Tetrahedron Letters No. 2, pp 155 - 158, 1977. Pergamon Press. Printed in Great Britain.

THE FACILE DEALKYLATION OF PHOSPHONIC ACID DIALKYL ESTERS BY BROMOTRIMETHYLSILANE (1)

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(Received in USA 11 October 1976; received in UK for publication 30 November 1976)

Phosphonic acids ($RP(O)(OH)_2$, (1)) are conveniently synthesized via dealkylation of corresponding phosphonic acid dialkyl esters ($RP(O)(OR')_2$, (2)). Acid-catalyzed hydrolytic dealkylation (2) is effective for this purpose, but in important classes of alkyl phosphonates R consists of, or comprises, a functional group that is too delicate to survive the harsh reaction conditions involved.

Conversion of (2) to a cognate form susceptible to very mild hydrolysis offers a solution (7) to this problem, provided that the conversion step itself is facile and compatible with sensitive R groups.

Some years ago it was shown that bis(trimethylsilyl) phosphonates ($RP(O)(OSiMe)_2$, (3)), prepared from alkyl phosphonate precursors by the action of chlorotrimethylsilane (4a), hydrolyze to phosphonic acids on contact with neutral H_2O at room temperature (14). In contrast to the gentle hydrolysis step, however, dealkylation required days, or even weeks, of reflux with excess silylating reagent for most of the examples given (14). Several recent reports (15-19) strengthen the impression that inadequate reactivity of (4a) may limit (20) the potential usefulness of this method as a reliable route to difficultly accessible phosphonic acids.

A proposed (14) mechanism for the reaction between (2) and (4a) invokes analogy with the Arbuzov reaction: attack on silicon by the phosphoryl oxygen of (2) is followed by substitution of the displaced halide ion on a phosphonate ester alkyl group of the same molecule to give the mixed alkyl trimethylsilyl diester of the phosphonic acid; a second cycle of the same reaction sequence would then yield the bis(trimethylsilyl)phosphonate. Consideration of this and similar possible mechanisms in which halide participates both as leaving group and nucleophile suggests that replacement of (4a) by bromotrimethylsilane (4b) (21) should (23) inevitably accelerate the reaction. It then remains to determine whether the magnitude of this expected rate enhancement with (4b) leads to general reaction conditions for the conversion of (2) to (3) that are sufficiently moderate to permit full exploitation of the subsequent easy hydrolysis of (3) to a phosphonic acid.

We wish to report that bromotrimethysilane smoothly and quantitatively converts a variety of dialkyl phosphonates and tetraalkyl gem-alkanediphosphonates to the corresponding bis or

TABLE I: Dealkylation of Dialkyl Phosphonates with Halotrialkylsilanes

Dialkyl Phosphonate $RP(O)(OR')_2$			+ Chlorotrimethylsilane				+ Bromotrimethylsilane			
Compound	R	R'	Equiva-lents	Temp. (C°)	Reaction Time	Yield[a] (%)	Equiv-alents	Temp. (°C)	Reaction Time	Yield[b] (%)
(2a)	CH_2=CH	Et	2.7	69-72	5 da	94[c]	1.5	25	1.2 hr	>99
(2b)	$PhCH_2$	Et	2.2	40	1 da	< 5[d]	1.7	25	2.0 hr	>99
(2c)	Ph(CO)	Me	1.9	25	9 da	12	1.5	25	1.7 hr	≥99
(2d)	$EtOCH_2CH_2$	Et	2.9	40	1 da	<10	1.7	25	0.7 hr	>99
(2e)	Cl_3C	Et	5.4	>72	8 da	13	1.5	61-69	2.7 hr	≥99
(2f)	$(MeO)_2P(O)CH_2$	Me	2.0	25	1 da	19	1.1	25	1.0 hr	≥99
(2g)	$(EtO)_2P(O)CH_2$	Et	1.5	66-106	5 da	66[e]	1.5	25	1.4 hr	≥97

[a]Estimated by ^1H nmr. [b]Estimated by ^1H and ^{31}P nmr. [c]At 75-95°+isolated yield of 92% silyl ester reported (14). [d]Isolated yield of 93% silyl ester reported (14) after 4 da reaction with 2.7 eq. (4a) at 92-95°+. [e]Distilled silyl ester.

TABLE II: NMR Spectral Properties of Bis(Trimethylsilyl) Phosphonates (3a)-(3f)[a]

	^1H			^{31}P		
Compound[b]	δ(ppmTMS)	Mult. (J in Hz)	Int. (H)	$\delta(H_3PO_4)$[c]	Mult. (J in Hz)	$\Delta\delta$[d](ppm)
(3a)	0.28	s	18	1.6	m	18.2
	~6.0	m	3			
(3b)	0.8	s	18	-8.0	t (22)	17.9
	3.02	d (23)	2			
	7.34	s	5			
(3c)	0.31	s	18	18.4	s	18.6
	7.3-8.8	m	5			
(3d)	0.30	s	18	-9.5	t of t (19,12)	18.3
	1.17	t (7)	3			
	1.93	d of t (19,7)	2			
	3.48	q (7)	4			
	3.61	d of t (12,7)				
(3e)	0.38	s	-	12.6	s	17.8
(3f)	0.33	s	36	-0.4	t (22)	23.0[e]
	2.44	t (22)	2			19.0[f]

[a]^1H nmr data: Varian T-60; ^{31}P nmr data: Varian XLFT-100. All samples neat. [b]Prepared using (4b); (3a) and (3b) were previously prepared using (4a)(14). Bp ((3c) → (3f)): (3c), 107°$_{0.5}$; (3d), 108-9°$_{.8}$; (3e), 67°$_{0.5}$; (3f), 120°$_{0.5}$. High resolution ms peak matches were obtained within 0.002 mass units for all compounds. Hydrolysis in all cases yielded the corresponding phosphonic acids, identified by comparison with authentic samples or by elemental analyses of the dicyclohexylamine salts. [c]External, dil. in D_2O. [d]δ(3) - δ(2). [e]δ(3f) - δ(2f). [f]δ(3f) - δ(2g).

tetrakis(trimethylsilyl) esters under exceedingly mild conditions, typically 1-2 hr at 25°. Specific examples comparing alkyl phosphonate silylations with (4a) and (4b) are presented in Table I. In a representative experiment, 1-2 mmol of the neat phosphonate alkyl ester in an N_2-filled, thermostatted nmr tube equipped with a septum stopper was treated with the indicated amount of (4b), injected with the aid of a plastic syringe. After mixing, the progress of the often noticeably exothermic (24) reaction was followed to completion by nmr spectrometry (see below). Alkyl bromide by-product and any excess bromosilane were then removed at 0.1-1.0 mm to afford the trimethylsilyl phosphonate (3). At 25°, 1-2 eq. of (4b) sufficed to effect rapid dealkylation of diethyl (or dimethyl) vinyl- (2a), benzyl- (2b), benzoyl- (2c), and 2-ethoxyethyl- (2d) phosphonate; the tetramethyl and tetraethyl methanediphosphonates (2f) and (2g) also quickly reacted with (4b) at 25° to give the same trimethylsilyl ester (3f), while silylation of the exceptionally resistant trichloromethylphosphonate (2e) was complete after several hours at a somewhat higher temperature (25). Under comparable conditions, (4a) was essentially unreactive with compounds (2a)-(2g). The data collected in Table I for much longer reaction periods with (4a) give some indication of the relative potency of (4b) as a dealkylating reagent for the alkyl phosphonates studied.

Table II summarizes ^{1}H and ^{31}P nmr spectral data for the trimethylsilyl phosphonates (3a)-(3f). The dealkylations were readily followed by observing the disappearance of the $P\text{-}O\text{-}CH_n$ proton resonance, or even more conveniently, by observing replacement of the starting alkyl phosphonate ^{31}P spectrum by the characteristically upfield-shifted resonance (26) of the silyl ester product. As shown, the magnitude of this chemical shift difference was ~20 ppm for the reaction systems examined. All trimethylsilyl phosphonates listed were hydrolyzed by H_2O to the expected phosphonic acids.

The strikingly facile dealkylation of alkyl phosphonates by bromotrimethylsilane, when coupled with hydrolysis of the resultant trimethylsilyl phosphonates, appears(27)to constitute a truly mild procedure for the preparation of phosphonic acids, with particular promise for synthesis of phosphonic acids incorporating sensitive functional groups - a category that includes compounds of biochemical interest (28).

Acknowledgements. This research was supported by grants from the Research Corporation. N.H.C. was a 1975 NSF Undergraduate Research Participant, and M-C. McK. received support from NSF grant BMS 13608. The Varian XLFT-100 nmr spectrometer used in these investigations was purchased with the aid of a departmental instrument grant from NSF.

References and Notes.

1. Presented in part at the 1975 Pacific Conference, North Hollywood, California, October 28-30, 1975.
2. E.g., by hot, concentrated HCl or HBr (3); phosphonic acids derived from dialkyl α-oxoalkylphosphonates have been obtained by cleavage of the latter with anhydrous HBr at 95-100° (4). Alkaline hydrolysis of (2) usually gives only the monodealkylated product (5), as does treatment of (2) with alkali (6a) or alkaline earth (6b) halides.
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7. An alternative approach is to form the phosphonate of interest or a precursor by Arbuzov condensation using a phosphite ($P(OR')_3$) in which R' can be eventually removed by some convenient means. Some examples: eliminative pyrolysis of alkyl phosphonates derived from secondary or tertiary alchols (e.g., R' = i-Pr or t-Bu) (8); catalytic hydrogenation of a benzyl phosphonate (12); and base catalyzed elimination of acrylonitrile from a 2-cyanoethyl phosphonate (13). These methods would seem to be unsuitable a priori for dealkylating phosphonates (2) in which R contains a thermally labile, unsaturated, or base-sensitive group, respectively.
8. Tetraisopropyl dichloromethanediphosphonate can be pyrolyzed at 150° to dichloromethanediphosphonic acid (9); the generality of this method (10) as applied to diisopropyl phosphonates is not established, and we have found that it may give poor yields, e.g., with other tetraisopropyl gem-oligophosphonates (11).
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20. Hampton (15) reported that treatment with (4a) failed to dealkylate two diethyl phosphonate-adenine nucleotide analogs. According to Ref. 16, dimethyl (4,6-di-O-acetyl-2,3,-didesoxy-β-D-erythro-hex-2-enopyranosyl)-phosphonate gave an unspecified yield of the corresponding bis(trimethylsilyl) ester when heated with 500 eq. of (4a) over a period of 200 hr. Good dealkylation yields from two different types of diethyl phosphonyl sugar derivatives apparently required prolonged heating (3-4 days at 70-75°) with a large excess (20-35 eq.) of (4a) ((17),(18)). Rosenthal and co-workers (19) reported only rare success in attempts to silylate alkyl phosphonolipids by the method of Ref. 14, although they did not mention whether this failure was due to insufficient reactivity of (4a) or to another cause such as a competing reaction (the desired bis(trimethylsilyl) lipid phosphonates were made via Arbuzov reactions between appropriate precursors and tris(trimethylsilyl phosphite); for a different application of the latter reagent see T. Haka, M. Sekine, and N. Kagawa, Chem. Lett., 635 (1975)).
21. Conveniently prepared by stirring hexamethyldisiloxane with PBr_3 overnight in the presence of an $FeCl_3$ catalyst, then distilling the product (22).
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24. For most scaled-up reactions, we recommend dropwise addition of (4b) to the stirred alkyl phosphonate under N_2, with provision for cooling.
25. The pronounced rate retardation seen with this compound is consistent with the development of some positive charge on phosphorous in the rate-determining step of the reaction, but of course does not prove the existence of a phosphonium intermediate.
26. ^{31}P resonances at chemical shifts spaced between those of the alkyl and trimethylsilyl phosphonate signals could be detected in spectra of some mixtures of (4b) with (2) (e.g., (2e)); this resonance, which grew in at an early stage of reaction and disappeared as product formation continued to completion, presumably was due to a mixed alkyl-trimethylsilyl phosphonate intermediate.
27. This communication presents a means to greatly facilitate the preparation of (3) from (2). The successful results reported here certainly do not preclude encounter of other limitations to the overall method imposed at the stage of either silylation or silyl ester hydrolysis, with particular alkyl phosphonate-phosphonic acid pairs.
28. Cf. Refs. 15-19, for example.