Selective *N*-Alkylation of Diethyl Phosphoramidate: Tetrabutylaminium Bromide as Catalyst for Nucleophilic Substitution in a Homogeneous Medium

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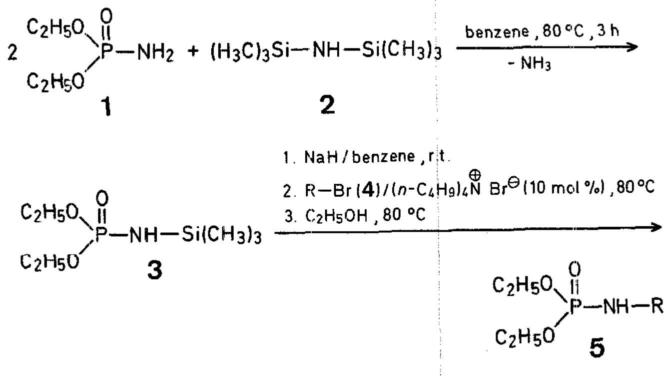
Diethyl *N*-alkylphosphoramidates can serve as useful starting materials for the preparation of secondary amines by phase-transfer catalysed *N*-alkylation followed by acidolytic removal of diethylphosphoryl group[1]. Despite of the (documented) possibility of selective phase-transfer catalysed *N*-alkylation of carboxamides[2] as well as diphenylphosphinamide[3], diethyl phosphoramidate (**1**) cannot be transformed into its monoalkyl derivatives by these or similar procedures. Conventional monoalkylation of **1** by reaction with stoichiometric amounts of sodium hydride and the corresponding alkyl halide in boiling benzene also meets with little success. Alkylation is not selective even when an equimolar amount of the halide is slowly added to the sodium salt of **1**. Mixtures containing considerable amounts of *N,N*-dialkyl derivatives are always obtained upon transmetallation and subsequent alkylation of primarily formed diethyl *N*-alkylphosphoramidates (**5**). For highly reactive halides (**4**), i.e., benzyl chloride or allyl bromide, practically no selectivity is observed and the respective monoalkyl and dialkyl derivatives are produced in almost equal amounts.

The recently devised approach involves *N*-protection in **1**, prior to alkylation, by the trimethylsilyl residue. Preparation of diethyl *N*-(trimethylsilyl)-phosphoramidate (**3**) by the action of hexamethyldisilazane (**2**) on diethyl phosphoramidate (**1**) at room temperature has been reported[4]. It was now found, however, that a mixture consisting of 42% of **3** and 58% of unreacted **2** (^{31}P-N.M.R.) is formed when the described procedure is followed. Also refluxing of 1 mol of **1** with 0.5 mol of hexamethyldisilazane (**2**) in benzene leads to an equilibrium mixture still containing ~8% of unreacted **1**. Pure diethyl *N*-(trimethylsilyl)-phosphoramidate (**3**) can be obtained in quantitative yield, however, when a 20 mol% excess of hexamethyldisilazane (**2**) is applied.



Owing to the markedly enhanced *N*—*H*-acidity of **3** as compared to **1** and the possibility of easily removing the trimethylsilyl group under neutral and mild conditions, diethyl *N*-(trimethylsilyl)-phosphoramidate (**3**) seems to be an ideal starting material for monoalkylation. As expected, it reacts smoothly with sodium hydride in benzene at room temperature to afford the *N*-sodio derivative. Similarly to the sodium derivative of hexamethyldisilazane (**2**)[5], the sodium derivative of **3** is readily soluble in benzene and other typical organic solvents and practically devoid of any nucleophilic reactivity. This behavior is probably due to its purely covalent structure in solution. No reaction took place when a benzene solution of the sodium derivative of **3** was refluxed with alkyl bromides for several hours. Alkylation with alkyl bromides (**4**) can be induced, however, and proceeds at a reasonable rate in boiling benzene upon addition of 10 mol% of tetrabutylaminium bromide to the reaction mixture. This spectacular catalytic activity of the tetraalkylaminium salt, which has not been observed so far for *N*-alkylations in homogeneous media, is not quite clear but it may possibly involve the formation of reactive ionised species in solution under the influence of the catalyst. Accordingly, effective monoalkylation of **3** is accomplished when its sodium derivative is refluxed in benzene for 4 h with a stoichiometric amount or an excess (see Table) of a primary alkyl bromide (**4**) in the presence of catalytic amount of tetrabutylaminium bromide. Desilylation carried out *in situ* by treating the product with excess ethanol at 80 °C affords the respective diethyl *N*-alkylphosphoramidate (**5**) in high yield and analytically pure state. The reaction is restricted to monofunctional primary alkyl bromides, possibly due to steric reasons. Attempted application of the method to some bifunctional halides, i.e. ethyl bromoacetate, ω-bromoacetophenone, chloroacetonitrile, and chloroacetone leads inevitably to complex mixtures or intractable tars.

Because of the possibility of easily deprotecting the amino group in diethyl *N*-alkylphosphoramidates (**5**)[6] and diethyl *N*,*N*-dialkylphosphoramidates (which can be readily prepared[1] from **5**) the reported procedure is a useful preparative variant of the Gabriel-type synthesis of primary and secondary amines from primary alkyl bromides.

Table 1. Diethyl *N*-Alkylphosphoramidates (**5**)

5	R	Excess of R—Br [mol%]	Yield [%][a]	n_D^{20}	Molecular formula[b]	
a	C_2H_5	10	87	1.4300	$C_6H_{16}NO_3P$	(181.2)
b	n-C_3H_7	50	89	1.4324	$C_7H_{18}NO_3P$	(195.2)
c	n-C_4H_9	10	81	1.4350	$C_8H_{20}NO_3P$	(209.2)
d	i-C_4H_9	50	37[c]	1.4346	$C_8H_{20}NO_3P$	(209.2)
e	n-C_5H_{11}	0	79	1.4357	$C_9H_{22}NO_3P$	(223.25)
f	n-C_8H_{17}	0	83	1.4417	$C_{12}H_{28}NO_3P$	(265.3)
g	$—CH_2—C_6H_5$	0	82	1.4991	$C_{11}H_{18}NO_3P$	(243.3)
h	$—CH_2—CH{=}CH_2$	0	95	—	$C_7H_{16}NO_3P$	(193.2)
i	$—CH_2—C{\equiv}CH$	10	80[d]	1.4505	$C_7H_{14}NO_3P$	(191.2)

[a] Yield of crude products.

[b] Satisfactory microanalyses were obtained: C ±0.42; H ±0.20; N ±0.23; P ±0.35.

[c] The reaction time was prolonged to 8 h.

[d] Yield of distilled compound; b.p. 74–75 °C/0.3 torr (bath temperature 100–110 °C).

Table 2. Spectrometric Data of Diethyl *N*-Alkylphosphoramidates (**5**)

5	I.R. (film)[a] ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS_{int})[b] δ [ppm], J [Hz]	^{31}P-N.M.R. (CCl_4/85% $H_3PO_{4\,ext}$)[c] δ [ppm]
4	3235 (NH), 2980, 2910, 1440, 1392, 1235 (P=O), 1167, 1132, 1057, 1033, 960, 862, 790	1.10 (t, 3H, $J=7.0$); 1.28 (t, 6H, $J=7.0$); 2.83 (dqt, 2H, $J=7.0$, $J=10.8$); 3.94 (qt, 4H, $J=7.0$); 4.95 (dt, 1H, $J=7.0$, $J=12.0$)	9.4
b	3220 (NH), 2970, 1455, 1395, 1250, 1232 (P=O), 1167, 1125, 1062, 1032, 965, 858, 800	0.90 (dist. t, 3H, $J=7.0$); 1.26 (t, 6H, $J=7.0$); 1.48 (sext, 2H, $J=7.0$); 2.70 (dq, 2H, $J=6.75$, $J=10.75$); 3.91 (qt, 4H, $J=7.0$); 4.93 (dt, 1H, $J=6.75$, $J=11.5$)	9.6
c	3250 (NH), 2970, 2895, 1465, 1395, 1240 (P=O), 1170, 1130, 1100, 1065, 1040, 965, 797, 750	0.89 (dist. t, 3H, $J=6.0$); 1.08–1.73 (m, 4H); 2.51–3.02 (m, 2H); 3.90 (qt, 4H, $J=7.0$); 4.88 (dt, 1H, $J=7.0$, $J=11.5$)	9.4
d	3220 (NH), 2960, 1470, 1445, 1392, 1235 (P=O), 1167, 1100, 1060, 1038, 965, 795	0.90 (d, 6H, $J=6.5$); 1.28 (t, 6H, $J=7.0$); 1.48–1.9 (m, 1H); 2.56 (dt, 2H, $J=6.5$, $J=9.5$); 3.95 (qt, 4H, $J=7.0$); 5.08 (dt, 1H, $J=6.5$, $J=11.5$)	9.5
e	3245 (NH), 2940, 2870, 1450, 1395, 1240 (P=O), 1167, 1100, 1060, 1035, 965, 797	0.89 (dist. t, 3H, $J=5.8$); 1.26 (t, 6H, $J=7.0$); 1.25–1.68 (m, 6H); 2.5–2.98 (m, 2H); 3.93 (qt, 4H, $J=7.0$); 4.94 (dt, 1H, $J=6.0$, $J=12.0$)	9.75
f	3250 (NH), 2985, 2870, 1465, 1395, 1237 (P=O), 1167, 1100, 1033, 967, 795	0.73–1.7 (m, 21H); 2.48–2.95 (m, 2H); 3.90 (qt, 4H, $J=7.2$); 4.83 (dt, 1H, $J=7.0$, $J=12.0$)	8.75
g	3200 (NH), 2960, 2900, 1452, 1392, 1237 (P=O), 1165, 1055, 1030, 965, 865, 795, 730, 695	1.13 (t, 6H, $J=7.1$); 3.88 (qt, 4H, $J=7.1$); 4.08 (dd, 2H, $J=7.0$); 5.58 (dt, 1H, $J=7.0$, $J=12.5$); 7.13–7.48 (m, 5H)	9.25
h	3215 (NH), 2965, 2895, 1640, 1440, 1392, 1250, 1230 (P=O), 1165, 1095, 1060, 1035, 960, 860, 795	1.23 (t, 6H, $J=7.1$); 3.18–3.68 (m, 2H); 3.95 (qt, 4H, $J=7.1$); 4.88–5.35 (m, 3H); 5.6–6.13 (m, 1H)	9.1
i	3280 (NH), 3215, 2965, 2910, 2110, 1448, 1393, 1290, 1250 (P=O), 1167, 1090, 1040, 965, 890, 850, 795, 763	1.00 (t, 6H, $J=7.0$); 2.13 (br. s, 1H); 3.33 (dd, 2H, $J=2.5$, $J=16.0$); 3.69 (qt, 4H, $J=7.0$)	9.1

[a] The I.R. spectra were recorded on a specord 71 IR (C. Zeiss) spectrophotometer.

[b] The ^{1}H-N.M.R. spectra were measured at 80 MHz with a Tesla BS 487 C spectrometer.

[c] The ^{31}P-N.M.R. spectra were measured at 24.3 MHz with a Jeol JNM-C-60 HL spectrometer. A Heteronuclear Spin Decoupler, JNM-SD-HC, was used for precise determinations of ^{31}P chemical shifts. A positive sign indicates downfield shifts from H_3PO_4.

Diethyl *N*-(Trimethylsilyl)-phosphoramidate (3):

A mixture of diethyl phosphoramidate[7] (**1**; 30.6 g, 0.2 mol), hexamethyldisilazane (**2**; 19.4 g, 0.12 mol), and benzene (60 ml) is refluxed gently for 3 h. After evaporation of the solvent and the excess of **2**, the residue is kept at 50-60 °C/0.5 torr for 1 h to remove traces of volatile material. The residual oil crystallises quickly on cooling to give analytically pure **3**; yield: 45.0 g (~100%); m.p. 47-48 °C. The product is strongly hygroscopic and should be kept in a sealed vessel or in a desiccator over phosphorus pentoxide.

$C_7H_{20}NO_3PSi$	calc.	N 6.2	P 13.7
(225.3)	found	6.1	13.7

I.R. (CCl_4): $\nu = 3380$, 3105 (NH); 2970, 2900, 1330, 1252 (P=O); 1220, 1167 [C—O—(P)]; 1100, 1068, 1038 [P—O—(C)]; 1013, 965, 867, 847 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.05$ (t, 6H, $J = 7.0$ Hz); 3.79 (qt, 4H, $J = 7.0$ Hz); 4.33 ppm (br. d, 1H, $J = 2.4$ Hz).

^{31}P-N.M.R. (benzene/85% $H_3PO_{4\,ext}$): $\delta = 9.5$ ppm.

Diethyl *N*-Alkylphosphoramidates (5); General Procedure:

A solution of diethyl *N*-(trimethylsilyl)-phosphoramidate (**3**; 6.76 g, 0.03 mol) in benzene (30 ml) is added dropwise with stirring to a suspension of sodium hydride (0.72 g, 0.03 mol; freshly separated from paraffin oil by washing with hexane) in benzene (20 ml) during 30 min at 15-20 °C. After evolution of hydrogen has ceased and a clear solution has been obtained the alkyl bromide **4** (for amount, see Table 1) and tetrabutylaminium bromide (0.97 g, 0.003 mol) are added and the mixture is refluxed with stirring for 4 h. Ethanol (25 ml) is then added and stirring is continued for 1 h at 80 °C. The resultant mixture is cooled to room temperature, diluted with benzene (100 ml), and treated with water (10 ml) to dissolve sodium bromide. The organic phase is separated and washed with water (2 x 10 ml). The aqueous layer is reextracted with benzene (3 x 10 ml; for compounds **5a, b, h, i** only) and the extracts are combined with the organic phase. The solution is dried with magnesium sulfate, evaporated, and kept at 30-40 °C/0.5 torr for 1 h to give the analytically pure product **5**.

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