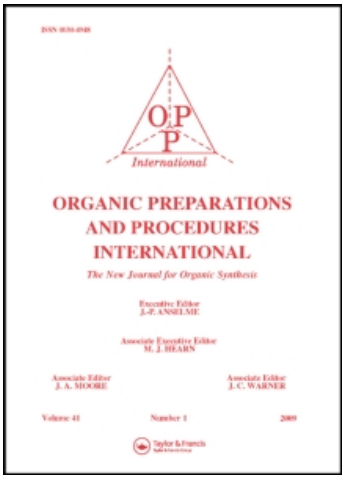

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A FACILE SYNTHESIS OF 1-BENZYLOXYCARBONYLAMINO-(SUBSTITUTED)PHENYLMETHYLPHOSPHINATES

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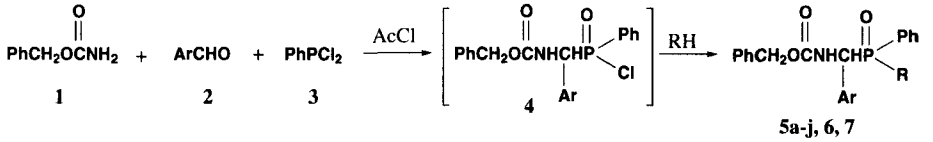
The synthesis of phosphonopeptides and phosphinopeptides with potential biological activity has attracted much attention.[1] Since the aminophosphonic acids cannot be used directly in condensation processes to form phosphonopeptides,[2] it is often necessary to convert them initially into the corresponding aminophosphonates. Therefore, the synthesis of aminophosphonates with readily removable protecting groups by a direct method is an important target in phosphonopeptide synthesis.[3-7] A survey of the literature shows that several methods have been developed for the preparation of dialkyl or diphenyl 1-(benzyloxycarbonylamino) alkylphosphonates[7-12] and for the removal of the protecting benzyloxycarbonyl group.[8-10] However, there are no reports for the preparation of the corresponding phenyl alkyl 1-(benzyloxycarbonylamino)alkylphosphinates, the building blocks of phosphinopeptides. This paper reports a facile synthesis of this class of compounds.

Benzyl carbamate (**1**) was treated with benzaldehyde (**2a**, Ar = Ph) and dichlorophenylphosphine (**3**) at -10° to 10° for 4 h in acetyl chloride as the solvent. After the removal of the solvent under vacuum, a white solid **4** was obtained. The crude **4** was reacted with excess alcohol to give the title compounds **5** directly; in addition, upon reaction with isopropylamine and ethylmercaptan in benzene, the corresponding phosphinamide **6** and phosphinthioate **7** were obtained respectively (Table 1).



1 2 3 4 **5a-j, 6, 7**

5a) Ar = Ph, R = MeO; **5b**) Ar = Ph, R = EtO; **5c**) Ar = Ph, R = PrO; **5d**) Ar = Ph, R = *i*-PrO; **5e**) Ar = *p*-Cl-Ph, R = MeO; **5f**) Ar = *p*-Cl-Ph, R = EtO; **5g**) Ar = *m*-Cl-Ph, R = EtO; **5h**) Ar = *p*-Me-Ph, R = EtO; **5i**) Ar = *m*-NO_2-Ph, R = EtO; **5j**) Ar = *p*-NO_2-Ph, R = EtO; **6**) Ar = Ph, R = *i*-PrNH; **7**) Ar = Ph, R = EtS

At first, the pale solid was assumed to be the corresponding phosphinic chloride **4**. However, the ^{31}P NMR spectrum of this compound showed two identical peaks at 53.1 and 50.0 ppm, indicating that the three-component condensation reaction might have produced two types of active phosphorus intermediates, presumably **9** and **10**. In order to establish the structures of **9** and **10**, the corresponding phosphinic acid **8** was chlorinated with thionyl chloride to form the corresponding phosphinic chloride **4**, the ^{31}P NMR spectrum of which also showed two identical peaks at 53.1 and 50.0 ppm, confirming that compounds **9** and **10** were the two disasteroisomers of compound **4**.

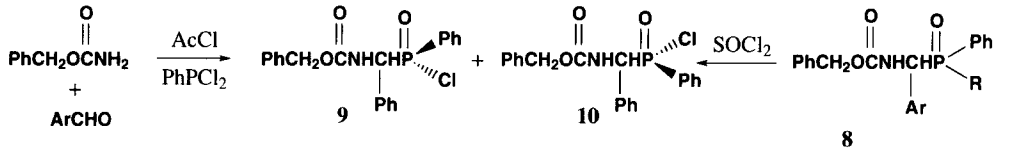


TABLE 1. The Physical Properties and Elemental Analyses of **5-7**

No.	R	mp. (°C)	Yield (%)	Elemental analysis (Found/calcd.) C(%)	N(%)	H(%)
5a	MeO	176-178	80.2	66.75 (66.84)	3.46 (3.54)	5.69 (5.57)
5b	EtO	173-175	85.6	67.61 (67.48)	3.34 (3.42)	5.91 (5.87)
5c	PrO	147-149	82.8	67.94 (68.08)	3.28 (3.31)	6.36 (6.15)
5d	*i*-PrO	143-145	78.4	68.12 (68.08)	3.24 (3.31)	6.30 (6.15)
5e	MeO	207-209	86.9	61.28 (61.47)	3.21 (3.26)	4.99 (4.89)
5f	EtO	178-179	88.6	62.39 (62.23)	3.01 (3.16)	5.28 (5.19)
5g	EtO	124-126	78.3	61.95 (62.23)	3.18 (3.16)	5.26 (5.19)
5b	EtO	180-182	85.8	67.94 (68.08)	3.28 (3.31)	6.25 (6.15)
5i	EtO	165-167	75.4	60.60 (60.53)	6.09 (6.17)	5.01 (5.07)
5j	EtO	170-172	84.3	60.71 (60.53)	6.05 (6.19)	4.98 (5.07)
6	*i*-PrNH	168-169	51.2	68.54 (68.25)	6.51 (6.64)	6.28 (6.40)
7	EtS	129-131	64.5	64.83 (64.94)	3.24 (3.29)	5.70 (5.65)

The role of acetyl chloride in this reaction is not quite clear yet.[8] However, it is evident that acetyl chloride makes it possible to produce stable phosphinic chloride **4**, which reacts with AcOH when present as the solvent. In addition, the ^{1}H NMR spectrum showed that some of the products also have two disasteroisomers. For example, the ^{31}P NMR spectrum of compound **5g** exhibits two peaks at 40.62 and 34.71 ppm. Furthermore, its ^{1}H NMR spectrum revealed that the two methylene hydrogen atoms in the ethyl group exhibit two groups of multiple peaks while the three methyl hydrogen atoms also exhibit two triplet groups. The integral area ratio of the two groups of peaks is nearly 1:1. A similar phenomenon was observed in some of the other products. We previously showed that a similar magnetic non-equivalence is caused by shielding and deshielding effects of the benzene ring at the α-position. [13] In the two disasteroisomers of the products, the alkoxy group lies on a different side of the benzene ring at the α-position. Therefore, the alkoxy group in **5g** exhibits two groups of peaks. Moreover, we still observed that the ratio of the two groups of peaks in different products are different. This may be due to the differences of the ratios of the two disasteroisomers obtained in different products. However, we are not clear as to the reason for the differences yet; it may be caused by the difference of the solubility of the two disasteroisomers in the recrystallization solution or by other more complex reasons.

EXPERIMENTAL SECTION

The melting points were uncorrected. Elemental analyses were determined on a Yanaco CHN Corder MT-3 apparatus. ^1H NMR and ^{31}P NMR spectra were recorded on a Bruker AC-P 200 spectrometer by using TMS and 85% H_3PO_3 as internal and external standards respectively.

Phenyl 1-Benzyloxycarbonylaminoarylmethylphosphinic Chloride (4).- A mixture of benzyl carbamate (**1**, 0.25 mol), dichlorophenylphosphine (**3**, 0.25 mol) and acetyl chloride (50 mL) was stirred in an ice-salt bath. The aromatic aldehyde **2** was then added dropwise (or in small portions if a solid). After stirring at r.t. for 4 h, the solvent was removed under vacuum to give crude **4**.

Phenyl 1-Benzyloxycarbonylaminoarylmethylphosphinate (5).- The crude **4** (5 mmol) was added to 10 mL of the anhydrous alcohol, and then the mixture was stirred at 40° for 1 h. After removal of the volatile components under reduced pressure, the residue was recrystallized from ethyl acetate and petroleum ether to give **5** in pure form in the yields of 75-88% (see Table 1 and Table 2).

TABLE 2. ^1H NMR Data of Compounds **5**, **6** and **7**

Cmpd	^1H NMR (δ, ppm, $CDCl_3$)
5a	7.16-7.60 (15 H, m, 3 x C_6H_5); 6.18 (1 H, br, NH); 4.95-5.22 (3 H, m, CH+CH_2); 3.68 (3 H, d, CH_3, $^3J_{P-H}$ = 10.53 Hz)
5b	7.16-7.67 (15 H, m, 3 x C_6H_5);~.05 (1 H, br, NH); 4.95-5.18 (3 H, m, CH+CH_2); 4.04 (2 H, m, CH_2O); 1.26 (3 H, t, CH_3)
5c	7.15-7.86 (15 H, m, 3 x C_6H_5); 6.08 (1 H, br, NH); 4.91-5.12 (3 H, m, CH+CH_2); 3.70-4.01 (2 H, m, CH_2O); 1.34-1.78 (2 H, m, CH_2); 0.73-0.91 (3 H, m, CH_3)
5d	7.14-7.88 (15 H, m, 3 x C_6H_5); 6.12 (1 H, br, NH); 4.95-5.24 (3 H, m, CH+CH_2); 4.28-4.80 (1 H, m, CHO); 0.95-1.26 (6 H, m, 2 x CH_3)
5e	7.10-7.75 (14 H, m, 2 x C_6H_5+C_6H_5); 6.02 (1 H, br, NH); 4.96-5.23 (3 H, m, CH+CH_2); 3.69 (3 H, d, CH_3. $^3J_{P-H}$ = 10.53 Hz)
5f	7.10-7.91 (14 H, m, 2 x C_6H_5+C_6H_4); 6.08 (1 H, br, NH.); 4.92-5.11 (3 H, m, CH+CH_2); 3.90-4.08 (2 H, m, CH_2O); 1.26 (3 H, t, CH_3)
5g	7.12-7.86 (14 H, m, 2 x C_6H_5+C_6H_4); 6.10 (1 H, br., NH); 4.86-5.15 (3 H, m, CH+CH_2); 3.70-4.20 (2 H, m, CH_2O); 1.06-1.28 (3 H, m, CH_3)
5h	7.00-7.75 (14 H, m, 2 x C_6H_5+C_6H_4); 5.98 (1 H, br, NH); 4.98-5.15 (3 H, m, CH+CH_2); 3.96-4.08 (2 H, m, CH_2O); 2.24 (3 H, s, CH_3-Ph), 1.25 (3 H, t, CH_3)
5i	7.24-8.36 (14 H, m, 2 x C_6H_5+C_6H_4); 6.70 (1 H, br, NH); 4.89-5.24 (3 H, m, CH+CH_2); 3.86-4.12 (2 H, m, CH_2O); 1.08-1.22 (3 H, m, CH_3)
5j	7.24-8.18 (14 H, m, 2 x C_6H_5+C_6H_4); 6.14 (1 H, br, NH); 4.94-5.30 (3 H, m, CH+CH_2); 3.86-4.14 (2 H, m, CH_2O); 1.10-1.33 (3 H, m, CH_3)
6	7.90 (1 H, br, NH-P); 7.10-7.66 (15 H, m, 3 x C_6H_5); 6.02 (1 H, br, NH-C(O)); 4.88-5.18 (3 H, m, CH+CH_2); 3.00-3.32 (1 H, m, CH), 0.93-1.19 (6 H, m,,2 x CH_3)
7	7.14-7.75 (15 H, m, 3 x C_6H_5); 6.20 (1 H, br, NH); 4.90-5.34 (3 H, m, CH+CH_2); 2.05-2.76 (2 H, m, CH_2S); 1.02-1.22 (3 H, m, CH_3)

Phenyl 1-Benzyloxycarbonylaminoarylmethylphosphinamide (6).- Crude **4** (5 mmol) was dissolved in dichloromethane (20 mL). Then a mixture of the amine (5 mmol), triethylamine (5 ramol), and dichloromethane (5 mL) was added dropwise at 0°. After stirring at r.t. for 4 h, the triethylamine hydrochloride was filtered off with suction. Then the filtrate was concentrated to dryness to give **6** in pure form in a yield of 51.2%. Compound **7** was synthesized likewise in a yield of 64.5% (see *Table 1 and 2*).

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