Studies on Organophosphorus Compounds XXVIII. An Improved Synthetic Route to 1-Amino-Substituted Benzyl Phosphonic and -Phosphinic Acids

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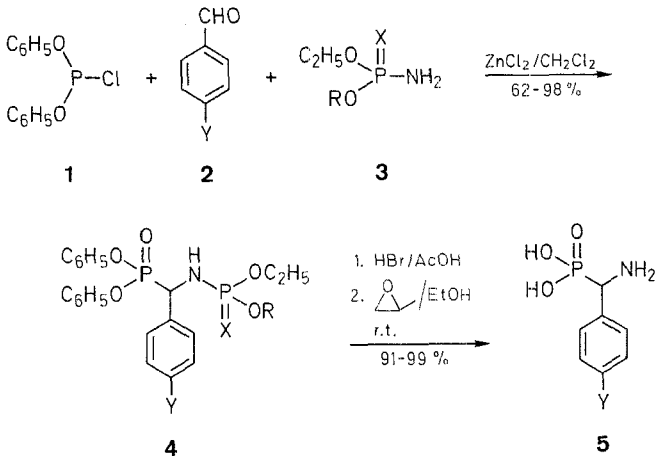
An improved method for the synthesis of 1-aminosubstituted benzyl phosphonic and -phosphinic acids under mild conditions is described. It consists of the reaction of diphenoxy chlorophosphine (**1**) or dichlorophenylphosphine (**6**) with substituted benzaldehydes **2** and a phosphoramidate **3** in the presence of a Lewis acid, followed by selective cleavage of the protective group of the resultant 1-(phosphorylamino)-substituted benzylphosphonate **4** or phosphinate **7**, **9**. A tentative reaction mechanism is postulated.

The potent biological activity and strong chelating effect of 1-aminoalkanephosphonic acids and their derivatives lead to extensive synthetic studies of these compounds. Among them, the method based on the reaction of aldehyde, alkylcarbamates or derivatives of acetamide, and urea with triphenylphosphite is experimentally simple, and fairly pure products are obtained in every step of the reaction sequence with high yield.[1-6] Unfortunately, wider applications of these methods are inhibited by their drastic reaction conditions. Herein we wish to describe an improved method for synthesizing 1-aminosubstituted benzylphosphonic and -phosphinic acids under mild conditions. Reaction of diphenoxy chlorophosphine (**1**), substituted benzaldehyde **2** and a dialkyl phosphoramidate or -thiophosphoramidate **3** in the presence of zinc chloride leads to diphenyl dialkoxyphosphorylamino-substituted benzylphosphonates **4**. This is converted to 1-amino-substituted benzylphosphonic acids **5** by treatment with 40% hydrobromic acid in acetic acid and followed by dehydrobromination.



1 2 3 4 5

The reactions proceed under very mild conditions. Formation of **4** is achieved at 40 °C with 80–90% yield in most cases, which is significantly higher than by the method reported by us recently[6] (Table 1). The yields of conversion from **4** to **5** are almost quantitative. (Table 2)

However, this reaction is significantly influenced by the nature of Lewis acid used as catalyst, since the yield of **4a** decreased in the order $ZnCl_2 > AlCl_3 > (C_2H_5)_2O{\cdot}BF_3 > SnCl_4$. It is probably associated with the steric hindrance during the attack of **2** with coordinated species resulting from **1** and a Lewis acid.[8]

Table 1. Compounds **4** Prepared

4	R	X	Y	Yield[a] (%)	mp (°C)	Lit. mp (°C)
a	C_2H_5	O	H	62 (53)	173–174	172.9–174[5]
b	C_2H_5	O	4-CH_3	65 (50)	150–152	151.2–151.7[5]
c	C_2H_5	O	4-Cl	78 (66)	130–132	131.5–133.8[5]
d	C_2H_5	S	H	98 (85)	129.5–131	129.5–130.5[6]
e	C_2H_5	S	4-CH_3	93 (58)	129–130.6	129.8–130.6[6]
f	C_2H_5	S	4-Cl	93 (54)	102.5–103.3	102–103[6]
g	C_2H_5	S	4-Br	91 (63)	107.5–108.4	107.4–108.4[6]
h	C_6H_5	S	H	69 (53)	96.5–97.4	96.2–97[6]
i	C_6H_5	S	4-CH_3	54 (62)	116.5–117.8	117–117.8[6]
j	C_6H_5	S	4-Cl	70 (53)	145–146.5	145.5–146.1[6]

[a] Yield of compound **4** prepared by the methods described in literature[5,6] are shown in parenthesis.

Table 2. Conversion of **4** to **5**

Educt	Product	Y	Yield (%)	mp (°C)	Lit. mp (°C)
4a	**5a**	H	96	218–282	281–281.2[1]
4c	**5b**	4-Cl	99	277–277.5	277–277.3[5]
4g	**5c**	4-Br	94	276–276.5	276.4–276.7[7]
4i	**5d**	4-CH_3	97	280.8–282	278–279[1]

Solvents with higher polarity accelerate the reaction, as the yield of **4a** increased markedly with the increase of the dielectric constant of the solvent, e.g. dioxane < chloroform < 1,2-dimethoxyethane (DME) < dichloromethane. It indicates that the process involves the participation of a charge separated intermediate.

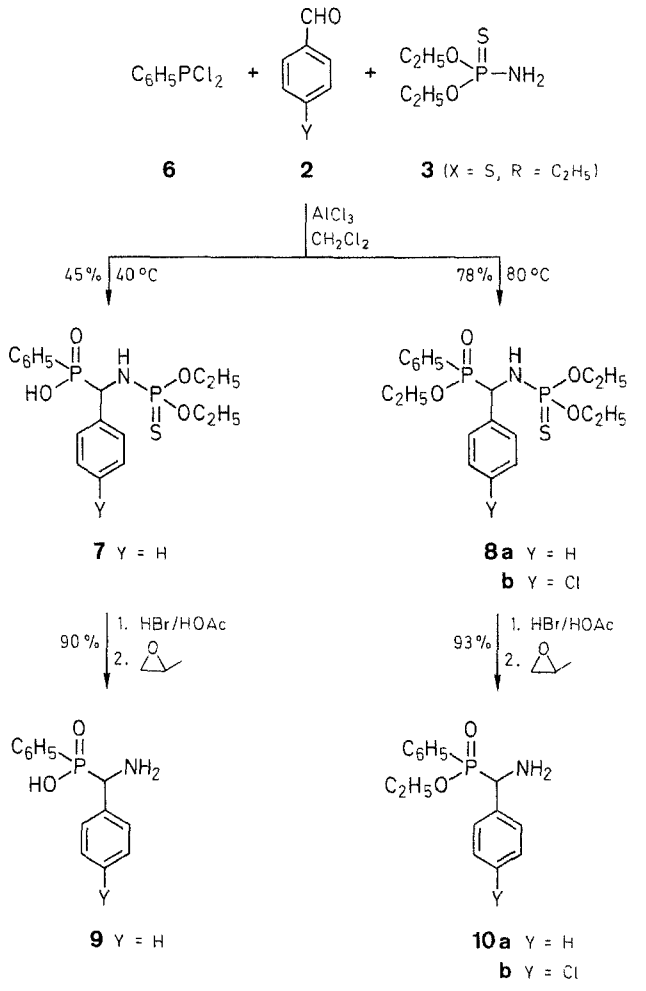
Analogous to the result reported by us[6] in the synthesis of **4**, thiophosphoramidate **3**, (X = S), also gave better yield than phosphoramide **3** (X = O) due to the strong nucleophilicity of the thioanalogue arised from the low electron negativity of the sulfur atom. The poor reactivity of ethyl phenyl thiophosphoramidate is associated with the electron-withdrawing ability of the benzene ring.

The cleavage of the protective phosphoryl or thiophosphoryl group of **4** was facilitated by treating the hydrobromide in acetic acid followed by dehydrobromination with methyl oxirane to give **5** in quantitative yield.

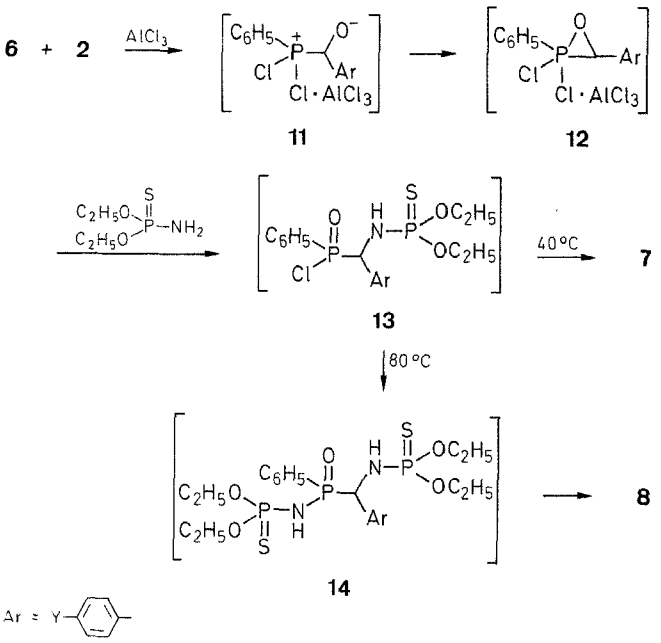
As an extention of the synthesis of aminophosphonic acids **5**, dichlorophenylphosphine **(6)** was used instead of **1** to prepare a series of hitherto unknown α-aminobenzyl(phenyl)phosphinic acids **9** and corresponding esters **10**.

With aluminum chloride as catalyst, reaction of **6** with **2** and **3** (X = S, R = C_2H_5) gave different products depending on the reaction temperature. At 40 °C reaction proceeded with the formation of α-(diethoxythiophosphorylamino)benzyl(phenyl)-phosphinic acids **7**, while at 80 °C the reaction afforded the corresponding ethyl esters **8**. Successive deprotection of *N*-(diethoxy-thiophosphoryl) group followed by treatment with methyloxirane in the usual manner[6] gave the free α-aminobenzyl(phenyl)phosphinic acids **9** and its esters **10**.

This reaction provides a new method for the synthesis of *N*-protected α-aminobenzyl(phenyl)phosphinic acids **7** and α-aminobenzyl(phenyl)phosphinic esters **10**, which are useful intermediates in phosphorus peptide synthesis, by controlling the reaction temperature.



Based on the experimental data, a tentative reaction mechanism is postulated.



Apparently, formation of **8** is attributed to some sort of rearrangement which proceed only at 80 °C. Meanwhile, the higher yield of **8** over **7** shows that 80 °C is the favourable temperature for the reaction. It was observed that the yield of **8** increased by increasing the amount of **3b** up to two equivalents.

Melting points were determined on a Metter FP 61 apparatus, UV spectra were recorded on a Perkin-Elmer Lambda 5 spectrometer. IR spectra were obtained on a Shimadzu 400 spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM-360L spectrometer; TMS was used as internal standard. Mass spectra were measured on a Finnigan 4021 apparatus.

Diphenyl α-(Diethoxyphosphoryl or -thiophosphorylamino)benzylphosphonates 4a–j; General Procedure:

To a stirred supension of $ZnCl_2$ (0.68 g, 5 mmol) in CH_2Cl_2 (20 mL) at −20 °C are added successively, diphenoxychlorophosphine (**1**; 1.26 g, 5 mmol), substituted benzaldehyde **2** (5 mmol) and the appropriate phosphoramidate or thiophosphoramidate **3** (5 mmol) in CH_2Cl_2 (10 mL) in a N_2 atmosphere. Stirring is continued for 0.5 h at room temperature and for 6 h at 40 °C. After cooling to 10 °C, $CHCl_3$ (150 mL) and H_3PO_4 (10 mL) are added. The mixture is washed successively with water (2 × 60 mL), dried ($MgSO_4$), and evaporated. The residue is purified by recrystallization from CH_2Cl_2. The melting points and spectroscopic data of **4a–j** thus obtained are identical with that described in the literature.[5,6]

α-Aminobenzylphosphonic Acid Hydrobromides 5a–d; General Procedure:

The appropriate benzylphosphonate **4** (0.5 mmol) is dissolved in a mixture of AcOH (8 mL) and 40% aq. HBr (15 mL) and refluxed at 120 °C for 3 h. It is then concentrated under reduced pressure and the residue is dissolved in EtOH (4–6 mL). To this solution, propylene oxide is added dropwise until pH 6 is attained. The precipitated solid is isolated and recrystallized from aqueous EtOH. The products **5** is obtained in quantitative yield and have melting point and spectroscopic data identical with that recorded in the literature.[1,5,7]

1-(Diethoxythiophosphorylamino)benzyl(phenyl)phosphinic Acid (7)

To a stirred mixture of $AlCl_3$ (17.7 mmol) in CH_2Cl_2 (15 mL) prepared at −20 °C is added dichlorophenylphosphine (**6**; 3.17 g, 17.7 mmol) and benzaldehyde (**2**; 1.88 g, 17.7 mmol) in a N_2 atmosphere. After stirring for 1 h at room temperature a solution of diethyl thiophosphoramidate [**3** (X = S, R = C_2H_5); 6.0 g, 35.4 mmol)] in DME (25 mL) is introduced and the stirring is continued for 5 h at 40 °C. The mixture is brought to room temperature and treated with EtOAc (150 mL) and H_3PO_4 (10 mL). The mixture is washed successively with sat. brine (2 × 100 mL), water (2 × 60 mL), and dried ($MgSO_4$), and evaporated. The residue obtained is recrystallized from cyclohexane/*n*-hexane, yield: 3.18 g (45%); mp 139.6–140.6 °C.

$C_{17}H_{23}NO_4P_2S$	calc.	C 51.12	H 5.80	N 3.51
(339.4)	found	51.38	5.94	3.34

IR (KBr): ν = 960 (P–OH), 1070 (P–OC_2H_5), 1220 (P=O), 3350 cm^{-1} (NH).

^{1}H-NMR (CCl_4): δ = 1.05 (m, 6H, $2CH_3CH_2$); 3.65 (m, 4H, $2CH_3CH_2$); 4.80 (br, 1H, CH); 7.30 (t, 11 H_{arom} + NH).

α-Aminobenzyl(phenyl)phosphinic Acid (9):

A mixture of **7** (0.25 g, 0.62 mmol), AcOH (7 mL) and 40% aq. HBr (10 mL) is heated to reflux for 2 h. To the residue obtained by evporation of the solvent, appropriate amount of anhydrous ethanol is added, followed by treatment with propylene oxide (50 mL). On cooling in an ice bath, the resulting colorless crystals are obtained, which are purified by crystallization from AcOH containing a small amount of propylene oxide; yield: 0.14 g (90%); mp 243–244 °C.

$C_{13}H_{14}NO_2P$	calc.	C 63.15	H 5.70	N 5.67
(247.5)	found	62.82	5.58	5.37

IR (KBr): ν = 950 (P–OH), 1210 cm^{-1} (P=O).

^{1}H-NMR (CF_3COOH): δ = 4.90 (br, 1H, CH); 7.00 (d, 10 H_{arom}); 7.30 (br, 2H, NH_2).

Ethyl α-(Diethoxythiophosphorylamino)benzyl(phenyl)phosphinates (8); General Procedure:

To a stirred suspension of anhydrous $AlCl_3$ (2.4 g, 18 mmol) in CH_2Cl_2 (15 mL) are added at 20 °C dichlorophenylphosphine (**6**; 3.3 g, 18 mmol), and substituted benzaldehyde **2** (18 mmol) in a N_2 atmosphere. The mixture is allowed to come to room temperature and a solution of diethyl thiophosphoramidate [**3** (X = S, R = C_2H_5); 6.1 g, 36 mmol] in DME (30 mL) is added. Stirring is continued for 0.5 h at ambient temperature and for another 5 h at 80 °C. The residue obtained by evaporation of the solvent is treated with CH_2Cl_2 (150 mL) and H_3PO_4 (10 mL). The resulting solution is worked up as described for the syntheis of **4**, and the crude product is purified by recrystallization from aq. EtOH. **8a** (Y = H): yield: 6.03 g (78%) (the yield was decreased to 53.3% if equivalent amount of **3** (X = S, R = C_2H_5) (3.05 g, 18 mmol) is used); mp 145–146.3 °C.

$C_{19}H_{27}NO_4P_2S$	calc.	C 53.39	H 6.37	N 3.28	P 14.49
(427.4)	found	52.98	6.15	3.13	14.39

MS (DEI): *m/z*: 428 (M + 1).

IR (KCl): ν = 1030 (P–OC_2H_5), 1220 (P=O) cm^{-1}.

^{1}H-NMR (CCl_4): δ = 1.10 (m, 9H, $3CH_3CH_2$); 3.8 (m, 6H, $3CH_3CH_2$); 5.8 (m, 1H, CH); 7.50 (m, 11 H_{arom} + NH).

8b (Y = Cl): yield: 4.57 g (55%); mp 178.8–179.8 °C.

$C_{19}H_{26}ClNO_4P_2S$	calc.	C 49.40	H 5.67	P 13.41
(461.9)	found	49.06	5.29	13.67

MS: *m/z* = 462 (M^+).

IR (KCl): ν = 1020 (P–OC_2H_5), 1204 (P=O) cm^{-1}.

^{1}H-NMR (CCl_4): δ = 1.20 (m, 9H, $3CH_3CH_2$); 3.80 (m, 6H, $3CH_3CH_2$); 5.10 (br, 1H, CH); 7.50 (br, 10 H_{arom} + NH).

Ethyl α-Aminobenzyl(phenyl)phosphinate (10a); Typical Procedure:

A mixture of **8a** (0.73 g, 1.7 mmol) and 5.6 N HBr in AcO (30 mL) is kept at room temperature for 3 days. After evaporation, dry ether is added, and the colorless crystals separated are dissolved in absolute EtOH and treated with excess propylene oxide. Recrystallization from aqueous ethanol gives pure **10a**; yield: 0.43 g (93%); mp 237.6–238.3 °C

$C_{15}H_{18}NO_2P$	calc.	C 65.44	H 6.59	P 11.25
(275.3)	found	65.08	6.48	11.41

MS: *m/z* = 275 (M^+).

IR (KCl): ν = 1025 (P–OC_2H_5), 1200 cm^{-1} (P=O).

^{1}H-NMR (DMSO-d_6): δ = 0.86 (t, 3H, CH_3CH_2); 3.16 (br, 2H, CH_3CH_2); 6.40 (br, 1H, CH); 7.26 (s, 10H, $2C_6H_5$); 8.0 (br, 2H, NH_2).

10b (Y = Cl): yield: 0.78 g (90%); mp 234.2–235.2 °C.

$C_{15}H_{17}NO_2PCl$	calc.	C 58.15	H 5.53	P 10.00
(309.8)	found	57.98	5.50	9.97

MS: *m/z* = 310 (M^+).

IR (KCl): ν = 1202 (P–OC_2H_5), 1205 cm^{-1} (P=O).

^{1}H-NMR (DMSO-d_6): δ = 0.95 (t, 3H, $CH_3CH_2$9; 3.40 (br, 2H, CH_3CH_2); 6.20 (br, 1H, CH); 7.30 (br, d, 9 H_{arom}); 7.9 (br, 2H, NH_2).

This project was supported by the National Natural Science Foundation of China.

Received: 16 September 1987; revised: 16 October 1987

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