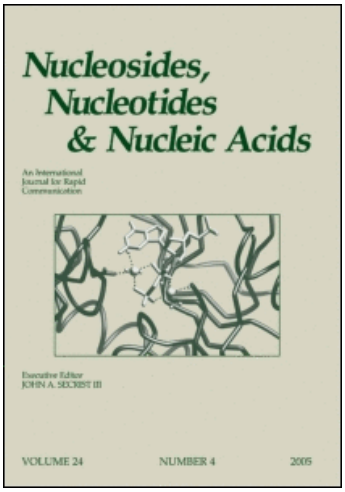

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DEALKYLATION OF PHOSPHONATE ESTERS WITH CHLOROTRIMETHYLSILANE

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ABSTRACT

Chlorotrimethylsilane completely dealkylates phosphonate esters at elevated temperature in a sealed reaction vessel. These conditions are tolerated by a variety of functional groups and lead to high conversions of dimethyl, diethyl and diisopropyl phosphonates to their corresponding phosphonic acids.

Phosphonic acids are generated from their dialkyl esters by reaction with conc. HCl or HBr, however the conditions are too harsh for many functional groups (1,2). Bromotrimethylsilane (TMSBr) selectively cleaves PO dialkyl esters yielding bis(trimethylsilyl) esters which are easily hydrolyzed with water under neutral conditions (3). In contrast, chlorotrimethylsilane (TMSCl) has been used mainly for deprotection of the more labile dimethyl phosphonates (4). For diethyl phosphonates, the low reactivity of TMSCl results in long reaction times and unsatisfactory yields (5). The rate of diester cleavage is accelerated by addition of sodium or lithium iodide (6). Here we report a procedure using TMSCl to completely dealkylate diethyl and diisopropyl phosphonates in high yield. The procedure is amenable to laboratory and industrial scale preparations.

To assess the ability of TMSCl to cleave dialkyl phosphonates, 1.0 M solutions of **1** in chlorobenzene were mixed with TMSCl in sealed glass pressure tubes and heated at temperatures ranging from 130–140°C (Fig. 1). As substitution to **2** progressed, modest increases in the internal pressure of the reaction vessels were observed due to the formation of volatile alkyl chloride. The pressure

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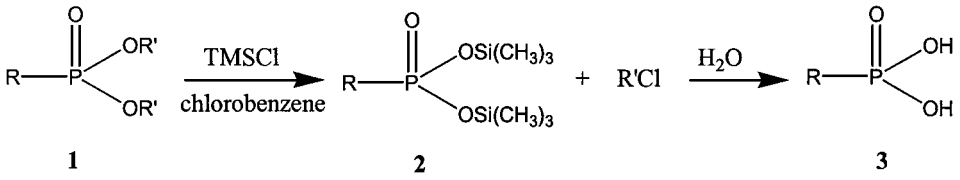

1 2 3

Figure 1. Cleavage of phosphonate diesters to phosphonic acids using TMSCl.

reached a maximum at reaction completion, then returned to atmospheric pressure on cooling back to room temperature. The conversions to phosphonic acids **3** were monitored by evaporating an aliquot of the reaction mixture, adding D_2O and observing the resulting formation of phosphonic acids **3** by ^1H and ^{31}P NMR (3) (Table 1).

Dialkyl phosphonates (**1a–g**) containing several functional groups were evaluated for ease of diester cleavage and compatibilty to the reaction conditions. Heating **1a–g** with TMSCl in chlorobenzene at 130–140°C, followed by hydrolysis, lead to complete conversions to phosphonic acids **3a–g** (Table 1). In most cases these deprotections went to completion in 8 to 12 hours. The high percent conversions to **3a–g** show that a variety of functional groups including carboxylic esters, ethers and alkenes are compatible with these conditions. Among the compounds evaluated, the more labile dimethyl phosphonate **1a** was the most easily deprotected by TMSCl in chlorobenzene. However, diethyl phosphonates **1b**, **1d–g** were also completely cleaved after slightly longer heating times and even the more hindered isopropyl ester groups of **1c** were removed if a greater excess of TMSCl was used. These rates of cleavage are consistent with their rates of cleavage by TMSBr (3). The heating time required for diester cleavage of diethyl phosphonates **1e** and **1f** with TMSCl in chlorobenzene was 10 h. By comparison, heating **1e** and **1f** with TMSCl, in the absence of solvent, afforded their phosphonic acids **3e** and **3f** after 4

Table 1. Cleavage of Dialkyl Phosphonates **1**[a] with Chlorotrimethylsilane in Chlorobenzene

Phosphonate **1**	R	R′	TMSCl (equiv.)	Temp. (°C)	Time (h)	% Conv.[b] **3**
1a	CH_3OOCCH_2	CH_3	3	130	8	98
1b	$C_2H_5OOCCH_2$	C_2H_5	4	140	18	98
1c	$C_2H_5OOCCH_2$	$(CH_3)_2CH$	6	140	36	98
1d	$C_6H_5OCCH_2$	C_2H_5	4	140	12	98
1e	$C_6H_5CH_2$	C_2H_5	4	140	10	99
1f	CH_2=CH	C_2H_5	4	140	10	98
1g	$CH_3OCH_2CH_2OCH_2$[c]	C_2H_5	4	140	8	>99

[a]For descriptions of R and R′, see Figure 1.
[b]Percent conversions of **1** to **3** were estimated by measuring their ^1H and ^{31}P NMR absorbances in D_2O.
[c]For preparation of this phosphonate see [7].

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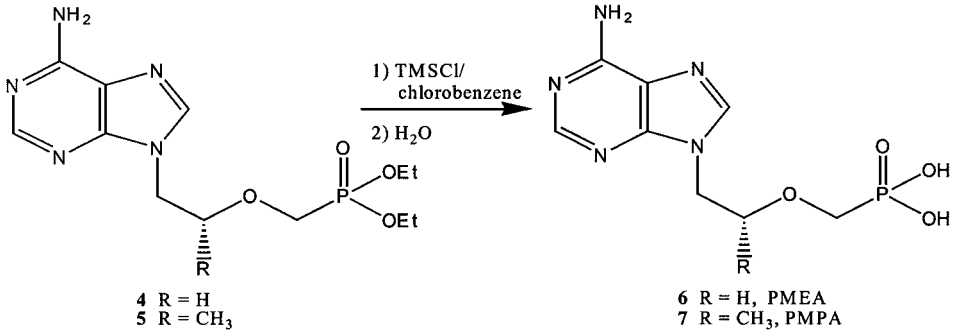

4 R = H
5 R = CH_3

6 R = H, PMEA
7 R = CH_3, PMPA

Figure 2. Preparation of PMEA and PMPA from their diethylesters using TMSCl.

and 5 days respectively (4). The deprotections with TMSCl also work well in DMF, acetonitrile, and dichloroethane. However the latter two solvents produce higher reaction vessel pressures.

The deprotection of dialkyl phosphonates using TMSCl is potentially very useful in the large scale synthesis of phosphonic acid derivatives as a replacement for TMSBr which is considerably more expensive and more difficult to handle. For instance, 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) **6** and (*R*)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA) **7** continue to attract widespread attention as broad spectrum antivirals including potent and selective activity against human immunodefficiency virus (8).

One reported synthesis of **6** and **7** utilizes TMSBr for cleavage to the phosphonic acids from the diethyl esters **4** and **5** (9). By comparison, the same deprotections were performed with TMSCl (10,11). (Fig. 2) affording **6** and **7** in equivalent yields and purities as those obtained with TMSBr. The process is amenable to large scale synthesis. Equivalent results were obtained for preparing **6** and **7** when the process was scaled to 5 kg in a 30 gal glass-lined Pfaudler reactor. The ease in which **4** and **5** are deprotected with TMSCl in chlorobenzene is in striking contrast to deprotection by heating with TMSCl in the absence of solvent, which is not effective in deprotecting adenosine diethyl phosphonates (12).

In summary, TMSCl in chlorobenzene readily cleaves dialkyl phosphonates in high yield in the presence of a wide variety of functional groups. These conditions also efficiently cleave the ethyl ester groups of adenine containing diethylphosphonates. TMSCl should be a useful and economical reagent for laboratory and industrial scale preparation of phosphonic acid derivatives.

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