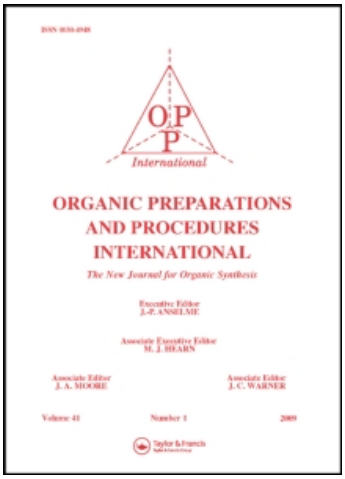

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A SIMPLE AND CONVENIENT METHOD FOR THE SYNTHESIS OF PHOSPHOROAMIDATES AND PHOSPHOROAMIDOTHIOATES UNDER SOLVENT-FREE CONDITION

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(01/10/08)

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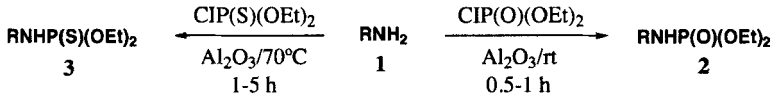
Amides of phosphoric and thiophosphoric acid are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[1] Phosphoroamidates and phosphoroamidothioates are of interest as analogues of biologically-important phosphates. These compounds may also be used as precursors for the synthesis of isothiocyanates, azirines and secondary amines.[2] Several effective processes for the preparation of phosphates have been developed,[3] but to the best of our knowledge, few synthetic routes to phosphoroamidates have been reported. These methods involve (1) phosphorylation of amines by the Atherton-Todd procedure, involving the use of diethyl phosphite/tetrachloromethane in the presence potassium hydrogen carbonate/potassium carbonate and tetrabutyl ammonium bromide as catalysts, (2) refluxing *N,N*-dibromophosphoroamidates in benzene solution over zinc *via* a nitrene intermediate, (3) hydrolysis of trialkoxy iminophosphoranes, and (4) phosphorylation of azides using silylphosphites.[4] Recently, a new method using of diethyl chloridophosphate in the presence of triethylamine as the base for the synthesis of phosphoroamidates has been reported.[5] However, these methods have problems, including the use of chlorinated solvents and strong bases, low yields, long reaction times, and side-reactions. In addition, some of the starting materials have to be synthesized. Cleavage of a Et-O-P bond of the phosphorylating agent occurred in the phosphorylation of amines using of diethyl chloridophosphate.[6]

Surface-mediated solid-phase reactions are of growing interest[7] because of the ease of set up, mild conditions, rapid reactions, selectivity, increased yields of the products and low cost compared with their homogeneous counterparts. As part of our efforts to explore the utility of solid-phase reactions for the synthesis of organophosphorus compounds,[8] we report a new method for the one-pot synthesis of phosphoroamidates and phosphoroamidothioates from the reaction of diethyl chloridophosphate and diethyl chloridothiophosphate with amines in the presence of alumina under solvent-free conditions producing good yields of phosphoroamidates and phosphoroamidothioates (*Scheme 1*, *Table 1*).

As shown in *Scheme 1* and *Table 1*, the reaction of a mixture of diethyl chloridophosphate and amines (*Entries 1-6*) under solvent-free condition using alumina at room temperature,

afforded the desired products in good yields (**2a-f**). The reaction with basic solids such as MgO, CaO and BaO gave desired product with low yields. Alumina and SiO_2 gave a better yield of phosphoroamidates with alumina giving the best result.



2a) R = C_6H_5-; **2b**) R = *p*-ClC_6H_4-; **2c**) R = *p*-BrC_6H_4-; **2d**) R = *p*-$CH_3OC_6H_4$-; **2e**) R = *m*-$O_2C_6H_4$-; **2f**) R = *o*-$CH_3C_6H_4$-; **3a**) R = C_6H_5-; **3b**) R = *p*-ClC_6H_4-; **3c**) R = *m*-$CH_3OC_6H_4$-; **3d**) R = *o*-$CH_3C_6H_4$-; **3e**) R = α-Naphthyl; **3f**) R = $C_6H_5CH_2$-

Scheme 1

A known method[9] for the preparation of phosphoroamidothioates in moderate yields involves prolonged heating (4 days) of a mixture of *O,O'*-diethyl chloridothiophosphate with amines in the presence of triethylamine as a base. Phosphorylation of *O,O'*-diethyl chloridothiophosphate with amines in the presence alumina at 70°C gave the desired compounds in high yields (**3a-f**). Without heating, only very low yields of adduct **3** (<5%) were obtained at room temperature, even after several days. Some of the phosphoroamidothioates prepared may be useful as antioxidants, pesticides, and for lubrication and fireproofing.

Table 1. Yields, mps and Combustion Data of Phosphoroamidates (**2**) and Phosphoroamidothioates (**3**)

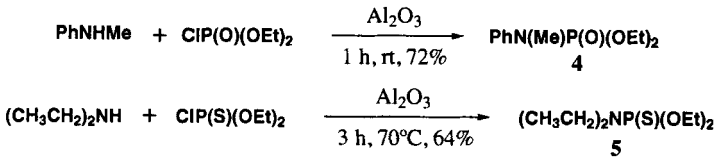
Cmpd	Yield[a] (%)	mp (°C)	*lit.* (°C)	Time (h)	Elemental Analysis (Found) C	H	N
2a	75	95-96	96-97[4e]	0.5	----	----	----
2b	70	74-76	75-77[4e]	0.5	----	----	----
2c	72	87-89[b]	----	0.7	39.09(39.12)	4.92(4.83)	4.56(4.41)
2d	78	64-65	65-65.5[4e]	0.7	----	----	----
2e	62	114-117[b]	----	1	43.78(43.96)	5.52(5.44)	10.21(10.03)
2f	70	81-83	83-84[4e]	1	----	----	----
3a	85	oil	oil[9]	1	----	----	----
3b	76	oil	oil[10]	1	----	----	----
3c	75	oil	oil[10]	1	----	----	----
3d	65	oil	oil[10]	5	----	----	----
3e	75	oil	oil	4	56.93(56.83)	6.15(6.04)	4.74(4.63)
3f	70	oil	oil[11]	5	----	----	----

a) Yields refer to pure products after column chromatography. b) Recrystallization from hexane/CH_2Cl_2

Table 2. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR Data of Compounds **2a-f** and **3a-f**

Cmpd.	^{1}H-NMR (δ)	^{13}C-NMR (δ)	^{31}P-NMR (δ)
2a	1.30 (t, 6H, *J*=7.0 Hz), 3.95-4.30 (4H, m), 6.80-7.35 (5H+NH, m)	16.1 (d, J_{PC}=6.9 Hz), 62.6 (d, J_{PC}=5.0 Hz), 117.2 (d, J_{PC}=7.5 Hz), 121.3, 129.2, 139.8	2.88
2b	1.27 (t, 6H, *J*=7.0 Hz), 3.85-4.20 (4H, m), 6.98 (d, 2H, *J*=8.25 Hz), 7.15 (d, 2H, *J*=8.25 Hz), 7.75 (d, 1H, *J*=9.5 Hz, NH)	16.0 (d, J_{PC}=7.5 Hz), 62.7 (d, J_{PC}=4.4 Hz), 118.5 (d, J_{PC}=8.2 Hz), 126.2, 129.1, 138.9	2.74
2c	1.35 (t, 6H, *J*=7.0 Hz), 3.90-4.25 (4H, m), 6.93 (d, 2H, *J*=8.3 Hz), 7.20-7.35 (2H+NH, m)	16.1 (d, J_{PC}=7.0 Hz), 62.7 (d, J_{PC}=4.8 Hz), 113.6, 118.9 (d, J_{PC}=7.6 Hz), 132.0, 139.3	2.48
2d	1.28 (t, 6H, *J*=7.0 Hz), 3.73 (s, 3H), 3.90-4.20 (4H, m), 6.80-6.80 (2H+NH, m), 6.95-7.10 (2H, m)	16.1 (d, J_{PC}=6.9 Hz), 55.5, 62.6 (d, J_{PC}=4.4 Hz), 114.5, 118.8 (d, J_{PC}=7.5 Hz), 133.2, 154.5	3.38
2e	1.38 (t, 6H, *J*=6.5 Hz), 4.05-4.50 (4H, m), 7.10-7.60 (3H+NH, m), 7.70-8.00 (1H, m)	16.1 (d, J_{PC}=6.9 Hz), 63.3 (d, J_{PC}=5.0 Hz), 111.9 (d, J_{PC}=7.5 Hz), 116.2, 123.2, 129.2, 141.9, 148.7	1.28
2f	1.38 (t, 6H, *J*=6.5 Hz), 2.24 (s, 3H), 3.95-4.40 (4H, m), 6.80-7.50 (4H+NH, m)	16.1 (d, J_{PC}=6.9 Hz), 17.7, 62.9 (d, J_{PC}=5.0 Hz), 117.0, 121.8, 127.0, 130.5, 137.7	2.34
3a	1.31 (t, 6H, *J*=7.0 Hz), 3.95-4.30 (4H, m), 6.90-7.35 (5H+NH, m)	15.7 (d, J_{PC}=8.2 Hz), 63.2 (d, J_{PC}=4.4 Hz), 117.9 (d, J_{PC}=6.9 Hz), 122.0, 129.3, 139.4	64.89
3b	1.26 (t, 6H, *J*=7.0 Hz), 3.85-4.20 (4H, m), 5.75-6.20 (br, NH), 6.95 (d, 2H, *J*=8.25 Hz), 7.12 (d, 2H, *J*=8.25 Hz)	15.8 (d, J_{PC}=8.2 Hz), 63.4 (d, J_{PC}=4.4 Hz), 119.1 (d, J_{PC}=8.2 Hz), 127.0, 128.9, 138.2	64.30
3c	1.28 (t, 6H, *J*=7.0 Hz), 3.74 (s, 3H), 3.90-4.25 (4H, m), 6.70-6.80 (2H+NH, m), 6.90-7.00 (2H, m)	15.8 (d, J_{PC}=8.3 Hz), 55.5, 63.1 (d, J_{PC}=4.4 Hz), 114.5, 119.7 (d, J_{PC}=6.4 Hz), 132.5, 132.6, 155.1	65.30
3d	1.38 (t, 6H, *J*=7.0 Hz), 2.24 (s, 3H), 3.95-4.40 (4H, m), 6.80-7.40 (4H+NH, m)	15.7 (d, J_{PC}=8.8 Hz), 17.7, 63.2 (d, J_{PC}=4.4 Hz), 118.0, 122.3, 125.4, 127.1, 130.6, 137.9	65.60
3e	1.38 (t, 6H, *J*=7.0 Hz), 3.95-4.50 (4H, m), 6.80-7.35 (7H+NH, m)	15.7 (d, J_{PC}=8.8 Hz), 63.5 (d, J_{PC}=5.0 Hz), 115.7, 121.3-128.8 (aromatic), 134.5, 143.5	66.00
3f	1.25 (t, 6H, *J*=7.0 Hz), 3.40-3.55 (br, NH), 3.80-4.15 (6H, m), 7.15-7.40 (4H, m)	15.8 (d, J_{PC}=8.8 Hz), 45.5 (d, J_{PC}=2.5 Hz), 62.9 (d, J_{PC}=5.0 Hz), 127.3, 127.5, 128.5, 139.4 (d, J_{PC}=6.3 Hz)	71.4

The secondary amine, *N*-methylaniline, also reacted with diethyl chloridophosphate to give the desired phosphoroamidate **4** in good yield (*Scheme 2*). Cleavage of a Et-O-P bond of the phosphorylating agent occurred in the phosphorylation of aliphatic amines using of diethyl chloridophosphate. Phosphorylation reaction *O,O'*-diethyl chloridothiophosphate with diethylamine in the presence alumina at 70°C, gave the desired product **5** in good yield (*Scheme 2*).



Scheme 2

In all the reactions reported here, cleavage of the Et-O-P bond of the phosphorylating agent was not detected and the conversion of the substrates to the corresponding phosphoroamidates and phosphoroamidothioates was clean. Work-up of the reaction mixture is very easy and gives highly pure products, which do not need further purification. All NMR data could be assigned and are in good agreement with characteristic of the products.

EXPERIMENTAL SECTION

All chemicals were commercial products and distilled or recrystallized before use. All melting points were obtained on a Buchi 510 apparatus and are uncorrected. Infrared (IR) spectra were determined using a FT-IR Brucker-Vector 22. NMR spectra were obtained on a DMX-250 Bruker Avance spectrometer in $CDCl_3$. Silica gel column chromatography was carried out on Silica gel 100 (Merck No. 10184). Merck Silica-gel 60 F254 plates were used for preparative TLC. Aluminium oxide 90 active acidic (activity stage I) was used for the reactions (Merck No. 1078).

General Procedure for the Synthesis of Phosphoroamidates 2.- Alumina (1 g) was added to a stirred mixture of diethyl chloridophosphate (2.1 g, 0.012 mol) and the amine (0.01 mol) at room temperature. The reaction mixture was stirred for 0.5-1 h at room temperature. The mixture was extracted with ethyl acetate (4 x 50 mL), dried over $CaCl_2$, and the solvent was evaporated to give the crude product. Chromatography on silica gel with EtOAc/*n*-hexane (1:9 to 4:6) and evaporation of the solvent under reduced pressure gave the pure products (62-78%). All the products gave satisfactory spectral data in accordance with the assigned structures and literature reports.

***O,O'*-Diethyl Methyl(phenyl)amidophosphate (4)**, colorless viscous oil.[12] ^{1}H-NMR (TMS-250 MHz, $CDCl_3$): δ 1.38 (t, 6H, J = 6.5 Hz), 3.15 (d, 3H, J_{PH} = 11.2 Hz), 3.85-4.15 (4H, m), 6.95-7.30 (5H, m); ^{31}P-NMR (101.2 MHz, $CDCl_3$, 85% H_3PO_4): δ 5.99; ^{13}C-NMR (62.9 MHz, $CDCl_3$): 16.0 (d, J_{PC} = 6.9 Hz), 36.7 (d, J_{PC} = 4.4 Hz), 62.5 (d, J_{PC} = 5.0 Hz), 121.8 (d, J_{PC} = 3.8 Hz), 123.4, 128.8, 143.9.

General Procedure for the Synthesis of Phosphoroamidothioates 3.- Alumina (1 g) was added to a stirred mixture of diethyl chloridothiophosphate (2.26 g, 0.012 mol) and the amine (0.01 mol) at room temperature. The reaction mixture was heated and stirred at 70°C for 1-5 h. The mixture was extracted with ethyl acetate (4 x 50 mL), dried over $CaCl_2$, and the solvent was evaporated to give the crude product. Chromatography on silica gel with EtOAc/*n*-hexane (1:9 to 3:7) and evaporation of the solvent under reduced pressure gave the pure products (65-85).

***O,O'*-Diethyl-*N,N'*-diethylphosphoroamidothioate (5)**, colorless viscous oil.[11] ^{1}H-NMR (TMS-250 MHz, $CDCl_3$): δ 1.15 (t, 6H, J = 7.0 Hz), 1.26 (t, 6H, J = 7.0 Hz), 2.55-2.63 (4H, m), 3.77-3.92 (2H, m), 4.09-4.19 (2H, m); ^{31}P-NMR (101.2 MHz, $CDCl_3$, 85% H_3PO_4): δ 76.51; ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 15.5 (d, J_{PC} = 8.8 Hz), 15.7 (d, J_{PC} = 8.2 Hz), 36.9 (d, J_{PC} = 3.8 Hz), 62.4 (d, J_{PC} = 5.0 Hz), 65.9 (d, J_{PC} = 6.9 Hz).

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