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A NEW METHOD FOR ACYLATION OF ENOLATES BY MEANS OF DIALKYL ACYLPHOSPHONATES AS ACYLATING AGENTS$^{1)}$

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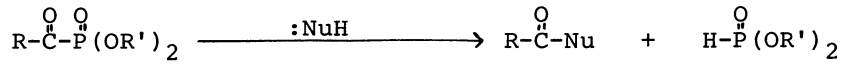
Acylations of various enolates by means of diethyl acylphosphonates were described. For the acylation of acetophenone, lithium bis(trimethylsilyl)amide (LSA) was found to be suitable as the base. The scope and limitation of the benzoylation using diethyl benzoylphosphonates were also described.

Among organophosphorus compounds, dialkyl acylphosphonates (1) possess the following characteristic features. The P-C bond of 1 is readily cleaved by nucleophiles such as alcohols$^{1-6)}$ and amines$^{4,7,8)}$ to afford acylated products with elimination of dialkyl phosphonates (2).



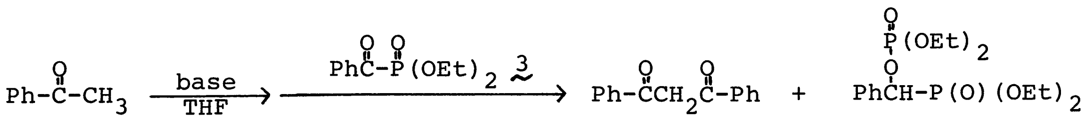
$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{P}}(OR')_2 \xrightarrow{\quad :NuH \quad} R{-}\overset{O}{\overset{\|}{C}}{-}Nu \; + \; H{-}\overset{O}{\overset{\|}{P}}(OR')_2}$$

1 2

Mechamism of the nucleophilic cleavage of the P-C bond of 1 has been studied in several laboratories.$^{9-12)}$ Recently, Guthrie$^{13)}$ reported the pKa value of 2 [$H\text{-}P(O)(OEt)_2$] which was estimated to be ca. 13. From this value, the diethoxyphosphoryl group can be expected to have the leaving ability between phenoxyl (PhOH: pKa=10) and ethoxyl (EtOH: pKa=17) groups. The P-C bond of 1 is more labile than expected from the pKa value since the P-C bond of 1 is gradually hydrolyzed even in air.$^{14)}$ The reaction mode of the P-C bond cleavage suggests the potential usefulness of 1 as acylating agents. Although these fascinating properties of 1 have been described, only a few have been known of reactions of 1 with carbanion species.$^{15-18)}$

In this paper, we wish to report a novel method for acylation of various enolates by means of 1.

First, we examined acylation of acetophenone enolates by use of 1 equiv. of diethyl benzoylphosphonate (3) under various conditions. When lithium diisopropylamide (LDA) was employed as the base, dibenzoylmethane (4) was obtained only in 24% yield. The use of LDA resulted in the formation of byproducts

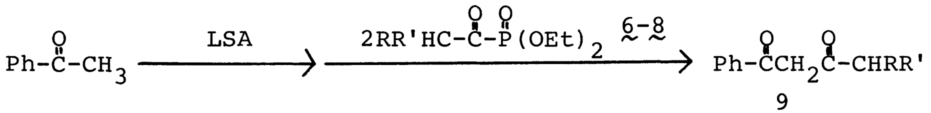


$$\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_3 \xrightarrow[THF]{base} \xrightarrow{\quad Ph\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{P}}(OEt)_2 \; 3 \quad} Ph{-}\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}{-}Ph \; + \; Ph\overset{\overset{\overset{O}{\overset{\|}{P}}(OEt)_2}{O}}{CH}{-}P(O)(OEt)_2}$$

4 5

derived from diethyl α-hydroxybenzylphosphonate, which was probably formed owing to the reduction of 3 with LDA or other carbanion species. In order to avoid such side reactions, potassium *t*-butoxide and lithium bis(trimethylsily)amide (LSA) were used since they had no α-hydrogen that participated in the unusual reduction.[19] By use of potassium *t*-butoxide as the base, the yield of 4 was increased to 44%. Furthermore, LSA gave 4 in a better yield (75%), when the stoichiometric reaction of 3 with acetophenone was performed. In these reactions, it was observed that diethyl phosphonate 2 (R=Et) resulting from the acylation reacted further with the remaining 3 to give diethyl α-[(diethoxyphosphinyl)oxy]benzylphosphonate (5) so that acetophenone was recovered to some extent. Therefore, 2 equiv. of 3 was employed in order to complete the acylation, whereby one equiv. of 3 served as a scavenger of 2. Thus, 4 was obtained in a high yield (86%) according to the following typical procedure: Under argon atmosphere, acetophenone (397 mg, 3.3 mmol) was added to a cooled THF solution (-78°C) of LSA (3.56 mmol) which was prepared by the lithiation of hexamethyldisilazane with an equimolar amount of n-butyllithium (2 M hexane solution) in THF (10 ml) at -78°C for 30 min. After the solution was stirred for 30 min, 3 (1.72 g, 7.1 mmol) was added. The mixture was stirred continuously for 30 min at -78°C and then poured into a vigorously stirred mixture of methylene chloride (20 ml) and 1 M NH_4Cl (20 ml). The organic layer was collected and the aqueous layer was further extracted with methylene chloride (3 x 10 ml). The organic extracts were combined, dried over Na_2SO_4, evaporated in vacuo, and the residue chromatographed on silica gel (hexane-ether) to give 4 (638 mg, 86%) and 5 (968 mg, 77%).

In a similar manner, aliphatic acylphosphonates (6-8) were employed for the acylation of 1. These results are summarized in Table 1.

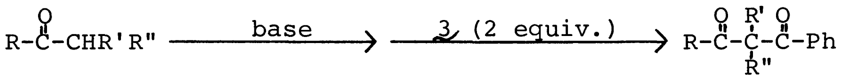


$$\text{Ph-}\overset{O}{\overset{\|}{C}}\text{-CH}_3 \xrightarrow{\text{LSA}} \xrightarrow{2\text{RR'HC-}\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{P}}(\text{OEt})_2 \;\; 6\text{-}8} \text{Ph-}\overset{O}{\overset{\|}{C}}\text{CH}_2\overset{O}{\overset{\|}{C}}\text{-CHRR'}$$

9

The yields of the acylated products (9) increased with the number of substituents at the α-position of 6-8. In the case of 6 or 7, a considerable amount of acetophenone was recovered. These results suggest that a side reaction analogous to the Claisen reaction might take place during the acylation in the case of aliphatic acylphosphonates.[20]

Next, the benzoylation of various enolates with two equiv. of 3 were examined in order to clarify the scope and limitation of the present acylation. These results are summarized in Table 2. For the acylation of relatively acidic active methylene compounds, sodium hydride was superior to LSA. Reactive enolates derived from carbonyl compounds having pKa 11-25 underwent smooth acylation with diethyl benzoylphosphonate 3, while the acylation of carbonyl compounds possessing pKa values of less than ca. 10 did not proceed.



$$\text{R-}\overset{O}{\overset{\|}{C}}\text{-CHR'R''} \xrightarrow{\text{base}} \xrightarrow{3\ (2\ \text{equiv.})} \text{R-}\overset{O}{\overset{\|}{C}}\text{-}\underset{R''}{\overset{R'}{C}}\text{-}\overset{O}{\overset{\|}{C}}\text{-Ph}$$

10 11

Table 1. Acylation of lithium acetophenone enolate generated by LSA

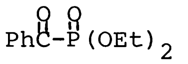
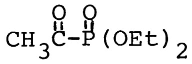
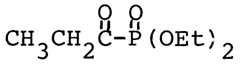
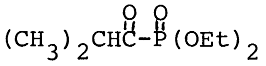
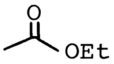
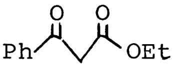
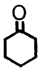
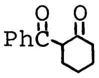
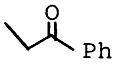
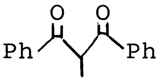
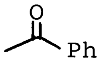
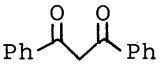
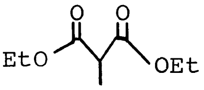
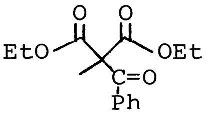
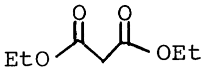
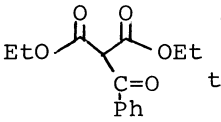
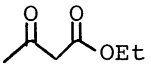
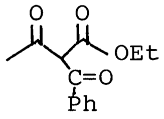
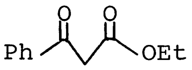
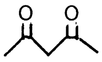
Acylphosphonate	Temp.(°C) [Time(min)]	Yield (%) Product (4 or 9)	Recovery(%) of 3
 $\mathrm{Ph\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{P}(OEt)_2}$ 3	-78 [30]	86	—
 $\mathrm{CH_3\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{P}(OEt)_2}$ 6	-78 [45] ⟶ r.t. [90]	48	34
 $\mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{P}(OEt)_2}$ 7	-78 [20] ⟶ r.t. [40]	68	30
 $\mathrm{(CH_3)_2CH\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{P}(OEt)_2}$ 8	-78 [30] ⟶ r.t. [60]	88	6

Table 2. Benzoylation of various enolates by means of 3

Carbonyl Compound	Base	Metalation[a] Temp.(°C) [Time(min)]	Benzoylation Temp.(°C) [Time(min)]	Product	Yield (%)
	LSA	-78[10]	-78→r.t.[50]		77
	LSA	-78[30]	-78[60]→r.t.[60]		38
	LSA	-78[30]	-78[45]→r.t.[60]		56
	LSA	-78[30]	-78[30]		86
	NaH	r.t.[10]	r.t.[60]		33[b]
	NaH	0→r.t.[60]	r.t.[60]		71
	LSA	-78[30]	-78[45]→r.t.[60]		trace
	NaH	0→r.t.[70]	r.t.[6.5h]		49
	LSA	-78[40]	-78[50]→r.t.[40]		4
	NaH	0[30]	r.t.[4.5h]	no reaction	
	LSA	-78[25]	-78→r.t.[3.5h]	no reaction	

[a] 1.05-1.10 Equiv. of the base was used.

[b] Ethyl 2,2-dibenzoylpropionate was obtained in 25% yield as the byproduct.

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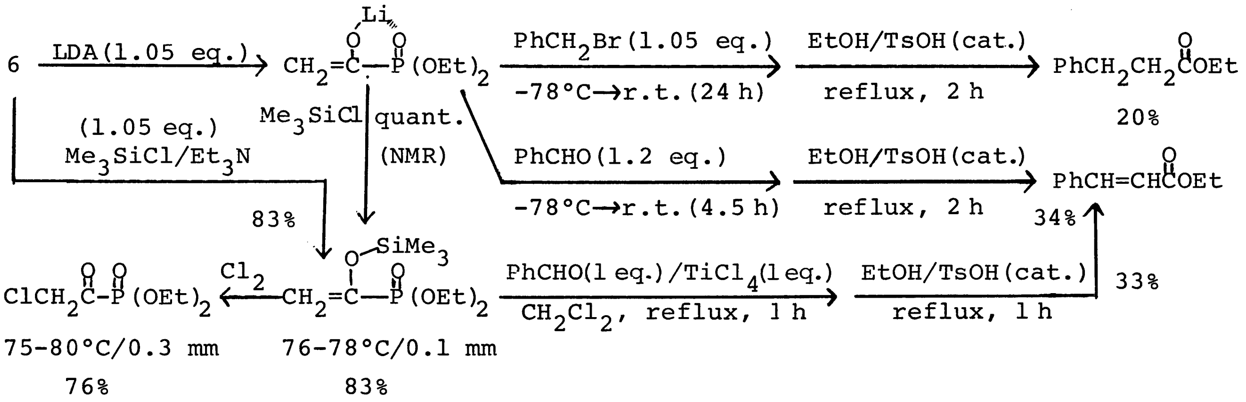
20) α-Lithiated species of **6** was readily obtained by treatment with LDA. Several reactions utilizing this intermediate and further transformations are illustrated as shown in the following scheme.



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