Studies on Organophosphorus Compounds; XLVI. A Facile and Direct Route to Dialkyl 1-(Benzyloxycarbonylamino)alkylphosphonates and Dialkyl or Diphenyl α-(Benzyloxycarbonylamino)benzylphosphonates

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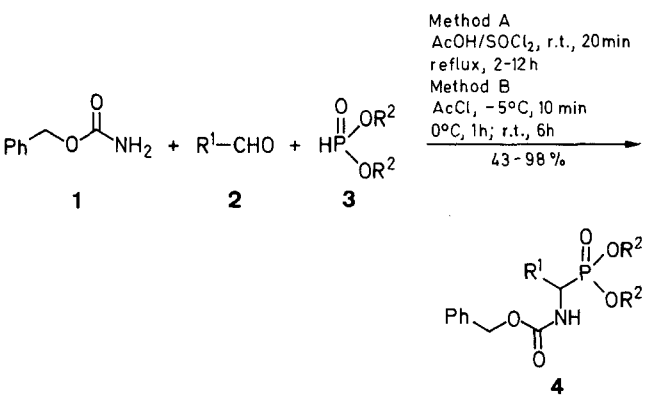
A simple and direct method for the preparation of dialkyl 1-(benzyloxycarbonylamino)alkylphosphonates and dialkyl or diphenyl α-(benzyloxycarbonylamino)benzylphosphonates in high yields consists of the three-component reaction of benzyl carbamate, an alkanal or a benzaldehyde, and a dialkyl (or diphenyl)-phosphite in acetyl chloride at 0 °C (for alkanals) or in acetic acid containing thionyl chloride at 20–70 °C (for benzaldehydes). Removal of the benzyloxycarbonyl group by standard methods or selective hydrolysis of the dialkyl phosphonate moiety leads to the formation of derivatives of aminoalkylphosphonic acids bearing free amino or acidic functions, which are useful intermediates in phosphonopeptide synthesis.

The synthesis of phosphonopeptides with potential biological activity has attracted much attention.[1] Numerous methods have been reported for the preparation of aminoalkylphosphonic acids, the building blocks of phosphonopeptides.[2–4] However, for peptide synthesis acidic functions or amino groups have to be protected during the condensation process.[5,6] On the other hand, the dibasic phosphonic acids behave quite differently in esterification reactions as compared with carboxylic acids. Complete esterification is achieved only by using *N*-protected aminophosphonic acids and a specific condensing agent,[7] or via multistep procedures[8–11] whereas partial esterification requires the cumbersome preparation of the corresponding phosphonic dichloride.

The synthesis of aminophosphonic acids with readily removable protecting groups by a direct method is an important target in phosphonopeptide synthesis.[1–8] We recently reported a convenient method for the preparation of the half-esters of α-(benzyloxycarbonylamino)benzylphosphonic acid, based on a three-component reaction of benzyl carbamate, a benzaldehyde, and phosphorus(III) chloride in acetic acid containing thionyl chloride, followed by direct alcoholysis.[12] As compared to a similar method,[13] our modification is a one-pot procedure which affords higher yields and purity of products. As an extention and modification of this method, we now report a facile and direct route to dialkyl (or diphenyl) α-(benzyloxycarbonylamino)benzylphosphonates **4a–l** by use of dialkyl (or diphenyl) phosphites **3** instead of phosphorus(III) chloride under the same conditions.[12] Dialkyl phosphites **3** undergo this condensation smoothly with benzaldehydes **2** (R^1 = aryl) and benzyl carbamate (**1**) to give > 80% yields of dialkyl (or diphenyl) α-(benzyloxycarbonylamino)benzylphosphonates **4a–l** (Method A). Under modified conditions (acetyl chloride in place of acetic acid/thionyl chloride,

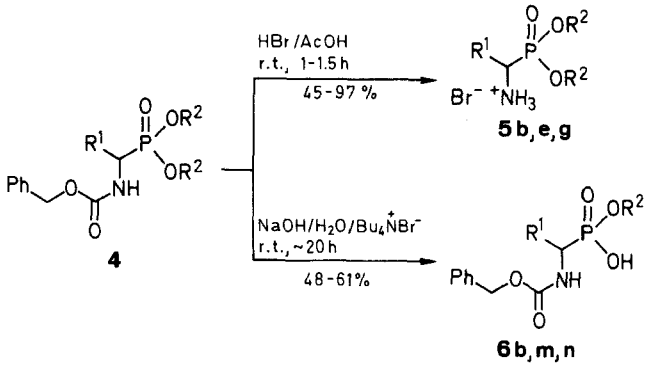


4	R^1	R^2	4	R^1	R^2
a	Ph	Me	**i**	4-$MeOC_6H_4$	Ph
b	Ph	Et	**j**	4-MeC_6H_4	Me
c	Ph	*i*-Bu	**k**	4-MeC_6H_4	Et
d	Ph	Bu	**l**	4-MeC_6H_4	Ph
e	Ph	Ph	**m**	Bu	Me
f	4-$MeOC_6H_4$	Me	**n**	*i*-Bu	Me
g	4-$MeOC_6H_4$	Et	**o**	*i*-Bu	Et
h	4-$MeOC_6H_4$	Bu			

at 0°C, Method B), simple aliphatic aldehydes **2** (R^1 = Pr, *i*-Pr) undergo the same condensation to give 43–68% yield of dialkyl 1-(benzyloxycarbonylamino)-alkylphosphonates **4m,n,o**.

Studies on the role of acetyl chloride and the scope of its application in aminoalkylation of phosphorus species are in progress in our laboratory.

Removal of the benzyloxycarbonyl group by the standard method using hydrogen bromide in acetic acid gave the hydrobromides **5b,e,g** of dialkyl (or diphenyl) α-aminobenzylphosphonates. The half esters **6b,m,n** of 1-(benzyloxycarbonylamino)alkylphosphonic acid resulted from selective hydrolysis of diesters **4b,m,n** in alkaline medium in the presence of a phase-transfer catalyst (TBAB). Both products **5** and **6** are important intermediates in phosphonopeptide synthesis.



5	R^1	R^2	6	R^1	R^2
b	Ph	Et	**m**	Pr	Me
e	Ph	Ph	**n**	*i*-Pr	Me
g	4-$MeOC_6H_4$	Et	**b**	Ph	Et

Melting points are uncorrected. IR spectra were obtained with a Shimadzu 400 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-360L spectrometer.

Dialkyl (or Diphenyl) α-(Benzyloxycarbonylamino)benzylphosphonates 4a–l and 1-(Benzyloxycarbonylamino)alkylphosphonates 4m,n,o; General Procedures:

Method A: To a mixture of AcOH (4 mL) and $SOCl_2$ (1.5 mL) is added a mixture of benzyl carbamate (**1**; 0.75 g, 5 mmol), the dialkyl phosphite **3** (5 mmol), and the benzaldehyde **2** (R^1 = aryl; 5.2 mmol). The mixture is stirred at r.t. for 20 min, then refluxed at 60–70°C for 2–12 h (Table 1). The solvent and volatile substances are removed under reduced pressure using a rotatory evaporator. The residue is dissolved in the minimum amount of EtOH and H_2O is added until the product has precipated. The mixture is then allowed to stand in a refrigerator overnight. The colorless crystalline product is isolated by suction and recrystallized from EtOH/H_2O or EtOAc/petroleum ether.

Method B: A mixture of benzyl carbamate (**1**; 0.6 g, 4 mmol), the dialkyl phosphite **3** (4 mmol) and AcCl (3 mL) is stirred at −5°C in an ice/salt bath, the aldehyde **2** (5 mol) is added dropwise during a period of 10 min, and stirring is continued at 0°C for 1 h. The cooling bath is removed, the mixture is stirred at ambient temperature for 6 h, and then allowed to stand overnight. The volatile components are removed under reduced pressure. The remaining product is recrystallized from EtOH/H_2O or EtOAc/hexane in the case of solids; oily products are dissolved in CH_2Cl_2 (15 mL), this solution is washed with H_2O (10 mL), sat. aq $NaHSO_3$ solution (2 × 10 mL), and dil. aq $NaHCO_3$ solution (3 × 10 mL), and acidified to pH 6 with 1 N aq HCl. The organic solution is washed with water (2 × 10 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the product **4**, which is pure enough for partial hydrolysis without further purification.

Dialkyl or Diphenyl α-Aminobenzylphosphonate Hydrobromides 5b,e,g; General Procedure:

To a stirred solution of diester **4b**, **4e**, or **4g** (3 mmol) in AcOH (2.2 mL), a 32.6% solution of HBr in AcOH (3.1 mL) is added and stirring is continued (1–1.5 h) until no more starting compound **4** can be detected by TLC on silica gel using EtOAc/hexane (1:1) as eluent. The solution is diluted with dry Et_2O until the hydrobromide precipitates.[14]

Compound **5b**; yield: 60%; mp 262–264°C (Lit.[16] mp 268–270°C).

IR (KCl): ν = 3350 (w, NH), 1520 (m, NH), 1220 (s, P=O), 1010 cm^{-1} (s, P–O–C).

^{1}H-NMR (TFA/TMS_{ext}): δ = 0.60–1.0 (q, 6H, $2CH_3$), 3.80 (m, 4H, $2CH_2CH_3$), 4.60 (br, 1H, *J* = 18 Hz, CH-P), 7.10 (s, 5H_{arom}).

Table 1. Compounds **4** Prepared

Product	Method	Reaction Time (h)	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	IR (KCl or neat) ν(cm^{-1})			
						N–H	C=O	P=O	P–O–C
4a	A	9	88	120–121	120–121[8]	3250	1716	1240	1040
4b	A	6	92	114–116	113–114[10]	3250	1720	1260	1035
	B	3	86	115–117					
4c	A	8	81	71–72	$C_{21}H_{28}NO_5P$ (405.4)	3200	1710	1246	1000
4d	A	6	87	97–99	$C_{23}H_{32}NO_5P$ (433.5)	3250	1720	1255	1030
4e	A	3	74	160–161	138–140[15]	3150	1700	1220	1000
4f	A	5.5	82	125–127	$C_{18}H_{22}NO_6P$ (379.3)	3250	1716	1240	1040
4g	A	11	93	103–105	$C_{20}H_{26}NO_6P$ (407.4)	3260	1720	1260	1040
	B	3	95	103–105					
4h	A	9	95	109–110	$C_{24}H_{34}NO_6P$ (463.5)	3290	1720	1240	1010
4i	A	5	70	159–160	$C_{28}H_{26}NO_6P$ (503.5)	3280	1720	1260	1060
4j	A	6	84	110–111	$C_{18}H_{22}NO_5P$ (363.35)	3300	1725	1260	1040
4k	A	12	98	116–117	$C_{20}H_{26}NO_5P$ (391.4)	3270	1910	1285	1190
4l	A	5	50	162–163	$C_{28}H_{26}NO_5P$ (487.5)	3150	1700	1220	1000
4m	B	6	68	oil	$C_{14}H_{22}NO_5P$ (315.3)	3250	1710	1250	1025
4n	B	6	66	oil	85–86[10]	3200	1710	1230	1030
4o	B	6	43	oil	oil[10]	3200	1710	1240	1040

[a] Satisfactory microanalyses: C ±0.35, H ±0.25, N +0.28.

Table 2. ^{1}H-NMR-Spectral Data of Compounds **4**

Compound	^{1}H-NMR (CCl_4/TMS) δ, J(Hz)
4a	3.14–3.63 (dd, 6H, J = 11, $2OCH_3$), 4.70–5.20 (m, 3H, CH_2Ph, CH–P), 6.50 (s, 1H, NH), 7.16 (s, $10H_{arom}$)
4b	1.00–1.40 (dt, 6H, $2CH_2CH_3$), 3.58–4.25 (m, 4H, $2OCH_2CH_3$), 4.95–5.45 (m, 3H, CH_2, CH–P), 6.2 (b, 1H, NH), 7.65 (s, $10H_{arom}$)
4c	1.05 [dd, 12H, J = 7, $2CH(CH_3)_2$], 4.35–4.70 [m, 2H, $2CH(CH_3)_2$], 4.75–5.35 (m, 1H, CH–P), 5.10 (s, 2H, CH_2Ph), 7.05–7.55 (m, $10H_{arom}$)
4d	0.95 (t, 6H, $2OCH_2CH_2CH_2CH_3$), 1.10–1.45 (m, 8H, $2CH_2CH_2CH_3$), 3.50–4.15 (m, 8H, OCH_3, $2POCH_2$, CH–P), 5.05 (s, 2H, CH_2Ph), 6.75–7.65 (m, $10H_{arom}$)
4e	5.0 (s, 2H, CH_2Ph), 5.2–5.75 (dd, 1H, J_{PH} = 12, J_{HH} = 10, CH–P), 6.64–7.51 (m, $21H_{arom}$, NH)
4f	3.33–3.95 (dd, 9H, J = 12, $2OCH_3$), 4.86–5.40 (m, 3H, CH_2Ph, CH–P), 6.87–7.83 (m, $10H_{arom}$, NH)
4g	0.88–1.30 (m, 6H, $2CH_2CH_3$), 3.48–4.25 (m, 7H, OCH_3, $2OCH_2CH_3$), 4.77–5.30 (m, 3H, CH_2Ph, CH–P), 6.68–7.70 (m, $10H_{arom}$, NH)
4h	0.85 (t, 6H, $2CH_2CH_3$), 1.40 (br, 8H, $2CH_2CH_2CH_2CH_3$), 3.50–4.02 (m, 7H, OCH_3, $2CH_2O$), 4.80–5.32 (m, 3H, CH–P, CH_2Ph), 6.7–6.8 (d, 4H, J = 7, $4H_{arom}$), 7.2–7.7 (m, $5H_{arom}$)
4i	3.80 (s, 3H, OCH_3), 5.10 (s, 2H, CH_2Ph), 5.01–5.25 (m, 1H, CH–P), 7.10–7.50 (m, $19H_{arom}$)
4j	2.49 (s, 3H, $C_6H_4CH_3$), 3.40–3.90 (dd, 6H, J = 12, $2OCH_3$), 5.00–5.50 (m, 3H, $PhCH_2$, CH–P), 7.40 (s, $9H_{arom}$)
4k	0.88–1.28 (m, 6H, $2CH_2CH_3$), 2.03–2.32 (d, 2H, J = 17, $C_6H_4CH_3$), 3.40–4.26 (m, 4H, $2OCH_2CH_3$), 4.75–5.28 (m, 3H, CH_2Ph, CH–P), 6.96–7.43 (m, $9H_{arom}$)
4l	2.35 (s, 3H, $C_6H_4CH_3$), 5.10 (s, 2H, CH_2Ph), 5.15–5.35 (m, 1H, CH–P), 6.70–7.65 (m, $19H_{arom}$)
4m	0.95 (t, 3H, CH_2CH_3), 1.55 (m, 4H, $CH_2CH_2CH_3$), 3.80 (d, 6H, J_{PH} = 10, $2OCH_3$), 3.85–4.25 (m, 1H, CH–P), 5.10 (s, 2H, CH_2Ph), 6.50 (br, 1H, NH), 7.35 (s, $5H_{arom}$)
4n	0.80–0.92 [d, 6H, J = 7.0, $CH(CH_3)_2$], 1.80–2.41 [m, 1H, $CH(CH_3)_2$], 3.43–3.62 (dd, 6H, J = 11, $2POCH_3$), 3.5–4.1 (m, 1H, CH–P), 4.96 (s, 2H, CH_2Ph), 6.4 (d, 1H, J = 12, NH), 7.16 (s, $5H_{arom}$)
4o	0.91 [d, 6H, J = 7.0, $CH(CH_3)_2$], 1.16–1.36 (t, 6H, $2OCH_2CH_3$), 1.80–2.41 [m, 1H, $CH(CH_3)_2$], 3.5–4.2 (m, 5H, CH–P, $2CH_2CH_3$), 4.95 (s, 2H, CH_2Ph), 5.7–5.86 (bd, 1H, J = 12, NH), 7.25 (s, $5H_{arom}$)

Compound **5e**; yield: 97%; mp 195–196°C (Lit.[15] mp 194–195°C).

IR (KCl): ν = 3350 (s, NH), 1200, 1175 (s, P=O), 940 cm^{-1} (s, P–O–C).

^{1}H-NMR (TFA/TMS_{ext}): δ = 5.00 (m, 1H, CH-P), 6.75 (m, $15H_{arom}$), 7.68 (br, 3H, NH).

Compound **5g**; yield: 45%; mp 193–194°C.

$C_{12}H_{21}BrNO_4P$ (354.2) calc. C 40.69 H 5.99 N 3.69; found 40.00 5.84 3.86

IR (KCl): ν = 3350 (w), 1500 (s, NH), 1250 (s, P=O), 1030 cm^{-1} (s, P–O–C).

^{1}H-NMR (TFA/TMS_{ext}): δ = 0.60–0.90 (dt, 6H, J = 6.5 Hz, $2CH_3$), 3.40–4.00 (m, 7H, OCH_3, $2CH_2CH_3$), 4.70 (br, 1H, J = 15 Hz, CH-P), 6.65–7.10 (m, 4H, H_{arom}).

Methyl Hydrogen 1-(Benzyloxycarbonylamino)-2-methylpropylphosphonate (6n); Typical Procedure:

A mixture of diester **4n** (0.4 g, 1.27 mol), 2N aq NaOH (2 mL), and Bu_4NBr (a catalytic amount) is stirred at r.t. for 6 h, then allowed to stand overnight. The mixture is diluted with H_2O (10 mL) and extracted with EtOAc (2 × 5 mL). The aqueous solution is acidified to pH 7 with 6N aq HCl; then, the solution is adjusted to pH 2 by dropwise addition of 2N H_2SO_4. The product is extracted with EtOAc (4 × 5 mL) and the extract is dried (Na_2SO_4). Removal of the solvent under reduced pressure gives an oily crude product which solidifies upon standing. Recrystallization from EtOAc/hexane affords **6n** as colorless crystalline solid; yield: 0.22 g (58%); mp 103–104°C (Lit.[15] mp 105–106°C).

IR (KCl): ν = 3300 (m, NH), 3240 (m, NH), 1700 (s, C=O), 1520 (s, NH), 1240 (s, P=O), 1040 cm^{-1} (s, P–O–C).

^{1}H-NMR (CCl_4/TMS_{ext}): δ = 0.90 [d, 6H, J = 6 Hz, $CH(CH_3)_2$], 2.0 [m, 1H, $CH(CH_3)_2$], 3.7 (d, 3H, J_{PH} = 10 Hz), 3.7–4.2 (m, 1H, CH-P), 5.02 (s, 2H, CH_2Ph), 5.4 (b, 1H, NH), 7.25 (s, $5H_{arom}$).

Ethyl Hydrogen α-(Benzyloxycarbonylamino)benzylphosphonate **(6b)** is prepared in an analogous manner; yield: 48%; mp 192–194°C (Lit.[15] mp 188–190°C).

IR (KCl): ν = 3250, 1550 (s, NH), 1710 (s, C=O), 1240 (s, P=O), 1040 cm^{-1} (s, P–O–C).

^{1}H-NMR (DMSO-d_6/TMS_{ext}): δ = 1.1 (t, 3H, J = 6.5 Hz, CH_2CH_3), 3.9 (m, 2H, CH_2CH_3), 4.7–5.1 (m, 1H, CH-P), 5.1 (s, 2H, $PhCH_2$), 7.2–7.6 (m, $10H_{arom}$), 8.1–8.4 (br, 1H, NH).

Methyl Hydrogen 1-(Benzyloxycarbonylamino)butylphosphonate **(6m)** is prepared in an analogous manner; yield: 61%; mp 113–115°C.

$C_{13}H_{20}NO_5P$ (301.3) calc. C 51.82 H 6.70 N 4.65; found 51.40 6.54 4.29

IR (KCl): ν = 3280, 1540 (s, NH), 1690 (s, C=O), 1220 (s, P=O), 1640 cm^{-1} (s, P–O–C).

^{1}H-NMR (CCl_4/TMS_{ext}): δ = 0.79 (br, 3H, CH_2CH_3), 1.40 (m, 4H, $CH_2CH_2CH_3$), 3.45–3.64 (d, 3H, J = 11 Hz, $POCH_3$), 3.50–4.20 (m, 1H, CH-P), 5.05 (s, 2H, CH_2Ph), 7.17 (s, $5H_{arom}$).

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