$. The solvent was removed and the residue was purified by distillation to give the compound (4).

C. *Generation of the ketones* [(4) → (5) → (6)]: Reduction of (4)(0.006∿0.008 mol) with sodium borohydride (0.006∿0.008 mol) in methanol at room temperature for 1∿5 hr in a usual manner afforded the diol (5), which is oxidized with lead tetraacetate (0.008∿0.01 mol) in anhydrous ether at room temperature for 2∿15 hrs. A saturated sodium bicarbonate solution is added, the resulting mixture is extracted with ether, and the extract is dried over $MgSO_4$. The solvent is removed to furnish the crude ketones (6), which are purified by silica-gel chromatography or by distillation to separate from the aldehydes produced as by-products.

Thus, the above reaction sequences do not involve any unit process carried out by heating. When a suitable ester is available, it could be converted to the valuable ketones by the present method. A useful application is described in the following communication.

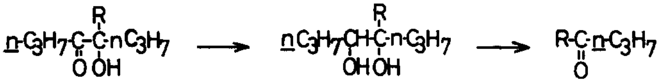
Table 1. Preparation of the α-hydroxy ketones (4) from the enediolate (3) derived from the enediol-bis-trimethylsilyl ether (2) and alkyl halides.



(2) (3) (4)

No.	Alkyl halide	Alkylation Yield (%)	b.p. °C(3mm/Hg)
1	ethyl iodide	82	60∿63
2	n-propyl iodide	84	66∿70
3	isopropyl iodide	78	60∿65
4	3-bromo-1-propanol	quant.	55∿60
5	n-pentyl bromide	80	80∿85
6	n-hexyl bromide	75	100∿105
7	benzyl bromide	90	115∿120
8	cyclohexyl iodide	64	95∿100

Table 2. Preparation of the ketones (6) from the α-hydroxy ketones (4).



(4) (5) (6)

No.	R	Reduction(NaBH$_4$) Yield (%)	Oxidation(Pb(OAc)$_4$) Yield (%)	Ketone b.p. °C(mm/Hg)
1	n-pentyl	quant.	95	65∿70(12)
2	n-hexyl	97	quant.	47∿48(2)
3	benzyl	quant.	97	107∿109(14)
4	cyclohexyl	quant.	90	50∿55(2)

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