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Efficient and Selective Dealkylation of Phosphonate Diisopropyl Esters Using Me_3SiBr

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***Abstract:** Diisopropyl phosphonates, having a variety of functional groups in the molecule, can be dealkylated with complete chemoselectivity by Me_3Si Br in dioxane at 60 °C*

Phosphonic acid analogues of naturally occurring phosphates or of carboxylic acids continue to attract considerable interest as potential regulators, mediators, or inhibitors of metabolic processes.[1]

In synthetic studies directed towards various types of phosphonates in our laboratory[2] and in others[3] it was found that it is often advantageous to use triisopropyl phosphite (TIP, over Me and Et phosphites) because of higher yields and cleaner reactions. Yet the use of isopropyl groups is being avoided because of difficulties anticipated in the ester cleavage step.[4]

Mc Kenna[5] introduced Me_3SiBr as a general reagent for removal of methyl and ethyl esters of phosphorus. Recently, however Green[6] failed in the selective dealkylation of diethyl phosphonates using Me_3SiBr in a variety of solvents. On the other hand, Cook[7] reported that Me_3SiI caused peptide bond cleavage in the deprotection of ethyl phosphonate moiety. Lately, Otaka[8] described the difficulties in the selective deprotection of diethyl phosphonates.

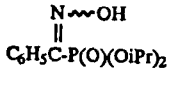
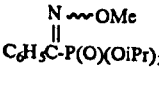
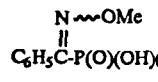
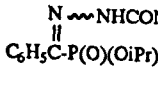
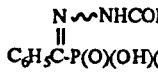
In this paper we wish to report that Me_3SiBr cleaves efficiently and chemoselectively isopropyl groups in diisopropyl phosphonates if used in excess in dioxane at 60 °C.[9] We established this by studying systematically a series of phosphonates containing a variety of functional groups. The results are summarized in the Table.[10]

The chemoselectivity of the Me_3SiBr was established clearly in the removal of the isopropyl esters of the acylphosphonate **4**, as well as in the oxime ether **6** and semicarbazone **7**. Complete chemoselectivity was obtained in the reaction with the triester **9** despite the temperature of the reaction, at which some carboxylate esters were reported to be cleaved.[5] Since the amide bond present in compound **10** also survived in these conditions, this method has important implications for phosphonopeptide chemistry.[6,8] In the case of the reactive phosphonothiolformate **8**, Me_3SiBr also showed complete selectivity as the C-S bond remained intact in the dealkylation process.[11]

In conclusion, the described method provides a convenient route for effective ester deprotection due to its ease of use, selectivity and high yields. It is likely to facilitate the utilization of diisopropyl protecting group in organophosphorus chemistry.

General Procedure: To a stirred solution of diisopropyl phosphonate (1 mmol) in dry dioxane[12] (5 mL) was added under N_2, Me_3SiBr (3 mmol) at room temperature. The solution was stirred at 60 °C for the required period of time (^{31}P NMR monitoring) and the solvent was evaporated to dryness under vacuum. A solution of NaOH (0.5 mmol) in methanol was added and the alcohol was removed under vacuum to give the corresponding monosodium salt in >97% purity (^{31}P and ^{1}H NMR).

Table. Dealkylation of Diisopropyl Phosphonates with Me_3SiBr

	Phosphonate	Conditions[a]	Product[b]	Yield(%)[c]
1	$(CH_2)_3CH_3$-P(O)(OiPr)$_2$	3eq. 60 °C, 4h	$(CH_2)_3CH_3$-P(O)(OH)(ONa)	92%
2	$C_6H_5CH_2$-P(O)(OiPr)$_2$	3eq. 60 °C, 4h	$C_6H_5CH_2$-P(O)(OH)(ONa)	88%
3	C_6H_5-P(O)(OiPr)$_2$	3eq. 60 °C, 14h	C_6H_5-P(O)(OH)(ONa)	96%
4	C_6H_5CO-P(O)(OiPr)$_2$	5eq.[13] 60 °C, 24h	C_6H_5CO-P(O)(OH)(ONa)	79%
5		3eq. 60 °C, 4h	Decomposition of the oxime	
6		3eq. 60 °C, 16h		91%
7		3eq. 60 °C, 20h		87%
8	$CH_3CH_2CH_2$-S-CO-P(O)(OiPr)$_2$	3eq. 60 °C, 16h	$CH_3CH_2CH_2$-S-CO-P(O)(OH)(ONa)	69%
9	EtOOC-CH_2-P(O)(OiPr)$_2$	3eq. 60 °C, 5h	EtOOC-CH_2-P(O)(ONa)	83%
10	$(Me)_2N$-$(CH_2)_3$-NHCO-P(O)(OiPr)$_2$	3eq. 60 °C, 16h	$(Me)_2N$-$(CH_2)_3$-NHCO-P(O)(OH)(ONa)	81%

a) The reactions were carried out in dioxane. b) All the products were isolated as monosodium salts. c) Isolated yields

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12. Similar results were observed when acetonitrile was used. Toluene, was unsuitable due to the insolubility of phosphonates **6** and **7**.
13. When 3 eq. of Me_3SiBr were used in the cleavage of phosphonate **4**, the reaction was incomplete after 48 h. as monitored by ^{31}P NMR.

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