Tetra-*n*-butylaminium Di-*t*-butyl Phosphate. A New, Effective Phosphorylating Agent for Alkyl Bromides[1]

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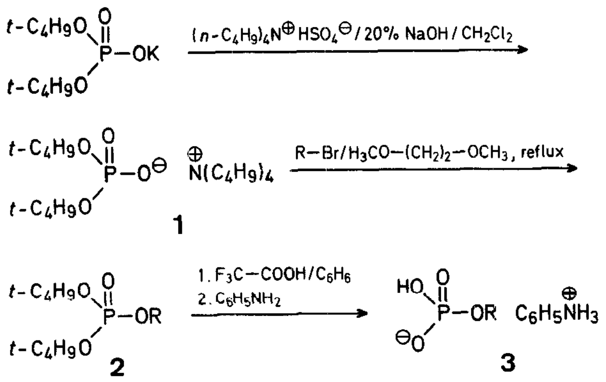
Some years ago a simple phosphorylation method for alkyl halides was devised in our laboratory. It is based on the direct nucleophilic displacement of halogen by di-*t*-butyl phosphate anion followed by subsequent deprotection of the intermediately formed alkyl di-*t*-butyl phosphate under mild acidic conditions[2].

In our opinion the method suffers from several substantial drawbacks and is relatively inconvenient, especially for large scale preparations:

- synthesis of the tetramethylaminium di-*t*-butyl phosphate used as a nucleophile is cumbersome, laborious, and relatively expensive;
- the reagent itself is strongly hygroscopic; it demands prolonged drying in vacuo over phosphorus pentoxide and is not very easy to handle;
- some less reactive halides, i.e. isobutyl and *sec*-butyl bromide, cannot be phosphorylated in high yields.

We have now found that tetra-*n*-butylaminium di-*t*-butyl phosphate (**1**) is a much superior reagent for the preparation of various monoalkyl phosphates, even on a large scale. It is readily available in almost quantitative yield (96%) from the reaction between potassium di-*t*-butyl phosphate[2] and tetra-*n*-butylaminium hydrogen sulfate. The ion exchange can be readily accomplished by the ion-pair extraction technique[3] using 20% aqueous sodium hydroxide and dichloromethane as extracting solvents.



Tetra-*n*-butylaminium di-*t*-butyl phosphate (**1**) is a colorless, crystalline non-hygroscopic solid, which can be stored for indefinite time at room temperature. When kept in an open vessel it is slowly transformed into the monohydrate (m.p. 73–75°) from which an anhydrous salt (m.p. 108–110°) can be easily recovered upon drying in vacuo over phosphorus pentoxide. When anhydrous **1** is heated under reflux for 3 h with an alkyl bromide in dimethoxyethane it gives rise to the corresponding alkyl di-*t*-butyl phosphate (**2**) which, upon treatment with trifluoroacetic acid in benzene, is converted into monoalkyl phosphate isolated and characterized as the stable, crystalline anilinium salt (**3**).

Yields, physical constants and spectroscopic data for alkyl di-*t*-butyl phosphates (**2**) and anilinium monoalkyl phosphates (**3**) are compiled in the Tables. Phosphorylation of alkyl bromides by means of **1** is in our opinion easier and more efficient in comparison to the previously reported procedure[2].

Tetra-*n*-butylaminium Di-*t*-butyl Phosphate (1):
20% Aqueous sodium hydroxide solution (12.5 ml) is added dropwise at 20° with stirring and external cooling to a solution of tetra-*n*-butylaminium hydrogen sulfate (17.0 g, 0.05 mol) in water (10 ml). A solution of potassium di-*t*-butyl phosphate[2] (12.4 g, 0.05 mol) in water (6 ml) is then added dropwise at 20°. Stirring

Table 1. Preparation of Alkyl Di-*t*-butyl Phosphates (**2**) and Anilinium Monoalkyl Phosphates (**3**)

Product No.	R	Yield [%]	n_D^{20} or m.p.	Molecular formula[a, b]
2a	*n*-C_3H_7	88	1.4214	$C_{11}H_{25}O_4P$ (252.3)
2b	*i*-C_3H_7	80	1.4150	$C_{11}H_{25}O_4P$ (252.3)
2c	*n*-C_4H_9	78	1.4210	$C_{12}H_{27}O_4P$ (266.3)
2d	*i*-C_4H_9	75	1.4180	$C_{12}H_{27}O_4P$ (266.3)
2e	*sec*-C_4H_9	60	1.4218	$C_{12}H_{27}O_4P$ (266.3)
2f	$H_2C{=}CH{-}CH_2$	80	1.4244	$C_{11}H_{23}O_4P$ (250.3)
3a	*i*-C_3H_7	62 (51)[c]	177–178°	$C_9H_{16}NO_4P$ (233.2)
3b	*n*-C_4H_9	76 (65)	147–148°	$C_{10}H_{18}NO_4P$ (247.2)
3c	*i*-C_4H_9	69 (41)	158–160°	$C_{10}H_{18}NO_4P$ (247.2)
3d	*sec*-C_4H_9	50 (36)	164–165°	$C_{10}H_{18}NO_4P$ (247.2)
3e	2-pentyl	46 (—)	155–156°	$C_{11}H_{20}NO_4P$ (261.3)

[a] All new compounds (**2a–f** and **3e**) have been satisfactorily analysed (C ±0.4%, H ±0.2%, P ±0.3%).

[b] Esters **2** were not distilled. Anilinium salts **3** were crystallized from anhydrous ethanol.

[c] Based on tetra-*n*-butylaminium di-*t*-butyl phosphate (**1**). The results obtained with tetramethylaminium di-*t*-butyl phosphate[2] are given in parentheses.

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is continued for 30 min at room temperature and the resultant mixture is extracted with dichloromethane (4 × 25 ml). The combined extracts are dried over anhydrous potassium carbonate and evaporated in vacuo to give the *tetra*-n-*butylaminium di*-t-*butyl phosphate* (**1**) as colorless, crystalline solid; yield: 21.7 g (96 %); m.p. 108–110°.

$C_{24}H_{54}NO_4P$	calc.	C 63.82	H 12.05	N 3.10	P 6.86
(451.7)	found	63.2	11.95	3.2	6.6

I.R. (KBr): $\nu_{max} = 1380, 1360$ (t-C_4H_9); 1210, 1075 ($PO_2^{\ominus}$); 965 cm^{-1} [P—O—(C)].

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.98$ (dist. t, 12 H, $J_{HH} = 6.5$ Hz), 1.40 (s, 18 H), 1.20–1.92 (m, 16 H), 3.25–3.61 ppm (8 H).

Phosphorylation of Alkyl Bromides; General Procedure:

A mixture of tetra-*n*-butylaminium di-*t*-butyl phosphate (**1**; 9.0 g, 0.02 mol), the corresponding alkyl bromide (0.022 mol), and dimethoxyethane (50 ml) is heated under reflux with stirring for 3 h and then cooled to room temperature. The precipitated tetra-*n*-butylaminium bromide is filtered off and washed with petroleum ether (20 ml). The filtrate is diluted with petroleum ether (30 ml) and the resultant solution washed with 20 % aqueous potassium carbonate (5 ml). The organic layer is dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue is kept at 35–40°/2 torr for 30 min in order to remove traces of solvent. The crude alkyl di-*t*-butyl phosphates (**2**) thus obtained as colorless mobile liquids are analytically pure. Their deprotection to monoalkyl phosphates, isolated and characterized as anilinium salts (**3**) is readily carried out according to the previously described procedure[2].

Table 2. Spectroscopic Data for Alkyl Di-*t*-butyl Phosphates (**2**)

Product No.	I.R.[a] ν_{max} [cm^{-1}]	^{1}H-N.M.R.[b], δ [ppm][c]
2a	1395, 1370, 1265, 1175, 1045, 1000	0.96 (t, 3 H, $J_{HH} = 7.5$ Hz); 1.42 (s, 18 H); 1.57 (sex, 2 H, $J_{HH} = 7.5$ Hz); 3.82 (q, 2 H, $J_{HH} \approx {}^3J_{PH} \approx 6.5$ Hz).
2b	1390, 1370, 1265, 1170, 1040, 995	1.25 (d, 6 H, $J_{HH} = 6.0$ Hz); 1.44 (s, 18 H); 4.53 (d sep, 1 H, $J_{HH} = 6.0$ Hz, $^3J_{PH} = 7.5$ Hz).
2c	1395, 1375, 1265, 1170, 1045, 1005	0.94 (dist. t, 3 H, $J_{HH} \approx 7.0$ Hz); 1.42 (s, 18 H); 1.17–1.74 (m, 4 H); 3.87 (q, 2 H, $J_{HH} \approx {}^3J_{HH} \approx 6.5$ Hz).
2d	1395, 1375, 1270, 1175, 1045, 1000	0.97 (d, 6 H, $J_{HH} = 6.5$ Hz); 1.45 (s, 18 H); 1.82 (9 lines, 1 H, $J_{HH} \approx 6.5$ Hz); 3.62 (t, 2 H, $J_{HH} \approx {}^3J_{PH} \approx 6.5$ Hz)
2e	1395, 1375, 1265, 1175, 1045, 1000	0.94 (dist. t, 3 H, $J_{HH} \approx 6.5$ Hz); 1.26 (d, 2 H, $J_{HH} = 6.0$ Hz); 1.44 (s, 18 H); 1.22–1.80 (m, 2 H); 4.27 (d sex, 1 H, $J_{HH} = 6.5$ Hz, $^3J_{PH} = 8.0$ Hz).
2f	1395, 1375, 1265, 1170, 1045, 1000	1.43 (s, 18 H); $ABXY_2$ system[d]: $\delta_y = 4.40$ (12 lines, 2 H), $\delta_{AB} = 5.26$ (8 lines, 2 H, $\delta_x = 5.92$ (12 lines, 1 H), $J_{AX} = 10.0$ Hz, $J_{BX} = 17.4$ Hz, $J_{AB} = 21.1$ Hz, $J_{XY} = 4.8$ Hz, $^3J_{PHY} = 7.5$ Hz.

[a] The I.R. spectra were recorded on a Specord 71 IR (C. Zeiss) spectrophotometer for liquid films. The strongest and most typical absorption bands are only given.

[b] The ^{1}H-N.M.R. spectra were measured for CCl_4 solutions at 80 MHz with a Tesla BS 487C spectrometer using TMS as internal standard.

[c] Abbreviations used: s, singlet; d, doublet; t, triplet, q, quartet; sex, sextet; dist. t., distorted triplet; d sex, double sextet; d sep, double septet; m, multiplet.

[d] First order treatment was applied.

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