N-Alkylation of Diethyl *N*-Alkylphosphoramidates in an Anhydrous Medium

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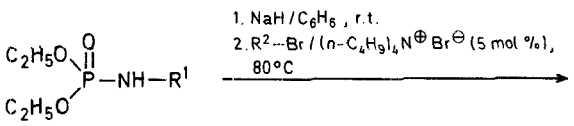
Diethyl *N*-alkylphosphoramidates **1** can be conveniently and economically prepared in quantitative yields from the corresponding primary amines by phosphorylation with diethyl phosphite/tetrachloromethane in the presence of potassium hydrogen carbonate/potassium carbonate and tetrabutylammonium bromide as catalyst[1]. An alternative approach to **1**, involving nucleophilic displacement of bromine by diethyl *N*-(trimethylsilyl)-phosphoramidate anion followed by desilylation, is restricted to monofunctional primary alkyl bromides[2].

Some years ago, it was demonstrated that diethyl *N*-alkylphosphoramidates **1** can be readily alkylated at the nitrogen atom under the conditions of phase-transfer catalysis to give the corresponding diethyl *N*,*N*-dialkylphosphoramidates **2**, which can be considered as diethoxyphosphoryl-protected derivatives of secondary amines[3]. Effective *N*-alkylation of **1** followed by easy deprotection of **2** offers a convenient access to secondary amines in which two different alkyl groups are linked to nitrogen[3]. The main limitation of the reported alkylation procedure evidently stems from the drastic reaction conditions, i.e. strongly alkaline medium (50% aqueous sodium hydroxide), high temperature, and prolonged reaction time. Such treatment is totally unsuitable for any alkali-labile starting materials which distinctly limits the preparative applicability of the method.

In a search for a more general and versatile approach to the problem, we have recently found that *N*-alkylation of diethyl *N*-alkylphosphoramidates **1** can be readily accomplished in boiling benzene after their deprotonation under anhydrous conditions by means of sodium hydride. Sodium salts of **1** are formed rapidly at room temperature and, in the majority of cases, are easily soluble in benzene. Contrary to our expectations, however, they are rather poor nucleophiles and react with alkyl bromides only sluggishly. The use of a relatively large excess of an alkylating agent does not lead to complete alkylation and the product formed is always contaminated with considerable amounts (up to 20%) of unreacted **1**.



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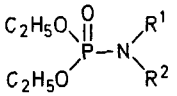

2

However, the nucleophilic reactivity of sodium diethyl *N*-alkylphosphoramidates can be drastically increased by adding catalytic amounts (5 mol%) of tetrabutylammonium bromide to the reaction mixture. A similar observation was previously reported for the alkylation of the *N*-sodio derivative of diethyl *N*-(trimethylsilyl)-phosphoramidate but its nature is not quite clear as yet.

In the presence of this catalyst, the alkylation of **1** proceeds smoothly in boiling benzene and the reaction is completed after 2 h. The scope of the reaction is confined to primary alkyl halides. According to ^{31}P-N.M.R. measurements, the crude diethyl *N*,*N*-dialkylphosphoramidates **2** are not contaminated with any unreacted starting materials **1**. After removal of volatile impurities in vacuo, the products **2** are analytically pure and need no further purification. Their yields and physical constants are compiled in Table 1. All com-

Table 1. Diethyl *N*,*N*-Dialkylphosphoramidates **2** prepared

Product No.	R^1	R^2	Excess of R^2-Br [mol %]	Yield[a] [%]	n_D^{25}	Molecular formula[b]
2a	*n*-C_4H_9	$-CH_2-COOC_2H_5$	10	90	1.4343	$C_{12}H_{26}NO_5P$ (295.3)
2b	*n*-C_4H_9	*n*-C_3H_7	50	78	1.4287	$C_{11}H_{26}NO_3P$ (251.3)
2c	*n*-C_3H_7	$-CH_2-CH=CH_2$	25	86	1.4346	$C_{10}H_{22}NO_3P$ (235.3)
2d	*n*-C_3H_7	$-CH_2-C\equiv CH$	25	88	1.4410	$C_{10}H_{20}NO_3P$ (233.2)
2e	$C_6H_5-CH_2$	C_2H_5	50	79	1.4833	$C_{13}H_{22}NO_3P$ (271.3)
2f	$C_6H_5-CH_2$	$-CH_2-COOC_2H_5$	10	88	1.4758	$C_{15}H_{24}NO_5P$ (329.3)
2g	$C_6H_5-CH_2$	$-CH_2-C\equiv CH$	25	78	1.4942	$C_{14}H_{20}NO_3P$ (281.3)
2h	C_6H_5	$-CH_2-COOC_2H_5$	10	86	1.4914	$C_{14}H_{22}NO_5P$ (315.3)
2i	*c*-C_6H_{11}	*n*-C_4H_9	10	62	1.4527	$C_{14}H_{30}NO_3P$ (291.4)

[a] Yield of analytically pure products.

[b] Satisfactory microanalysis obtained: C ±0.35, H ±0.20, N ±0.23, P ±0.34.

Table 2. Spectral Data of Compounds **2**

Product	I.R. (film)[a] ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/$TMS_{int.}$) δ [ppm]	^{31}P-N.M.R. (neat/85% $H_3PO_{4\,ext.}$)[b] δ [ppm]
2a	2990, 1750 (C=O), 1440, 1365, 1250 (P=O), 1180, 1030, 960, 790		9.1
2b	2900, 1680, 1540, 1460, 1385, 1245 (P=O), 1163, 1040, 960, 790		10.2
2c	2920, 1635, 1440, 1385, 1365, 1250 (P=O), 1160, 1030, 960, 810, 795	0.90 (t, 3H, J_{HH} = 7.25 Hz); 1.22 (t, 6H, J_{HH} = 7.0 Hz); 1.40 (sex., 2H, J_{HH} = 7.0 Hz); 2.65–3.15 (m, 2H); 3.55 (dd, 2H, J_{HH} = 6.0 Hz, J_{PH} = 11.0 Hz); 3.92 (qt, 4H, $J_{HH} \approx {}^3J_{PH} \approx$ 7.0 Hz); 4.92–6.17 (m, 3H)	9.8
2d	3200 (≡C—H), 2960, 1680, 1445, 1390, 1365, 1250 (P=O), 1145, 1050, 1030, 965, 815, 795		9.0
2e	2975, 1490, 1450, 1380, 1245 (P=O), 1135, 1030, 955, 780, 745, 700	1.00 (t, 3H, J_{HH} = 7.25 Hz); 1.23 (t, 6H, J_{HH} = 7.0 Hz); 2.87 (dq, 2H, J_{HH} = 7.0 Hz, $^3J_{PH}$ = 12.0 Hz); 3.93 (qt, 4H, $J_{HH} \approx {}^3J_{PH} \approx$ 7.0 Hz); 4.05 (d, 2H, $^3J_{PH}$ = 9.5 Hz); 7.0–7.5 (m, 5H)	10.05
2f	2970, 2930, 1750, 1740 (C=O), 1445, 1365, 1250 (P=O), 1200, 1160, 1030, 950, 815, 735, 695		8.8
2g	3210 (≡C—H), 2970, 2910, 1490, 1475, 1450, 1440, 1390, 1370, 1245 (P=O), 1140, 1040, 950, 815, 790, 695	1.25 (t, 6H, J_{HH} = 7.0 Hz); 2.67 (t, 1H, J_{HH} = 2.5 Hz); 3.55 (dd, 2H, J_{HH} = 2.5 Hz, $^3J_{PH}$ = 11.0 Hz); 3.98 (qt, 4H, $J_{HH} \approx {}^3J_{PH} \approx$ 7.0 Hz); 4.23 (d, 2H, $^3J_{PH}$ = 8.5 Hz); 7.0–7.4 (m, 5H)	8.6
2h	2970, 2920, 1755 (C=O), 1595, 1495, 1445, 1390, 1370, 1320, 1250 (P=O), 1140, 1050, 965, 890, 795, 750, 695	1.18 (t, 9H, J_{HH} = 7.0 Hz); 4.05 (qt, 4H, $J_{HH} \approx {}^3J_{PH} \approx$ 7.0 Hz); 4.10 (q, 2H, J_{HH} = 7.0 Hz); 4.27 (d, 2H, $^3J_{PH}$ = 6.0 Hz); 6.8–7.4 (m, 5H)	9.0
2i	2920, 1450, 1390, 1255 (P=O), 1165, 1040, 960, 895, 855, 825, 790, 745, 725		9.7

[a] C. Zeiss Specord 71 IR Spectrometer.

[b] Bruker HFX 90 Spectrometer at 36.43 MHz.

pounds reported give I. R. spectra (see Table 2) fully compatible with the anticipated structures; some selected ^{1}H-N.M.R. data are also given.

The devised procedure broadens the spectrum of secondary amines which can be prepared by an alkylative route using diethoxyphosphoryl group for protection of the amino function[1].

Diethyl *N*,*N*-Dialkylphosphoramidates 2; General Procedure:
A solution of diethyl *N*-alkylphosphoramidate **1** (0.02 mol) in benzene (20 ml) is added dropwise with stirring to a suspension of sodium hydride (0.53 g, 0.022 mol; freshly separated from paraffin oil by washing with hexane) in benzene (15 ml) during 15 min at 15–20 °C. After evolution of hydrogen has ceased, the alkyl bromide (for amount, see Table 1) and tetrabutylammonium bromide (0.32 g, 0.001 mol) are added and the mixture is refluxed with stirring for 2 h. The resultant mixture is cooled to room temperature, diluted with benzene (50 ml), and treated with water (10 ml) to dissolve sodium bromide. The organic phase is separated, washed with water (3 × 20 ml), dried with magnesium sulfate, evaporated, and kept at 50–60 °C/0.5 torr for 1 h to give the analytically pure phosphoramide **2**.

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[1] A. Zwierzak, K. Osowska-Pacewicka, *Synthesis* **1984**, 223.
[2] A. Zwierzak, *Synthesis* **1982**, 920.
[3] A. Zwierzak, J. Brylikowska-Piotrowicz, *Angew. Chem.* **89**, 109 (1977); *Angew. Chem. Int. Ed. Engl.* **16**, 107 (1977).