A Convenient Synthesis of Phenyl α-(Benzyloxycarbonylamino)benzylphosphinic Acids

Qing Dai,* Ruyu Chen
Institute and State's Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, People's Republic of China
Fax +86(22)3503438; E-mail: rychen@public.tpt.tj.cn

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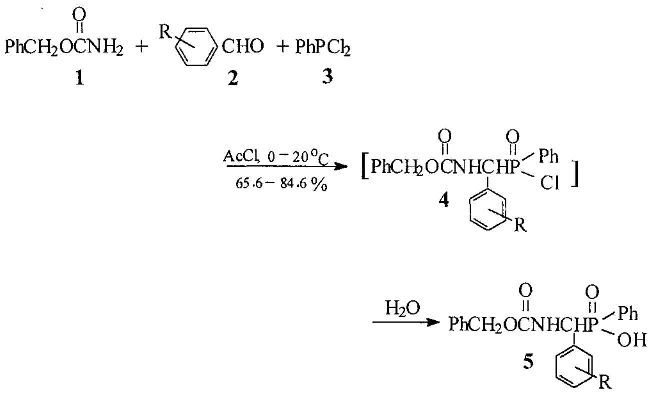
A series of phenyl α-(benzyloxycarbonylamino)benzylphosphinic acids are prepared from benzyl carbamate, substituted benzaldehydes and phenyldichlorophosphine in acetyl chloride via the corresponding phosphinic chloride **4**. The reaction proceeds smoothly at room temperature and affords the title compounds in good yields.

The present interest in phospho(i)nopeptides centers around the biological activity and the search for convenient syntheses of these compounds.[1] Phospho(i)nopeptides with P–N bonds are of significant interest due to the fact that they are excellent mimetics of the tetrahedral transition state and consequently are potential inhibitors of proteases, such as carboxypeptidase A and angiotensin-converting enzymes.[1–5] Although many methods have been developed for the synthesis of monoesters of *N*-protected aminoalkylphosphonic acids[6–10] which are the key intermediates for the synthesis of phosphonopeptides, reports on the synthesis of the corresponding phosphinic acids which are the key intermediates for the synthesis of phosphinopeptides are much fewer.[10,11] We previously reported that a three-component reaction of benzyl carbamate, aldehydes and phenyldichlorophosphine in acetic acid led to the formation of phenyl α-(benzyloxycarbonylamino)alkylphosphinic acids smoothly,[10] however, this method appeared to be limited to only some aliphatic aldehydes because attempts to extend the reaction to aromatic aldehydes failed. On the other hand, acetyl chloride has been employed as a good solvent in the synthesis of 1-amino(aryl)methylphosphonic acid derivatives.[12,13] Therefore, we attempted to modify our previous procedure by using acetyl chloride as the solvent instead of acetic acid to make the reaction adapt to aromatic aldehydes. Thus, by using acetyl chloride as the solvent, we found that aromatic aldehydes reacted readily with benzyl carbamate and phenyldichlorophosphine to give firstly phenyl α-(benzyloxycarbonylamino)benzylphosphinic chlorides **4**, which were then hydrolyzed to give the corresponding phosphinic acids **5** in satisfactory yields.

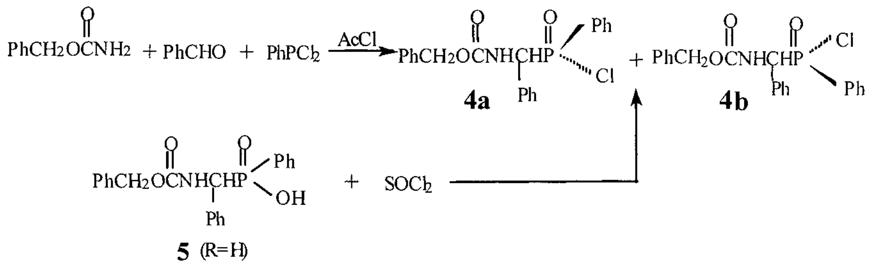


By using acetyl chloride as the solvent, benzyl carbamate (**1**) was reacted with benzaldehyde (**2a**) (R = H) and dichlorophenylphosphine (**3**) at −10 ~ 10 °C for 4 hours. After the removal of the solvent under vacuum, a pale solid was obtained. It was treated separately with water or alcohol to give phosphinic acid **5** or the corresponding

Table. Compounds 5 Prepared

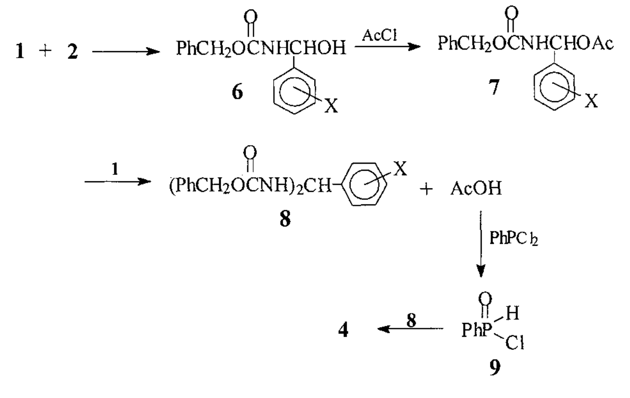
Product	R	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H NMR ([b]DMSO-d_6, [c]$CDCl_3$/TMS)
5a	H	85	216–218	$C_{21}H_{20}NO_5P$	4.80–5.15 (m, 1H, CH), 4.88 (d, 2H, C*H*$_2$Ph), 7.17–7.70 (m, 15H$_{arom}$), 8.20 (d, 1H, NH)[c]
5b	*p*-Me	76	243–245	$C_{22}H_{22}NO_5P$	2.30 (s, 3H, CH_3), 4.76–5.22 (m, 1H, CH), 4.90 (d, 2H, C*H*$_2$Ph), 7.08–7.88 (m, 14H$_{arom}$), 8.12–8.30 (m, 1H, NH)[b]
5c	*m*-Cl	72	214–216	$C_{21}H_{19}ClNO_5P$	4.90 (d, 2H, C*H*$_2$Ph), 4.98–5.26 (m, 1H, CH), 7.16–7.89 (m, 14H$_{arom}$), 8.20–8.40 (m, 1H, NH)[b]
5d	*p*-Cl	68	253–255	$C_{21}H_{19}ClNO_5P$	4.76–5.28 (m, 1H, CH), 4.92 (d, 2H, C*H*$_2$Ph), 7.16–7.88 (m, 14H$_{arom}$), 8.22–8.40 (m, 1H, NH)[b]
5e	2,4-Cl_2	80	194–196	$C_{21}H_{18}Cl_2NO_5P$	4.80–5.20 (m, 1H, CH), 4.94 (d, 2H, C*H*$_2$Ph), 7.16–7.96 (m, 13H$_{arom}$), 8.16–8.28 (m, 1H, NH)[b]
5f	*o*-MeO	66	158–160	$C_{22}H_{22}NO_6P$	3.37 (s, 3H, CH_3O), 5.76 (m, 1H, CH), 5.01 (d, 2H, C*H*$_2$Ph), 6.56–7.53 (m, 14H$_{arom}$), 8.44 (br s, 1H, NH)[c]
5g	*p*-MeO	83	226–228	$C_{22}H_{22}NO_6P$	3.76 (s, 3H, CH_3O), 4.76–4.20 (m, 1H, CH), 4.90 (d, 2H, C*H*$_2$Ph), 6.56–7.53 (m, 14H$_{arom}$), 8.44 (br s, 1H, NH)[c]
5h	*m*-NO_2	77	219–221	$C_{21}H_{20}N_2O_7P$	4.80–5.22 (m, 1H, CH), 4.94 (d, 2H, C*H*$_2$Ph), 7.08–7.96 (m, 14H$_{arom}$), 8.16–8.44 (m, 1H, NH)[b]
5i	*p*-NO_2	79	257–259	$C_{21}H_{20}N_2O_7P$	4.76–5.24 (m, 1H, CH), 4.94 (d, 2H, C*H*$_2$Ph), 7.16–7.94 (m, 14H$_{arom}$), 8.14–8.40 (m, 1H, NH)[b]

[a] Satisfactory microanalyses: C ± 0.45, H ± 0.28, N ± 0.22.



phosphinate. At first the pale solid was assumed to be the corresponding phosphinic chloride **4**; however, the ^{31}P NMR of this compound showed two identical peaks at $\delta = 53.1$ and 50.0 indicating that the three-component condensation reaction might give two kinds of active phosphorus intermediates, presumably **4a** and **4b**. In order to establish the structures of **4a** and **4b**, compound **5** (R = H) was chlorinated with thionyl chloride to form the corresponding phosphinic chloride **4**, the ^{31}P NMR of which also showed two identical peaks at $\delta = 53.1$ and 50.0, confirming that compounds **4a** and **4b** are, in fact, the two disasteroisomers of compound **4**.

As for the role of the acetyl chloride in this reaction, it is reasonable to postulate that it can help to form the intermediate **8** by the route shown below. Carbonyl addition of **1** to **2** forms the unstable adduct **6**, which is immediately chlorinated by acetyl chloride to give an *O*-acetyl derivative **7**. With another molecule of **1**, compound **7** is then converted to intermediate **8** by eliminating acetic acid, which can be separated in the course of the reaction and characterized. Obviously, the presence of acetic acid is unfavorable for the formation of intermediate **8**. This is perhaps the reason acetic acid is not suitable to be the solution in this reaction. In addition, we found that the intermediate **8** can not react directly with phenyldichlorophosphine in pure acetyl chloride. However, our experiment reveals that this reaction takes place smoothly with the addition of a little amount of acetic acid. Therefore, we suggest that acetic acid perhaps can react with phenyldichlorophosphine to form intermediate **9**, which then reacts with **8** to give the corresponding phosphonic chloride **4**.[14,15]



In contrast to the previous methods,[10] the present procedure offers a much more convenient method to form the corresponding phosphinic chloride **4**. Therefore, this reaction might also be used to synthesize the corresponding phosphinopeptide derivatives directly by forming **4**, followed by reaction with an amino acid ester without purification. These studies are in progress in our laboratory.

The melting points were uncorrected. Elemental analyses were measured by a Yanaco CHN Corder MT-3 apparatus.
^1H NMR spectra were recorded on a Bruker AC-200 spectrometer by using TMS as internal standard.

Phenyl α-(Benzyloxycarbonylamino)benzylphosphinic Acids 5; General Procedure:

Aldehyde **2** (5 mmol) was slowly added to a mixture of benzyl carbamate (**1**; 0.76 g; 5 mmol), phenyldichlorophosphine (**3**) (0.90 g, 5 mmol) and AcCl (10 mL) under cooling with ice-salt. After stirring at 0 °C for 0.5 h and then at r.t. for 1 h, the solvent was removed under reduced pressure. The residue was then solved in benzene (20 mL) and H_2O (2 mL) was added to the solution. After stirring at r.t. for 2 h, the solid was filtered and then crystallized from DMF and H_2O to give pure compound **5**. (Table)

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