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STUDIES ON ALKYLATION OF ACYL ANION EQUIVALENTS: UNSYMMETRICAL KETONE SYNTHESIS BY USE OF DIETHYL 1-TRIMETHYLSILYLOXY-ALKYLPHOSPHONATES

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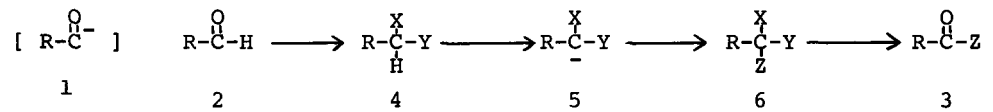
Summary: Novel acyl anion equivalents, lithiated diethyl 1-trimethylsilyloxy-alkylphosphonates, were successfully alkylated and converted to the corresponding ketones. The mechanism of the alkylation is discussed in connection with the Brook-Wittig rearrangement.

In recent years, considerable attention has been paid to acyl carbanions (1) as synthetic intermediates in organic synthesis and various equivalents have been proposed in several laboratories.[2] Particularly, these acyl anion equivalents have been frequently utilized for the conversion of aldehydes (2) to ketones (3) as shown in the following scheme.



In the above reaction sequence, the following requisites should be accepted; 1) aldehydes (2) can be easily converted to speaces (4) masked with X and Y; 2) the α-proton of 4 can be abstracted under mild conditions and the carbanion (5) is sufficiently reactive toward alkylating agents; 3) the protecting groups, X and Y, are easily removed from alkylated products (6); 4) R of 2 should not be limited. From the point of view, acyl anion equivalents stabilized by both a α-trimethylsilyloxy group and certain electron-withdrawing group might be attractive since organosilicon agents such as trimethylsilyl cyanide[3] and trimethylsilyl phosphites[4,5,6] react with aldehydes under very mild conditions (especially in the later case) to give masked carbonyl insertion products and the carbonyl groups are expected to be regenerated by cleavage of the Si-O bonds followed by elimination of CN^- and phosphonate ion. However, the unsymmetrical ketone synthesis utilizing α-trimethylsilyloxy cyanides is limited to aromatic ketones where R is phenyl, pyridyl, or furyl group[3]. We have recently reported a new method for the synthesis of ketones utilizing 1-trimethylsilyloxy-benzyl-phosphonate (7).[5] However, when α-trimethylsilyloxy-alkylphosphonates (8) were used, no alkylated products were obtained in these experiments.

In order to overcome the limitation, we examined several experiments and found a novel Wittig rearrangement of the trimethylsilyl group and a convenient

method applicable to the synthesis of unsymmetrical aliphatic ketones using 8.

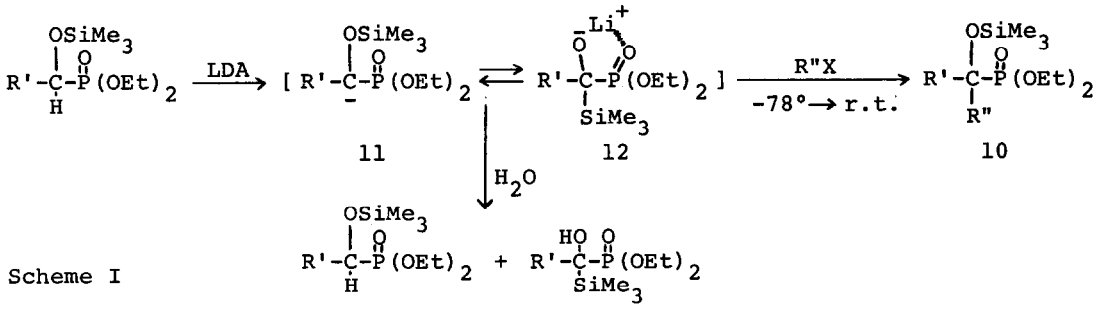
Diethyl 1-trimethylsilyl-ethylphosphonate (8a) was treated with $(i\text{-Pr})_2NLi$ (LDA: 1.1 equiv.) at -78°C for 1 h and further with methyl iodide (1.1 equiv.) at -78°C for 30 min. The mixture was then quenched with dilute ammonium chloride. After extraction of the aqueous solution with methylene chloride, the extracts were concentrated and the residue was applied to a silica gel column. Elution was performed with n-hexane/ether. After evaporation of the solvent, an oily material, which crystallized gradually at r.t., was obtained. The product was confirmed as diethyl 1-hydroxy-1-trimethylsilyl-ethylphosphonate (9b) by means of its NMR and IR spectra. The methylated productd (10b) was not obtained under these conditions. It has been well recognized as the Brook rearrangement that the trialkylsilyl group of 1-trialkylsilylalcohols migrates from carbon to oxygen by treatment with bases to give 1-trialkylsilyl ethers. This C→O rearrangement is generally considered as a result of the strong affinity of the silicon atom with the oxygen atom. On the other hand, only a few examples are known of O→C rearrangement of trialkylsilyl groups (anti-Brook rearrangement or Wittig rearrangement). West[8] studied reversibility between these rearrangements. For example, trimethylsilyl benzyl ether is known to be converted into α-trimethylsilylbenzyl alcohol by treatment with an excess of t-butyl lithium.

Treatment of 8b with LDA without addition of methyl iodide at -78°C gave 9b in 91 % yield. The fact of such a smooth anti-Brook rearrangement by the use of LDA led us to examine the reaction of other 1-trimethylsilyloxyphosphonates (9a, 9b, and 9d) with LDA. These results are summarized in Table I.

Table I Treatment of 8 with LDA

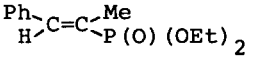
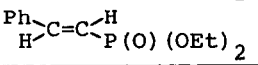
	8	The Ratio of 9/8(%)	
	R	-78°	r.t.
a	H	87/0	78/0
b	Me	91/0	42/22
c	Et	37/45	0/40
d	i-Pr	0/85	0/32

Treatment of 8c with LDA at -78°C gave 1-hydroxyphosphonate (9c) in 37 % yield and 45 % of 8c was recovered. Compound 9d could not be lithiated under the same conditions and was recovered. It is probably due to the steric hindrance of 9d. Table I implies that the equilibrium between a α-carbanion (11) and an alkoxide ion (12) exists and the ratio of the two isomers depends on the α-alkyl substituent and the reaction temperature. The ratio of 11/12 grows up with increasing temperature and bulkiness of the α-substituents. Probably the anti-Brook rearrangement of 8a and 8b is attributable to that the O-lithio derivatives (12a and 12b) can be stabilized by an intramolecular chelation with the neighbering group as shown in Scheme I. In consideration of these facts, it was expected that C-alkylation may be achieved by warming the reaction mixture from -78°C up to a higher temperature in the presence of alkyl halides. According to our expectation, the



Scheme I

Table II Alkylation of 8 with alkyl halides

	8 R'	Solvent	Lithiation Time (h)	R"X	Alkylation Yield (%) of 10
a	H	THF	0.5	MeI	86
			0.5	$PhCH_2Br$	80
			0.5	EtI	77
			0.5	$PhCH_2CH_2I$	48
b	Me	THF	0.5	MeI	95
			0.5	$PhCH_2Br$	76
c	Et	THF	5	MeI	84
			5	$PhCH_2Br$	58
			5	$PhCH_2I$	63
d	i-Pr	THF	15	MeI	0
e	$n\text{-}C_7H_{15}$	DME	1	MeI	86
			1	$PhCH_2Br$	29
f	Ph	THF	0.5	MeI	 57
			0.5	H_2O	 41

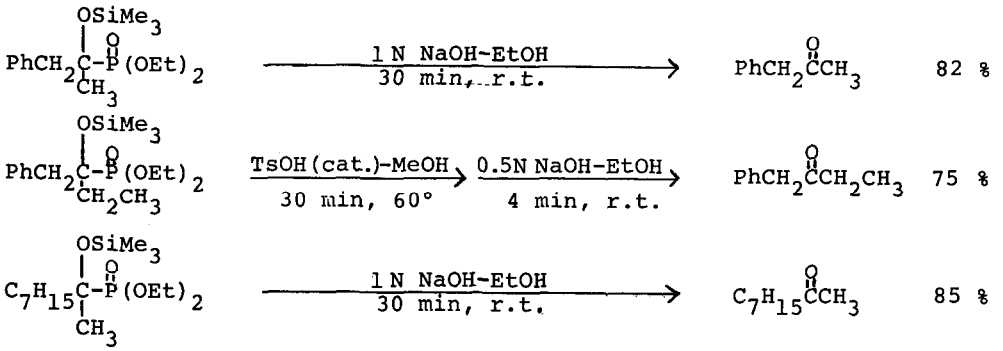
In these reactions, 1.03-1.09 equivs. of LDA and 1.00-1.26 equiv. of alkyl halides were used.

C-alkylated products were successfully obtained at r.t. (see Table I).

In the case of the alkylation of 8e having a long alkyl chain, dimethoxyethane was more suitable solvent than tetrahydrofuran, although the later was used satisfactorily for the metallation of 8a-8c. In the case of the alkylation of 8f having a relatively acidic proton at the β-position, α,β-unsaturated vinylphosphonates were obtained as the main products. These vinylphosphonates were found to be stereoselectively Z-isomers from their NMR spectra. The 1:1 adduct, 8a, obtained from formaldehyde and diethyl trimethylsilyl phosphite would be a useful reagent because it is alkylated stepwise with the different kinds of alkyl halides.

In the present alkylation, the presence of the α-phosphoryl group seems important because the phosphoryl group plays a role of the stabilization of the O-anion through a five membered ring chelation so that the O-anion does not further decompose to acylsilane and phosphonate ion. This view is supported by the fact that lithiated 1-trimethylsilyloxy-alkylcyanides, the O-anion of which can not form intramolecular chelations, readily decompose to afford the self-condensation products.[9]

Several alkylated products obtained in the above experiments are successfully converted to the corresponding carbonyl compounds by treatment with 1 N NaOH-EtOH (1:1, v/v)[6] or by two-steps procedure involving pre-treatment with p-toluenesulfonic acid (cat.) in methanol according to the following equations.



References and Notes

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