Selective Demethylation of Mixed Alkyl Methyl Phosphates

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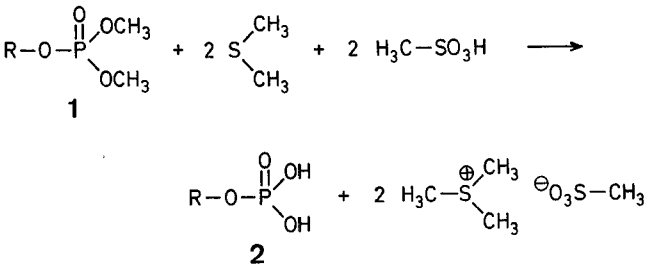
The C—O bond in alcohols, ethers, carboxylic esters, and lactones can in many cases be easily cleaved by treatment with sulfides or thiols in the presence of Brønsted or Lewis acid catalysts[1,2,3]. Application of this method to the cleavage of methyl phosphates might provide a useful tool in the field of blocking and deblocking of phosphate groups[4-7]. Deblocking of such groups is usually effected with nucleophiles, bases, or red-ox reagents. Only *t*-butyl esters are cleaved under non-aqueous acidic conditions[8,9].

Mixed alkyl methyl phosphates are readily available by three main routes:

- reaction of a methyl phosphate derivative such as dimethyl phosphorochloridate with an alcohol[4-7] or of dimethyl potassium phosphate with an alkyldiphenylsulfonium salt[10];
- methylation of hydrogen phosphates with diazomethane[4-7];
- oxidation of the corresponding phosphite[5,6,7,11-14].

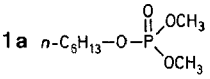
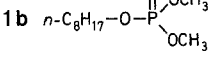
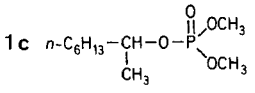
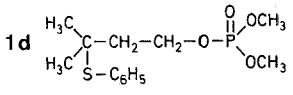
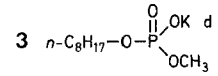
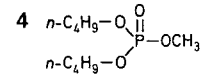
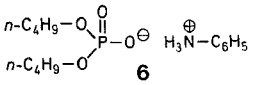
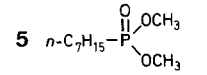
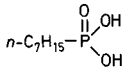
Non-hydrolytic deblocking of methyl phosphate groups is usually carried out with amines[15,16], thiourea[17], thiolates[18], or nucleophilic inorganic reagents such as potassium cyanide[18] or iodide[6,19]. Under the usual conditions, these techniques cleave only one methyl group. In order to cleave a second methyl group present in the phosphoric ester moiety it is necessary to reprotect the just unprotected hydroxy group; this is usually done by silylation[20].

In the course of other work, we observed that methyl phosphates such as, for example, alkyl dimethyl phosphates **(1)** are demethylated upon treatment with dimethyl sulfide in the presence of methanesulfonic acid, i.e., under the conditions used for converting an alkene into a sulfonium salt.



We have investigated a number of representative cases (including the mixed dialkyl potassium phosphate **3**, the dialkyl methyl phosphate **4**, and also the dimethyl alkanephosphonate **5**) in order to delineate the scope of this method (Table 1).

Table 1. Demethylation of Mixed Alkyl Methyl Phosphates **(1, 3, 4)** and of Dimethyl Heptanephosphonate **(5)** using Dimethyl Sulfide (2.5 equiv) and Methanesulfonic Acid (10 equiv)

Substrate	Product	Reaction conditions		Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c] or m.p. [°C] reported
		Scale [mmol]	Time [h]			
1a 	**2a** · $H_2N-C_6H_5$	10	22	82 (93)	133-134°	$C_{12}H_{22}NO_4P$
		5	7	(88)	(ethanol)	(275.3)
		5	12	(93)		
		5	48	(98)		
		5	19	65		
1b 	**2b** · $H_2N-C_6H_5$	10	92	83	135-137°	129-130°[22]
		10	52[e]	83	(acetone)	(ethanol)
		5	19	68		
1c 	**2c** · $H_2N-C_6H_5$	10	92	79	154°	$C_{14}H_{26}NO_4P$
					(ethanol)	(303.3)
1d 	**2d** · $H_2N-C_6H_5$	5	20	(90)	131-132°	$C_{17}H_{24}NO_4PS$
					(acetone)	(369.4)
3  [d]	**2b** · $H_2N-C_6H_5$	10	18	68	137-139°	
					(acetone)	
4 	 **6**	10	18	70	65-67°	67-68°[23]
					(pentane)	
5 	 **7**	5	20	53	104-105°	103-103.5°[24]
		10	54	66	(hexane)	

[a] Yield of crystalline product before recrystallization. Yields in parentheses were determined by ^{1}H-N.M.R. spectrometry.
[b] m.p. of recrystallized product.
[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.32; H, ±0.09; N, ±0.35; P, ±0.18; S, ±0.09.
[d] Prepared from octyl dimethyl phosphate by demethylation with potassium benzenethiolate[18].
[e] Experiment with ethanethiol instead of dimethyl sulfide.

Table 2. Spectral Data of the Demethylation Products obtained

Product	I.R. (KBr)[a] ν [cm^{-1}]	^{1}H-N.M.R. (TMS$_{int}$)[b] δ [ppm]	^{13}C-N.M.R. (TMS$_{int}$)[c] δ [ppm]	^{31}P-N.M.R. (H_3PO_{4ext})[d] δ [ppm]
2a · $H_2N—C_6H_5$	1225 (P=O)	(DMSO-d_6): 0.88 (complex t, 3H); 1.2–1.4 (m, 6H); 1.6–1.75 (m, 2H); 3.83 (dt, 2H, $J_{HH}=J_{HP}=7$ Hz); 6.2 (s); 6.65–7.2 (m, 5H)	(DMSO-d_6): 14.0; 22.2; 24.9; 30.0 (d, $J=7.3$ Hz); 31.0; 65.0 (d, $J=5.1$ Hz); 115.3; 117.6; 128.6; 145.3	(DMSO-d_6): −1.1
2b · $H_2N—C_6H_5$	1225 (P=O)	(CD_3OD): 0.90 (complex t, 3H); 1.2–1.45 (m, 10H); 1.5–1.7 (m, 2H); 3.89 (dt, 2H, $J_{HH}=J_{HP}=7$ Hz); 5.2 (s); 7.25–7.5 (m, 5H)	(DMSO-d_6): 14.1; 22.3; 25.4; 28.9; 30.2 (d, $J=7.3$ Hz); 31.4; 64.9 (d, $J=5.1$ Hz); 116.2; 118.7; 128.7; 144.0	(CD_3OD): 0.4
2c · $H_2N—C_6H_5$	1225 (P=O)	(CD_3OD): 0.90 (complex t, 3H); 1.2–1.65 (m, 13H); 1.27 (d, 6H, $J=6$ Hz); 4.33 (m, 1H); 5.0 (s); 7.05–7.4 (m, 5H)	(DMSO-d_6): 14.0; 21.6; 22.2; 24.7; 28.7; 31.3; 37.3 (d, $J=6.6$ Hz); 72.2 (d, $J=5.1$ Hz); 115.0; 117.2; 128.5; 145.8	(CD_3OD): −0.4
2d · $H_2N—C_6H_5$	1225 (P=O)	(CD_3OD): 1.25 (s, 6H); 1.82 (t, 2H, 7.5 Hz); 4.18 (dt, 2H, $J_{HH}=7.5$ Hz, $J_{HP}=7$ Hz); 5.2 (s); 7.25–7.6 (m, 10H)	(CD_3OD): 27.6; 41.1 (d, $J=7.3$ Hz); 46.4; 61.8 (d, $J=5.1$ Hz); 119.6; 124.2; 127.2; 127.6; 128.3; 130.7; 136.2	(CD_3OD): −0.2
6	1190 (P=O)	($CDCl_3$): 0.85 (t, 6H, $J=7.5$ Hz); 1.28 (tq, 4H, $J=7.5$ Hz); 1.50 (tt, 4H, $J=7$ Hz); 3.82 (dt, 4H, $J_{HH}=J_{Hp}=7$ Hz); 7.1–7.6 (m, 8H)	($CDCl_3$): 13.7; 18.8; 32.5 (d, $J=8.1$ Hz); 65.4 (d, $J=5.9$ Hz); 122.3; 126.0; 128.8; 134.2	(CD_3OD): 0.1
7	1010[e] [P—O(—H)]	($CDCl_3$): 0.89 (complex t, 3H); 1.2–1.45 (m, 8H); 1.5–1.85 (m, 4H); 9.2 (2H)	($CDCl_3$): 14.2; 22.2; 22.4; 22.8; 28.9; 30.6 (d, $J=16.9$ Hz); 31.7	($CDCl_3$): 36.2

[a] Recorded on a Perkin-Elmer 597 spectrometer.
[b] At 250 MHz in FT mode using a Cameca-Oxford Instrument spectrometer.
[c] At 22.63 MHz in FT mode using a Bruker WH-90 spectrometer.
[d] At 36.4 MHz in FT mode using a Bruker WH-90 spectrometer; positive shift values for low-field signals.
[e] In agreement with Ref.[25].

In the absence of a sulfide, trimethyl phosphate is stable in trifluoromethanesulfonic acid[21]. Likewise no reaction occurs upon refluxing a mixture of dimethyl sulfide and 1-octyl dimethyl phosphate overnight. Ethanethiol may be used in place of dimethyl sulfide in the demethylation reaction, the yields of alkyl dihydrogen phosphate **(2)** being similar. According to ^{1}H-N.M.R. data it appears that the cleavage rates of the first and the second methyl group of **1** are roughly equal.

It is remarkable that by varying the reaction conditions an alkyl group can be transferred from a sulfonium salt to a potassium phosphate group[10], and a methyl group can be transferred from a methyl phosphate to a thioether.

Octyl Dihydrogen Phosphate (2b) Aniline Salt from Dimethyl Octyl Phosphate (1b); Typical Procedure:

To methanesulfonic acid (4.55 ml, 70 mmol) cooled in an ice bath, dimethyl sulfide (1.8 ml, 25 mmol) and then dimethyl octyl phosphate (**1b**; 2.38 g, 10 mmol) are added under argon, and the mixture is stirred at room temperature overnight. It is then diluted with ether (100 ml), washed with water (2 × 15 ml), and dried with magnesium sulfate. Aniline (0.91 ml, 10 mmol) is added, the resultant precipitate is isolated by suction, washed with ether, dried in vacuum over phosphorus pentoxide; yield: 2.53 g (83%); m.p. 130–132 °C. For purification, the product is recrystallized from ethanol; yield: 2.12 g (70%); m.p. 135–137 °C.

Generous support by the C.N.R.S. (L.A. 32) is gratefully acknowledged.

Received: November 29, 1982

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F. Babudri, L. Di Nunno, S. Florio, *Synthesis* **1983** (3), 230–231:

The title compounds **5** and **7** should be named (*Z*)-2-alkylidene-4-methyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazines; compound **10** as 11-methyl-3-(2-methylaminophenylthio)-2-oxo-4,5-diphenyl-2,5-dihydro-11*H*-oxepino[3,2-*b*][1,4]benzothiazine.

Y. Kurasawa, Y. Moritaki, A. Takada, *Synthesis* **1983** (3), 238–240:

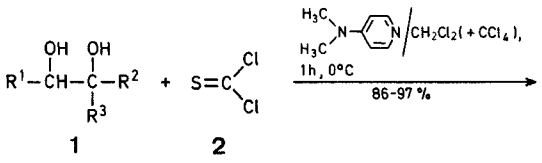
The title compounds **6** and **7** should be named 3-(1-ethoxyalkylidenehydrazinocarbonylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines and 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines, respectively.

Abstract **6589**, *Synthesis* **1983** (3), 247:

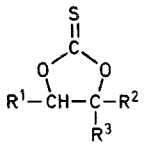
The title should be *N*-(1-Aroyloxyalkyl)-pyridinium and *P*-(1-Aroyloxyalkyl)-phosphonium Salts.

Abstract **6593**, *Synthesis* **1983** (4), 335:

The formula scheme **1** + **2** ⟶ **3** should be:



1 **2**



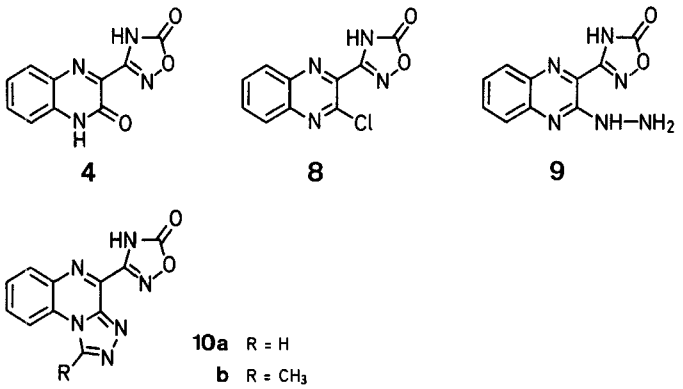
3

Y. Otsuji, S. Nakanishi, N. Ohmura, K. Mizuno, *Synthesis* **1983** (5), 390:

The substituents for compound **2g** (Table) should be R=H, X=H, n=1.

Y. Kurasawa, M. Ichikawa, A. Sakakura, A. Takada, *Synthesis* **1983** (5), 399–400:

The structures of products **4, 8, 9,** and **10** given have since been found to be erroneous, the corrected structures are given below. A revision will be published in *Chem. Pharm. Bull.* in 1984.

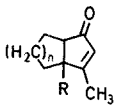


4 **8** **9**

10a R = H
b R = CH_3

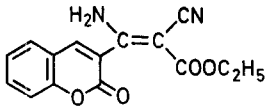
C. Santelli-Rouvier, M. Santelli, *Synthesis* **1983** (6), 429–442:

The structure of the third product in Table 4 (p. 435) should be:



S. M. Fahmy, R. M. Mohareb, *Synthesis* **1983** (6), 478–480:

The structure of product **5** should be:



L. Jacob, M. Julia, B. Pfeiffer, C. Rolando, *Synthesis* **1983** (6), 451–452:

The first three entries in Table 1 (p. 451) should be as follows:

Table 1. Demethylation of Mixed Alkyl Methyl Phosphates **(1, 3, 4)** and of Dimethyl Heptanephosphonate **(5)** using Dimethyl Sulfide (2.5 equiv) and Methanesulfonic Acid (10 equiv)

Substrate	Product	Reaction conditions		Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c] or m.p. [°C] reported
		Scale [mmol]	Time [h]			
1a $n\text{-}C_6H_{13}\text{-}O\text{-}P(=O)(OCH_3)_2$	**2a** · $H_2N\text{-}C_6H_5$	10	22	82 (93)	133–134° (ethanol)	$C_{12}H_{22}NO_4P$ (275.3)
1b $n\text{-}C_8H_{17}\text{-}O\text{-}P(=O)(OCH_3)_2$	**2b** · $H_2N\text{-}C_6H_5$	5	7	(88)	135–137° (acetone)	129–130°[22] (ethanol)
		5	12	(93)		
		5	48	(98)		
		5	19	65		
		10	92	83		
		10	52[c]	83		
1c $n\text{-}C_6H_{13}\text{-}CH(CH_3)\text{-}O\text{-}P(=O)(OCH_3)_2$	**2c** · $H_2N\text{-}C_6H_5$	5	19	68	154° (ethanol)	$C_{14}H_{26}NO_4P$ (303.3)
		10	92	79		