A CONVENIENT METHOD OF KETONE SYNTHESIS UTILIZING THE REACTION OF DIETHYL TRIMETHYLSILYL PHOSPHITE WITH CARBONYL COMPOUNDS<sup>1</sup> Tsujiaki Hata<sup>\*</sup>, Akio Hashizume, Masashi Nakajima, and Mitsuo Sekine Department of life Chemistry, Tokyo Institute of Technology Ookayama, Meguro-ku, Tokyo 152, Japan (Received in Japan 5 October 1977; received in UK for publication 29 November 1977)

In a previous paper<sup>1g</sup>, we have reported that tris(trimethylsilyl) phosphite (la) reacted with carbonyl compounds including  $\alpha,\beta$ -unsaturated system to afford regioselectively  $\alpha$ -trimethylsilyloxyphosphonates (2a or 3a) or 1,4adducts (4a) in high yields. More recently, Evans has reported similar results using dimethyl trialkylsilyl phosphites<sup>2</sup>. Our attention was focused on the synthesis of unsymmetrical ketones from aldehydes by means of alkylation of relatively acidic  $\alpha$ -hydrogen of carbonyl adducts obtained by the reaction of la with aldehydes followed by elimination of dialkyl phosphonate.



However, the Si-O bond of trimethylsilyl-esters of phosphonic acids was known to be labile toward metallating agents such as n-BuLi<sup>3</sup> and to be easily hydrolyzed even when the esters were exposed to air<sup>1g</sup>. On the other hand, dimethyl-esters of phosphonic acids seem to be also unstable toward nucleophiles such as iodide ion produced during the alkylation reactions to decompose partially giving demethylated by-products. In consideration of the above facts, ethyl group was chosen as the ester group of the phosphonic acids and the reactions of diethyl trimethylsilyl phosphite (lb) with various carbonyl

363

compounds were examined. Consequently, the addition compounds (2b and 3b) were found to be sufficiently stable during work-up of extraction and silicagel column chromatography. The results were summarized in Table 1. In these reactions, 1b was found to be somewhat less reactive toward carbonyl compounds than  $la^{lg}$ . The reaction patterns were essentially almost the same as those<sup>1g</sup> described previously in the case of the reactions of la with  $\propto, \beta$ -unsaturated carbonyl compounds, indicating high regioselectivities and high yields (see Table).

For the extension of these reactions to unsymmetrical ketone synthesis, we chose diethyl  $\alpha$ -trimethylsilyloxy-benzylphosphonate (2c) because the reaction can be monitored by ultraviolet absorbtion.

2c was treated with  $(i-Pr)_2NLi$  (1.12 equiv.) at -78° in dry THF for 30 min, whereupon white precipitate of a lithio-derivative (6) was separated, and it was further treated with methyl iodide (1.14 equiv.) at -78° for 25 min. After quenching the reaction mixture with aqueous dilute NH<sub>4</sub>Cl followed by extraction with chloroform from the aqueous layer, a methylated product (7) was obtained in 90% yield after silicagel column chromatography. The structure of 7 was determined by comparison with the authentic sample obtained by the reaction of 2b with acetophenone (see Table 1).



Similarly, several alkylated products were isolated in high yields (see Table 2). Hünig and his co-workers reported an unsymmetrical ketone synthesis utilizing carbonyl adducts of trimethylsilyl cyanide<sup>4</sup>. It seems to be one of useful methods for the synthesis of ketones<sup>5</sup>. According to their reports, the conversion of the alkylated products to ketones required two-steps treatment with 2 N HCl followed by 0.5 N NaOH.

We found a notable finding that the alkylated phosphonates obtained in our experiments were directly converted simply by mild alkaline treatment without pre-treatment of acid to the corresponding ketones in high yields (see Table 2). Therefore, the present method has a promising feature more widely applicable to the synthesis of ketones having acid-labile functional groups. This facile P-C bond cleavage might be explained as follows. From an intermediate (8) formed initially as a result of the attack of hydroxyl ion on the phosphorus atom of the alkylated products, the trimethylsilyl group was rapidly rearranged to the anionized oxygen atom via a five membered transition state. An intermediate (9) newly formed was then irreversibly transformed to diethyl phosphonate and

364

сн<sub>з</sub>

OEt

reflux

R <sub>1</sub>	R2	R <sub>3</sub>	R4	temp.	time (hr)	yield (%)			bp
						2	3	4	(°C/mmHg)
Ph	СНЗ			reflux	19	78			132-133/0.58
Ph	н			r.t.	6	91			118-123/0.08
i-Pr	н	_		r.t.	6	90			91-94/0.2
		н	н	r.t.	6		89		105/0.25
		CH 3	н	r.t.	6		73		110-113/1.8
		Ph	н	r.t.	6		85		160/1.35
		н	CH 3	r.t.	22			84	101/0.24
		H	CH	reflux	6		_	91	108-110/0.25

Table 1 Reaction of diethyl trimethylsilyl phosphite with carbonyl compounds

All the reactions were carried out in dry benzene. In each reaction, one equiv. or a slight excess of 1b was used.

16

Table 2Alkylation of diethyl <-trimethylsilyloxy-benzylphosphonate and<br/>conversion of the alkylated products to ketones

RX (i-P (equiv.) (e	r) <sub>2</sub> NLi quiv.)	time (min)	alkylated product yield(%)	ketone ketone method A yield method B yield (%) (%)			
CH <sub>3</sub> I (1.14)	1.12	25	90	TSOH-MeOH(60°,30min) 1 N NaOH-EtOH $\rightarrow$ 0.5 N NaOH(r.t., 90 (1:1 v/v,r.t., 86 20min) 20min)			
C <sub>2</sub> H <sub>5</sub> I(1.21)	1.13	40	87	TsOH-MeOH(60°,1.5hr)			
$C_{2^{H}5}^{Br}(1.12)$	1.18	30	13	→0.5 N NaOH-dioxane 90			
n-C <sub>3</sub> H <sub>5</sub> I (1.24)	1.13	70	81	2 N HCl-MeOH(1:1 v/v, 1 N NaOH-EtOH r.t.,3.5hr) -> 0.5 N 81 (1:1 v/v,r.t., 88 NaOH-EtOH(1:1 v/v, 20min) r.t.,10min)			
n-C <sub>4</sub> H <sub>9</sub> I (1.15)	1.15	50	84	TSOH-MeOH(60°,40min) →0.5 N NaOH-EtOH 94 (1:1 v/v,r.t.,60min)			
PhCH <sub>2</sub> Br (1.05)	1.05	30	85	TsOH-MeOH(60°,90min)       1 N NaOH-EtOH         →0.5 N NaOH-EtOH       93 (1:1 v/v,r.t., 94         (1:1 v/v,r.t.,10min)       30min)			
PhSSPh (1.05)	1.05	30	81 Ph	$\begin{array}{cccc} & 1 & N & \text{NaOH-EtOH} & (1:1) \\ OSiMe_3 & v/v, r.t., 60min) & 90% \\ -C-P(O)(OEt)_2 & product: & O \\ SPh & PhCOH \end{array}$			

120-122/2.15

16



the corresponding ketones through the subsequent reaction pathways as described in the above scheme.

On the other hand, when the alkylated products were treated with dilute HCl at room temperature or a catalytic amount of p-toluenesulfonic acid in methanol at 60°, the trimethylsilyl group was removed to give the corresponding  $\alpha$ -hydroxyphosphonates (10) in almost quantitative yields as the sole product. For further conversion of the  $\alpha$ -hydroxyphosphonates to the ketones, the successive alkaline treatment was carried out without isolation of 10 (see Table 2).

Finally, it was shown that 2c could be also converted by the reaction with diphenyl disulfide to the corresponding sulfenylated product (7b) in 81% yield. In this case, the alkaline treatment of 7b gave benzoic acid in 90% yield.

Further extended studies on alkylation and improved ketone synthesis are now in progress.

## REFERENCES

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