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A FACILE SYNTHESIS OF PHENYL 1-BENZYLOXYCARBONYL-AMINO ARYLMETHYLPHOSPHINOPEPTIDE DERIVATIVES

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ABSTRACT: With acetyl chloride as the solvent, benzyl carbamate reacted with aromatic aldehyde and dichlorophenylphosphine to give phenyl 1- aryl methylphosphinic chloride, which reacted with an amino acid ester to give corresponding phosphinopeptide derivatives.

The synthesis of phosphonopeptides with potential biological activity have attracted much attention.[1] While numerous methods have been reported for the preparation of the derivatives of 1-benzyloxycarbonylamino phosphonic acid, which are important intermediates for the synthesis of phosphonopeptides,[2-5] there were few reports for the preparation of 1-benzyloxycarbonylamino phosphinic acid

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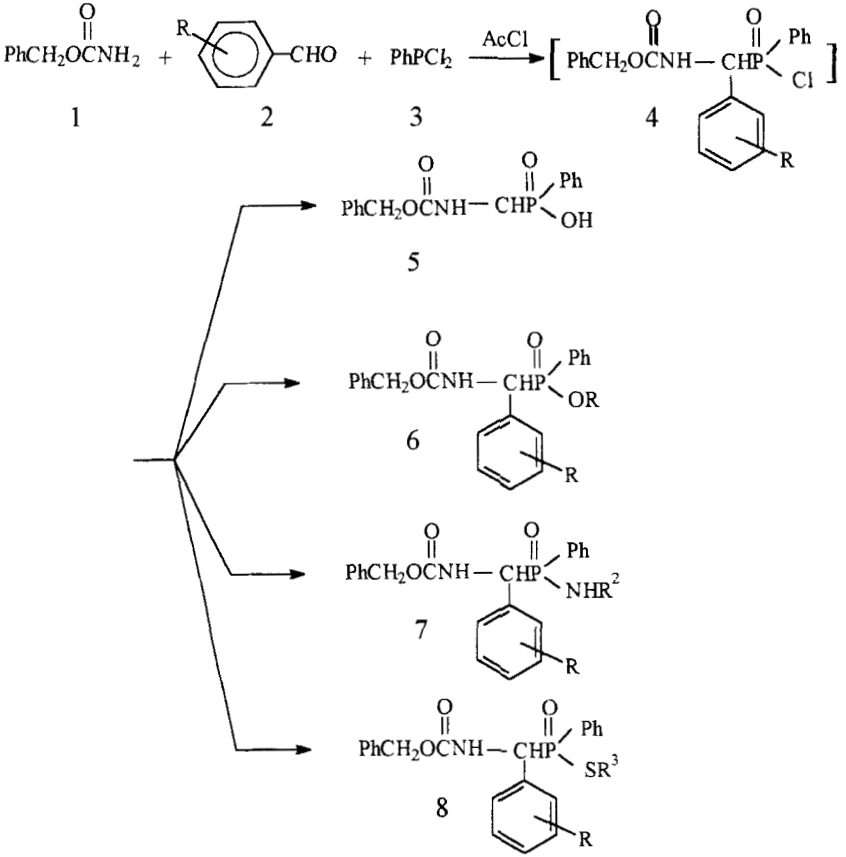
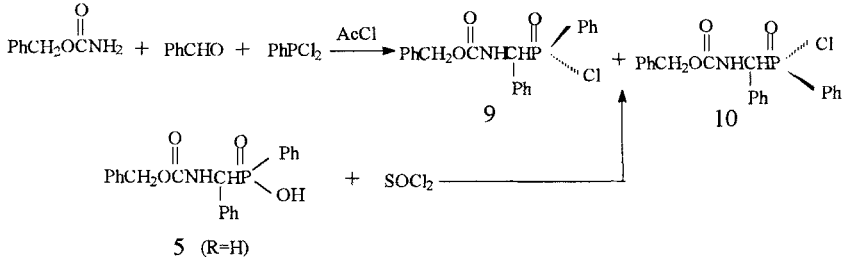
derivatives, except for the corresponding acid **5** , which could be prepared by a three-component reaction of benzyl carbamate 1 , aldehyde and dichlorophenyl-phosphine **3** with acetic acid as the solvent.[6] Compound **5** reacted with thionyl chloride first to form phosphinic chloride 4 , then reacted with an ester of an amino acid to afford the corresponding phosphinopeptide derivatives[6~8]. In this paper, we described a convenient approach to α-amino phosphinic acid and phosphinopeptide derivatives.



R=H, *o*-Cl, *m*-Cl, *p*-Cl, *p*-Me, *o*-MeO, *p*-MeO, *o*-NO_2, *m*-NO_2, *p*-NO_2

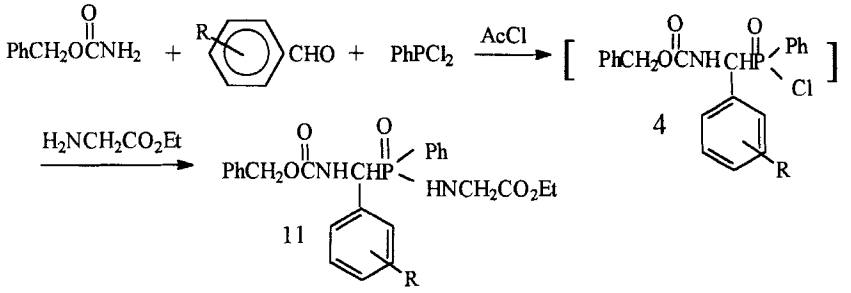
R^1=Me, Et, Pr, i-Pr; R^2=Pr, i-Pr; R^3=Et

By using acetyl chloride as the solvent, benzyl carbamate **1** was reacted with benzylaldehyde **2** (R=H) and dichlorophenylphosphine at -10 ~ 10 ℃ for 4 h, After the removal of the solvent under vacuum, a pale solid was obtained. It was treated separately with water, an alcohol, an amine or a mercaptan to give corresponding phosphinic acid **5**, phosphinate **6**, phosphinamide **7** and phosphinthioate **8** respectively. Therefore, the pale solid was assumed to be the corresponding phosphinic chloride **4** at first. However, the ^{31}P NMR of this compound showed two identical peaks a 53.1 and 50.0 ppm, indicating that the three-component condensation reaction might give two kinds of active phosphorus intermediates, presumably **9** and **10**. In order to establish the structure of **9** and **10,** 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 53.1 and 50.0 ppm, confirming that compound **9** and **10** are the two disasteroisomers of compound **4**.



The role of acetyl chloride in this reaction is not quite clear yet.[9] However, It is clear that acetyl chloride makes it possible to produce stable phosphinic chloride

4, which will react with AcOH in the case of acetic acid as the solvent. In addition, without purification, **4** could also react with esters of amino acids in a "one-pot" manner to give the phosphinopeptide derivative 11 as shown in the following equation. Thus, this approach have simplified significantly the previous procedure for synthesis phosphinopeptide derivatives containing P-N bond.



EXPERIMENTAL (General Procedure)

1. **Phenyl 1-benzyloxycarbonylamino arylmethylphosphinic chloride (4)**

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

2. **Phenyl 1-benzyloxycarbonylamino arylmethylphosphinic acid (5)**

The crude **4** (5 mmol)was added to benzene (20 mL), and then 1 mL of water was added into the mixture. After stirring at r.t. for 1 h, the white solid was

filtered and recrystallized from DMF and H_2O to give pure **5** in the yields of 45 ~ 76%.

3. **Phenyl 1-benzyloxycarbonylamino arylmethylphosphinate (6)**

The crude **4** (5 mmol) was added to 10 mL of anhydrous alcohol, and then the mixture was stirred at 40 ℃ for 11 h. After removal of the volatile components under reduced pressure, the residue was recrystallized from ethyl acetate and petroleum ether to give **6** in pure form in the yields of 52 ~ 78%.

4. **Phenyl 1-benzyloxycarbonylamino arylmethylphosphinamide (7)**

The crude **4** (5 mmol) was dissolved in dichloromethane (20mL). Then a mixture of amine (5 mmol), triethylamine (5 mmol) and dichloromethane (5 mL) was added dropwise at 0 ℃. After stirring at r.t. for 4 h, the triethylamine hydrochloride was filtered with suction. Then the filtrate was concentrated to dryness to give **7** in pure form in the yields of 42 ~ 65%. Compound **8** (R=H) were synthesized likewise in yield of 6.7% and 46%, respectively.

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