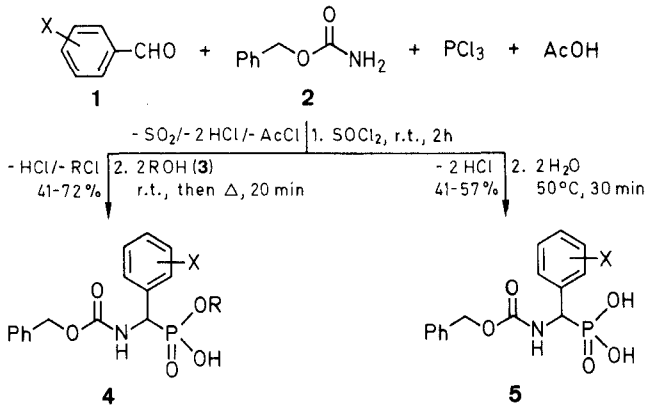
Studies on Organophosphorus Compounds; XLI. A Convenient Synthesis of Alkyl Hydrogen α-(Benzyloxycarbonylamino)benzylphosphonates

Chengye Yuan,* Guohong Wang

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Linglin Lu, Shanghai 200032, People's Republic of China

Alkyl hydrogen α-(benzyloxycarbonylamino)benzylphosphonates are prepared from substituted benzaldehydes, benzyl carbamate, and phosphorus(III) chloride in acetic acid containing thionyl chloride and subsequent alcoholysis. The reactions proceed smoothly at room temperature and afford the title compounds in moderate to good yield.

The present interest in phosphonopeptides centers around the biological activity and the search for convenient syntheses of these compounds.[1] Phosphonopeptides with P–N bonds are of significant interest due to the fact that they are excellent mimetics of the tetrahedral transition states of enzymatic peptide hydrolysis and consequently are potential inhibitors of proteases.[1-4] The key intermediates for the synthesis of peptides having a phosphonamide linkage are the monoesters of *N*-protected aminoalkylphosphonic acids which are usually prepared by a multistep procedure involving blocking of the amino function and partial esterification of the phosphonic acid moiety with an appropriate alcohol in the presence of a specific condensing agent.[5-7] Partial hydrolytic or non-hydrolytic cleavage of *N*-protected dialkylaminoalkylphosphonates also leads to the corresponding monoesters. One of the limitations of this method is that the dialkyl phosphonates required in this process are not easily available, since phosphonic acid is resistant to esterification under the usual conditions.



4	R	X	4	R	X
a	Me	H	**g**	Me	4-OMe
b	Et	H	**h**	Et	4-OMe
c	Pr	H	**i**	*i*-Pr	4-OMe
d	*i*-Pr	H	**j**	CH_2CH_2Ph	4-OMe
e	CH_2Ph	H	**k**	Et	4-Cl
f	CH_2CH_2Ph	H	**l**	Et	4-Br

5	X	5	X
a	H	**d**	3-Br
b	4-Me	**e**	4-OMe
c	4-Cl		

We report here a novel convenient method for the synthesis of alkyl hydrogen α-(benzyloxycarbonylamino)-benzylphosphonates **(4)** by the reaction of substituted benzaldehydes[1] with benzyl carbamate **(2)** and phosphorus(III) chloride in glacial acetic acid containing thionyl chloride, followed by alcoholysis. If the final alcoholysis is replaced by hydrolysis, the reaction affords the corresponding phosphonic acids **5** in moderate yields.

The role of the thionyl chloride used in the reaction is not quite clear. As has been reported,[5] the reaction of a dibasic phosphonic acid with an alcohol and thionyl chloride always affords the monoester and neither the use of larger amounts of thionyl chloride and alcohol nor a prolonged reaction time yield the corresponding diester. It should further be mentioned that the reaction of phosphonic acid dihalides with 2 mole equivalents of an alcohol without the addition of thionyl chloride also affords the monoesters.[9]

In contrast to a similar method[8] reported for the preparation of 1-(alkylamino)alkylphosphonic and 1-(alkylamino)alkylphenylphosphinic acids from aldehydes, benzyl alkylcarbamates, and phosphorus(III) chloride or phenyldichlorophosphine, respectively, the present method provides a one-pot procedure for the preparation of monesters of *N*-protected 1-aminoalkylphosphonic acids. The yields are satisfactory, the products are of high

Table 1. Compounds **4** and **5** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a] Lit. mp (°C)
4a	41	175–177[b]	174–175[6]
4b	56	191–193[b]	189–190[6]
4c	68	188–191[b]	$C_{18}H_{22}NO_5P$ (363.2)
4d	57	194–196[b]	198–199[6]
4e	61	151–153[c]	152–154[6]
4f	72	149–151[c]	$C_{23}H_{24}NO_5P$ (435.2)
4g	41	160–162[b]	$C_{17}H_{20}NO_6P$ (365.2)
4h	47	187–189[b]	$C_{18}H_{22}NO_6P$ (379.16)
4i	58	182–184[c]	$C_{19}H_{24}NO_6P$ (393.2)
4j	45	164–166[c]	$C_{24}H_{26}NO_6P$ (455.2)
4k	61	178–179[b]	$C_{17}H_{19}ClNO_5P$ (383.6)
4l	53	175–177[b]	$C_{17}H_{19}BrNO_5P$ (428.1)
5a	48	147–149[d]	152–153[9]
5b	56	148–150[d]	$C_{16}H_{18}NO_5P$ (335.2)
5c	41	154–156[d]	$C_{15}H_{15}ClNO_5P$ (356.5)
5d	68	142–144[d]	$C_{15}H_{15}BrNO_5P$ (400.0)
5e	57	147–149[d]	$C_{16}H_{18}NO_6P$ (351.1)

[a] Satisfactory microanalyses: C ±0.28, H ±0.24, N ±0.25, P ±0.18.
[b] From ROH **(3)**/H_2O.
[c] From $CHCl_3$/hexane.
[d] From EtOAc/hexane.

Table 2. Spectral Data of Compounds **4** and **5**

Compound	IR (KBr) ν (cm^{-1})				^{1}H-NMR (DMSO-d_6/TMS) δ, J(Hz)
	N–H	C=O	P=O	P–O–C	
4a	3300	1720	1240	1020	3.65 (d, 3H, J = 11, $POCH_3$), 4.80–5.30 (m, 1H, CH–P), 5.10 (s, 2H, $C\underline{H}_2Ph$), 7.10–7.70 (m, 10H_{arom}), 8.10–8.30 (m, 1H, NH)
4b	3310	1720	1250	1050	1.10 (t, 3H, J = 7, $CH_2C\underline{H}_3$), 3.90 (m, 2H, $C\underline{H}_2CH_3$), 4.70–5.30 (m, 1H, CH–P), 5.10 (s, 2H, $C\underline{H}_2Ph$), 7.20–7.60 (m, 10H_{arom}), 8.10–8.40 (m, 1H, NH)
4c	3310	1710	1240	1040	0.80 (t, 3H, $CH_2CH_2C\underline{H}_3$), 1.40–1.70 (m, 2H, $CH_2C\underline{H}_2CH_3$), 3.40–3.60 (m, 2H, $CH_2CH_2CH_3$), 4.80–5.10 (m, 1H, CH–P), 5.00 (s, 2H, $C\underline{H}_2Ph$), 7.10–7.50 (m, 10H_{arom}), 8.00–8.40 (m, 1H, NH)
4d	3340	1730	1250	1040	1.10 [d, 6H, J = 6, $CH(C\underline{H}_3)_2$], 4.10–4.50 (m, 1H, POCH), 4.60–5.20 (m, 1H, CH–P), 5.00 (s, 2H, $C\underline{H}_2Ph$), 7.90–8.30 (m, 1H, NH)
4e	3300	1720	1250	1050	4.70–5.30 (m, 5H, $C\underline{H}$–P, $C\underline{H}_2C\underline{H}_2Ph$), 7.00–7.80 (m, 15$H_{arom}$), 8.00–8.30 (m, 1H, NH)
4f	3310	1740	1260	1040	2.55 (t, 2H, J = 6, CH_2CH_2Ph), 3.10–3.90 (m, 2H, CH_2CH_2Ph), 4.60–5.20 (m, 1H, CH–P), 5.00 (s, 2H, $C\underline{H}_2Ph$), 7.00–7.60 (m, 15H_{arom}), 7.90–8.30 (m, 1H, NH)
4g	3300	1720	1240	1040	3.60 (d, 3H, J = 11, $POCH_3$), 3.75 (s, 3H, $C_6H_4OC\underline{H}_3$), 4.80–5.20 (m, 1H, CH–P), 5.10 (s, 2H, $C\underline{H}_2Ph$), 6.85–7.70 (m, 9H_{arom}), 8.10 (m, 1H, NH)
4h	3330	1730	1250	1050	1.00 (t, 3H, J = 6.5, $CH_2C\underline{H}_3$), 3.65–3.95 (m, 2H, $C\underline{H}_2CH_3$), 3.70 (s, 3H, $C_6H_4OC\underline{H}_3$), 4.80–5.20 (m, 1H, CH–P), 5.00 (s, 2H, $C\underline{H}_2Ph$), 6.70–7.50 (m, 9H_{arom}), 7.90–8.20 (m, 1H, NH)
4i	3350	1730	1260	1040	1.00 [d, 6H, J = 6.5, $CH(C\underline{H}_3)_2$], 3.70 (s, 3H, $C_6H_4OC\underline{H}_3$), 4.20–4.60 (m, 1H, POCH), 4.80–5.20 (m, 1H, CH–P), 5.10 (s, 2H, $C\underline{H}_2Ph$), 6.60–7.40 (m, 9H_{arom}), 7.90–8.20 (m, 1H, NH)
4j	3340	1740	1240	1025	2.50 (t, 2H, J = 7, CH_2CH_2Ph), 3.70 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.20–3.90 (m, 2H, CH_2CH_2Ph), 4.80–5.30 (m, 1H, CH–P), 5.10 (s, 2H, $C\underline{H}_2Ph$), 7.10–7.70 (m, 14H_{arom}), 8.10–8.40 (m, 1H, NH)
4k	3350	1760	1220	1025	1.00 (t, 3H, J = 7, $CH_2C\underline{H}_3$), 3.95 (m, 2H, $C\underline{H}_2CH_3$), 4.80–5.20 (m, 1H, CH–P), 5.10 (s, 2H, $C\underline{H}_2Ph$), 7.10–7.70 (m, 9H_{arom}), 8.10–8.40 (m, 1H, NH)
4l	3350	1720	1220	1020	1.15 (t, 3H, J = 7, $CH_2C\underline{H}_3$), 3.70–4.15 (m, 2H, $C\underline{H}_2CH_3$), 4.80–5.30 (m, 1H, CH–P), 5.10 (s, 2H, $C\underline{H}_2Ph$), 7.10–7.70 (m, 9H_{arom}), 8.10–8.40 (m, 1H, NH)
5a	3280	1700	1250		5.20 (d, 2H, J = 8, $C\underline{H}_2Ph$), 5.05–5.30 (m, 1H, $C\underline{H}$–P), 6.80–7.50 (m, 10H_{arom})
5b	3400	1730	1230		2.30 (s, 3H, $ArC\underline{H}_3$), 5.20 (s, 2H, $C\underline{H}_2Ph$), 5.00–5.30 (m, 1H, CH–P), 6.85–7.50 (m, 9H_{arom})
5c	3350	1720	1250		5.22 (d, 2H, J = 9.5, $C\underline{H}_2Ph$), 5.10–5.30 (m, 1H, CH–P), 6.80–7.50 (m, 9H_{arom})
5d	3320	1750	1240		5.20 (d, 2H, J = 9, $C\underline{H}_2Ph$), 5.00–5.30 (m, 1H, CH–P), 6.85–7.50 (m, 9H_{arom})
5e	3250	1700	1220		3.60 (s, 3H, $C_6H_4OC\underline{H}_3$), 5.20 (s, 2H, J = 8.5, $C\underline{H}_2Ph$), 5.10–5.30 (m, 1H, CH–P), 6.80–7.60 (m, 9H_{arom})

purity (Tables 1 and 2), and the procedure is simple. However, this method appears to be limited to benzaldehydes and benzyl carbamate, since attempts to extend the reaction to aliphatic aldehydes and simple carboxamides (acetamide, benzamide, trifluoroacetamide) failed.

Melting points were determined in capillary tubes and are uncorrected. IR spectra were recorded on a Shimadzu 440 spectrophometer and ^{1}H-NMR spectra on a Varian EM-360L spectrometer.

Alkyl Hydrogen α-(Benzyloxycarbonylamino)benzylphosphonates 4a–l; General Procedure:

The freshly distilled aldehyde **1** (0.0012 mol) is slowly added to a stirred mixture of benzyl carbamate (**2**; 152 mg, 0.001 mol), PCl_3 (138 mg, 0.001 mol), AcOH (5 mL), and $SOCl_2$ (2 mL). After 2 h, the solvent and low-boiling components are removed under reduced pressure and the alcohol **3** (5–10 mL) is added slowly. The reaction is continued until the mixture has completely solidified. The mixture is then heated under reflux for 20 min, the volatile components are removed on a rotatory evaporator under reduced pressure (heating on an oil bath), and the solid residue is recrystallized from the alcohol **3** or $CHCl_3$ hexane. (Tables 1, 2).

α-(Benzyloxycarbonylamino)benzylphosphonic Acids 5; General Procedure:

The freshly distilled benzaldehyde **1** (0.0012 mol) is slowly added to a stirred mixture of benzyl carbamate (**2**; 152 mg), PCl_3 (138 mg, 0.001 mol), AcOH (10 mL), and $SOCl_2$ (2 mL). Stirring is continued at r.t. for 2 h and the mixture then heated at reflux temperature for 15 min. The volatile products are removed on a rotatory evaporator under reduced pressure (heating on an oil bath). The oily residue is dissolved in H_2O (10 mL) and this solution is heated at 50 °C for 30 min, then cooled to ambient temperature. The organic layer is extracted with Et_2O (3 × 20 mL), dried ($MgSO_4$), and evaporated. The remaining crude product is recrystallized from EtOAc/hexane. (Tables 1, 2).

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