A Novel Method for the Synthesis of Bis(1-diethoxyphosphorylalkyl)amines from Diimines

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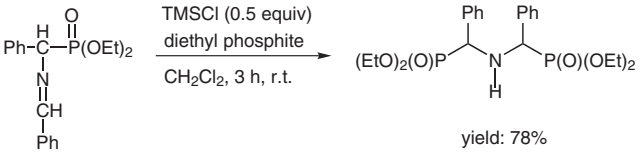
Abstract: A novel and convenient method for the synthesis of bis(1-diethoxyphosphorylalkyl) amines has been developed. As described below, treatment of aromatic diimines with diethyl phosphite in the presence of chlorotrimethylsilane gave bis(1-diethoxyphosphorylalkyl)amines. This method is easy, rapid, and good-yielding for the synthesis of bis(1-diethoxyphosphorylalkyl)amines from simple starting materials.

Key words: TMSCl, diethylphosphite, diimines, bis(1-diethoxyphosphorylalkyl)amines, addition reaction

α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[1–4] Among α-functional phosphonic acids, 1-aminophosphonic acids are an important class of compounds that exhibit a variety of interesting and useful properties. The 1-aminophosphonic acids are important substitutes for the corresponding α-amino acids in biological systems.[5] Indeed a number of potent antibiotics,[6] enzyme inhibitors,[7] and pharmacological agents[8] are 1-aminophosphonic acids or peptide analogues. Aminophosphonic acids are also found as constituents of natural products.[9] In contrast to the widely studied 1-aminophosphonic acid derivatives,[10–13] relatively few papers have reported on the chemistry of bis(1-diethoxyphosphorylalkyl)amines as an important class of 1-aminophosphonic acid derivatives. Bis(1-dialkoxyphosphorylalkyl)amines have been used as chelating agents for polyvalent ions, particularly for alkaline earth metal ions.[14] Many effective methods for the preparation of 1-aminophosphonic acids have been developed, but, to the best of our knowledge, few synthetic routes to bis(1-diethoxyphosphorylalkyl)amines have been reported. These methods involve prolonged heating of primary amines with chloromethylphosphonic acids in alkaline solution[15] and a Mannich-type reaction of an amine, formaldehyde, and phosphorous acid has also been reported.[16] Recently, a new direction for the preparation of bis(1-diethoxyphosphorylalkyl)amines in the reaction of 1-iminocarboxylate salts with dialkyl chlorophosphites has been reported.[17] However, these methods have drawbacks, including harsh reaction conditions, long reaction times, and side reactions. On the other hand, prolonged heating of chloromethylphosphonic acids in alkaline solution also leads to the competitive hydrolysis of the chlorine–carbon bond to give hydroxymethylphosphonic acid.[15] As part of our efforts to introduce novel methods for the synthesis of organophosphorus compounds,[18] in this report a new method for the synthesis of bis(1-diethoxyphosphorylalkyl)amines is described. Recently, we reported that reaction of aromatic aldehydes with ammonia solution followed by reaction with diethyl phosphite, gave diethyl *N*-(arylmethylene)-1-aminoaryl methylphosphonate in good yields that can be easily hydrolyzed to diethyl 1-aminoarylmethylphosphonates.[19] We also reported that the reaction of diethyl *N*-(phenylmethylene)-1-aminophenyl methylphosphonate, as a model compound, with diethyl phosphite in the presence of chlorotrimethylsilane (0.5 equiv) yielded bis(1-diethoxyphosphorylphenylmethyl)amine as the sole product (Scheme 1).[20]



Scheme 1

Diimines serve as a good precursor for the synthesis of numerous organic compounds especially heterocyclic compounds.[21,22] Herein, a new method for the synthesis of bis(1-diethoxyphosphorylalkyl)amines by using of diimines as precursor is described. The reaction of *N*,*N*′-bis(phenylmethylidene)phenylmethane diamine, as a model compound, with diethyl phosphite in the presence of chlorotrimethylsilane (0.5 equiv) gave bis(1-diethoxyphosphorylphenylmethyl)amine as the sole product (Scheme 2).

The ^{31}P NMR spectrum of **2a** exhibited two peaks at δ = 23.36 and 23.68 ppm due to diastereoisomers. A moderate diastereoselection can be obtained in this reaction (68:32).

Because of the presence of two stereogenic carbons bonded to the nitrogen atom, this compound exists in two diastereomeric forms: one meso (*syn*) and one racemic pair (*anti*). Recently stereochemical assignment of diastereoisomers of **2a** has been reported in the literature.[17] According to this report, the *syn* diastereoisomer **2a** has a signal at lower field (δ = 23.68 ppm) in the ^{31}P NMR spectra.

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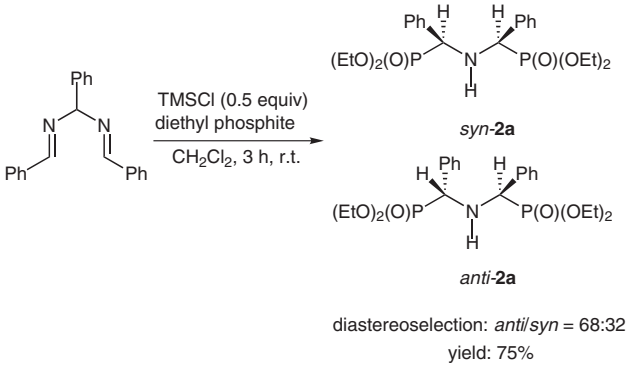
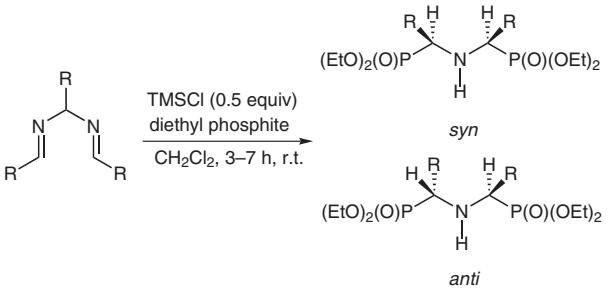


Scheme 2

This process was successfully applied to other diimines (**1**) as summarized in Table 1. As shown in Table 1, *N*,*N*′-bis(arylmethylidene)arylmethane diamines react with diethyl phosphite and chlorotrimethylsilane to afford the desired products in good yields (**2b**–**h**; Scheme 3). Reaction between ammonium hydroxide and aliphatic aldehydes failed and did give not any diimines **1**.



Scheme 3

In summary, fast reaction rates, mild reaction conditions, good yields, the simple workup, and relatively clean reactions with no tar formation make this method an attractive and a useful contribution to present methodologies. Indeed, a wide range of aromatic diimines **1** were converted into the corresponding bis(1-diethoxyphosphorylalkyl)amines using this method. Further investigations on this reaction are now in progress.

All chemicals are commercial products and were distilled or recrystallized before use. All melting points were obtained on a Buchi 510 apparatus and are uncorrected. NMR spectra were taken with on a 250 Bruker Avance instrument and the chemical shifts are reported on δ (ppm) scale. The coupling constants are expressed in Hz. For ^{13}C NMR, the designation 'c' refers to complex peak. Silica gel column chromatography was carried out with Silica gel 100 (Merck No. 10184). Merck Silica gel 60 F254 plates (No. 5744) were used for the preparative TLC. Microanalyses were performed on a CHNO-Foss-Heraeus model by Research Institute of Petroleum Industry (RIPI).

Synthesis of Diimine 1; General Procedure

The aldehyde (15 mmol) was added to NH_4OH (30%, 15 mL) and the solution was stirred for 5 h at reflux. During this time, a white precipitate formed. The precipitate (diimine) was removed by filtration and dried.[19]

Synthesis of Bis(1-diethoxyphosphorylalkyl)amines 2; General Procedure

Chlorotrimethylsilane (2 mmol) was added to a mixture of compound **1** (4 mmol) and diethyl phosphite (8 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred for 3–7 h at r.t. Evaporation of solvent and chromatography on plug of silica gel with EtOAc–MeOH (9:1) and evaporation of the solvent under reduced pressure gave the pure product as a colorless oil in 61–85% yields. All products gave satisfactory spectral data, which are in accord with the assigned structures.

Bis(1-diethoxyphosphorylphenylmethyl)amine (2a)

Yield: 75%; colorless oil.

^1H NMR (250 MHz, $CDCl_3$, TMS): δ = 1.10 (t, *J* = 7.1 Hz, 6 H), 1.26 (t, *J* = 7.1 Hz, 6 H), 2.93 (br, 1 H, NH), 3.65–4.35 (m, 10 H), 7.29 (s, 10 H).

^{13}C NMR (62.9 MHz, $CDCl_3$, TMS): δ = 134.3, 128.8, 128.2, 128.1, 62.6–62.9 (c), 57.4 (dd, J_{PC} = 155.1, 17.9 Hz), 16.1–16.3 (c).

Table 1 Reaction of Diimines **1** with Diethyl Phosphite with Chlorotrimethylsilane as Catalyst

1	R	Time (h)	Yield (%)[a] **2**	Diastereoselection[b] (*anti*/*syn*)	^{31}P NMR (δ (ppm) *anti, syn*
a	C_6H_5	4	75	68:32	23.36, 23.68
b	*p*-$MeOC_6H_4$	3	71	72:28	23.78, 24.00
c	*p*-ClC_6H_4	6	72	79:21	22.53, 22.90
d	*p*-FC_6H_4	4	85	73:27	22.30, 22.67
e	*p*-MeC_6H_4	5	65	86:14	23.69, 23.97
f	*m*-FC_6H_4	7	61	89:11	21.71, 22.17
g	*m*-$NO_2C_6H_4$	4	69	88:12	21.04, 21.58
h	β-Naphthyl	4	67	63:37	23.27, 23.60

[a] Isolated yields.
[b] Diastereoselection was determined from ^{31}P NMR spectrum.

^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4): δ = 23.36/23.68 (68:32).

Anal. Calcd for $C_{22}H_{33}NP_2O_6$: C, 56.3; H, 7.1; N, 3.0. Found: C, 56.2; H, 7.1; N, 2.8.

Bis(1-diethoxyphosphoryl-*p*-methoxyphenylmethyl)amine (2b)
Yield: 71%; colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 1.14 (t, *J* = 7.1 Hz, 6 H), 1.29 (t, *J* = 7.1, 6 H), 1.69 (br, 1 H, NH), 3.68−4.35 (m, 16 H), 6.87 (d, *J* = 8.5 Hz, 4 H), 7.22 (d, *J* = 8.5 Hz, 4 H).

^{13}C NMR (62.9 MHz, $CDCl_3$, TMS): δ = 159.4, 129.9, 125.9, 113.8, 62.4−62.8 (c), 56.4 (dd, J_{PC} = 156.7, 17.9 Hz), 55.1, 16.1−16.3 (c).

^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4): δ = 23.78/24.00 (72:28).

Anal. Calcd for $C_{24}H_{37}NP_2O_8$: C, 54.4; H, 7.0; N, 2.6. Found: C, 54.3; H, 7.1; N, 2.7.

Bis(1-diethoxyphosphoryl-*p*-chlorophenylmethyl)amine (2c)
Yield: 72%; colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 1.15 (t, *J* = 7.1 Hz, 6 H), 1.29 (t, *J* = 7.1 Hz, 6 H), 2.19 (br, 1 H, NH), 3.65−4.35 (m, 10 H), 7.23 (d, *J* = 8.25 Hz, 4 H), 7.33 (d, *J* = 8.25 Hz, 4 H).

^{13}C NMR (62.9 MHz, $CDCl_3$, TMS): δ = 134.1, 132.9, 130.1, 128.9, 62.9−63.2 (c), 56.9 (dd, J_{PC} = 155.4, 17.6 Hz), 16.3−16.4 (c).

^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4): δ = 22.53/22.90 (79:21).

Anal. Calcd for $C_{22}H_{31}Cl_2NP_2O_6$: C, 52.2; H, 6.1; N, 2.7. Found: C, 52.3; H, 5.9; N, 2.6.

Bis(1-diethoxyphosphoryl-*p*-fluorophenylmethyl)amine (2d)
Yield: 85%; colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 1.04 (t, *J* = 7.0 Hz, 6 H), 1.18 (t, *J* = 7.0 Hz, 6 H), 2.82 (br, 1 H, NH), 3.57−4.22 (m, 10 H), 6.80−6.97 (m, 4 H), 7.10−7.22 (m, 4 H).

^{13}C NMR (62.9 MHz, $CDCl_3$, TMS): δ = 162.0 (d, J_{CF} = 246.5 Hz), 130.4, 115.7, 115.3, 62.6−63.0 (c), 56.6 (dd, J_{PC} = 156.6, 17.6 Hz), 16.1−16.3 (c).

^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4): δ = 22.30/22.67 (73:27).

Anal. Calcd for $C_{22}H_{31}F_2NP_2O_6$: C, 55.8; H, 6.5; N, 3.0. Found: C, 55.7; H, 6.5; N, 3.2.

Bis(1-diethoxyphosphoryl-*p*-methylphenylmethyl)amine (2e)
Yield: 65%; colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 1.04 (t, *J* = 7.1 Hz, 6 H), 1.19 (t, *J* = 7.1, 6 H), 2.24 (s, 6 H), 2.85 (br, 1 H, NH), 3.60−4.25 (m, 10 H), 6.95−7.15 (m, 8 H).

^{13}C NMR (62.9 MHz, $CDCl_3$, TMS): δ = 137.7, 131.1, 129.2, 128.7, 62.4−62.9 (c), 57.0 (dd, J_{PC} = 156.0, 18.2 Hz), 21.1, 16.1−16.3 (c).

^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4): δ = 23.69/23.97 (86:14).

Anal. Calcd for $C_{24}H_{37}NP_2O_6$: C, 57.9; H, 7.4; N, 2.8. Found: C, 57.7; H, 7.6; N, 2.9.

Bis(1-diethoxyphosphoryl-*m*-fluorophenylmethyl)amine (2f)
Yield: 61%; colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 1.11 (t, *J* = 7.0 Hz, 6 H), 1.24 (t, *J* = 7.0 Hz, 6 H), 2.92 (br, 1 H, NH), 3.65−4.25 (m, 10 H), 6.85−7.09 (m, 6 H), 7.15−7.32 (m, 2 H).

^{13}C NMR (62.9 MHz, $CDCl_3$, TMS): δ = 162.9 (d, J_{CF} = 246.8 Hz), 137.1, 130.1, 124.5, 115.7, 115.3, 62.9−63.2 (c), 57.2 (dd, J_{PC} = 155.1, 17.4 Hz), 16.1−16.3 (c).

^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4): δ = 21.71/22.17 (89:11).

Anal. Calcd for $C_{22}H_{31}F_2NP_2O_6$: C, 55.8; H, 6.5; N, 3.0. Found: C, 55.7; H, 6.4; N, 3.1.

Bis(1-diethoxyphosphoryl-*m*-nitrophenylmethyl)amine (2g)
Yield: 69%; colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 1.14−1.35 (m, 12 H), 3.82−4.23 (m, 11 H), 7.40−7.70 (m, 4 H), 8.05−8.41 (m, 4 H).

^{13}C NMR (62.9 MHz, $CDCl_3$, TMS): δ = 148.5, 136.9, 134.7, 129.8, 123.4, 123.3, 62.8−63.7 (c), 57.3 (dd, J_{PC} = 154.5, 16.6 Hz), 55.1, 16.0−16.5 (c).

^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4): δ = 21.04/21.58 (88:12).

Anal. Calcd for $C_{22}H_{31}N_3P_2O_{10}$: C, 47.2; H, 5.5; N, 7.5. Found: C, 47.0; H, 5.3; N, 7.4.

Bis(1-diethoxyphosphoryl-β-naphthylmethyl)amine (2h)
Yield: 67%; colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 1.10 (t, *J* = 7.0 Hz, 6 H), 1.31 (t, *J* = 7.0, 6 H), 3.03 (br, 1 H, NH), 3.70−4.57 (m, 10 H), 7.35−7.92 (m, 14 H).

^{13}C NMR (62.9 MHz, $CDCl_3$, TMS): δ = 133.3, 132.0, 131.9, 128.4, 127.9, 127.7, 126.2, 62.8−63.1 (c), 57.7 (dd, J_{PC} = 155.1, 17.8 Hz), 16.1−16.3 (c).

^{31}P NMR (101 MHz, $CDCl_3$, H_3PO_4): δ = 23.27/23.60 (63:37).

Anal. Calcd for $C_{30}H_{37}NP_2O_6$: C, 63.3; H, 6.5; N, 2.5. Found: C, 63.2; H, 6.5; N, 2.5.

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