NOTE

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A Convenient Method for the Synthesis of Aminomethylmonoalkylphosphinate

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Starting from the readily available 4-methylbenzoic acid, an efficient protocol for the preparation of ethyl 4-(aminomethyl) benzyl (methyl) phosphinate (**1**), a novel aminomethylmonoalkylphosphinate was reported in this communication. The important step involves the selective monochlorination of phosphonic ester by $POCl_3$ and forming the phosphonochloridate, and followed by nucleophilic addition of CH_3MgBr to the acid chloride intermediate.

Keywords aminomethylmonoalkylphosphinate, nucleophilic addition, Mitsunobu reaction

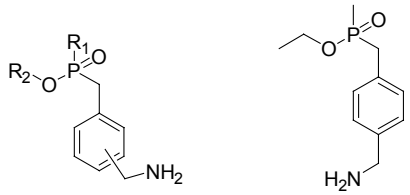
Introduction

Phosphinate esters are of paramount importance in a variety of fields, especially as intermediates for the synthesis of phosphine ligands, and in the preparation of biologically active compounds.[1] Functionalized, differentially substituted phosphinate esters $R^1R^2P(O)(OR)$ are also important organophosphorus intermediates particularly in the synthesis of medicinally relevant protease inhibitors.[2] Specifically, numerous amino phosphinate derivatives are developed as the biologically active compounds for example serine protease inhibitors, LAP inhibitors and NMDA antagonists.[3] Some of these compounds have been identified as natural products.[4] In this content, novel aminomethylmonoalkylphosphinate derivatives, which contain the aminomethyl group connecting the aromatic ring were proposed (Scheme 1). Owing to their unique structures, and furthermore, these compounds offered the opportunities for their potential as starting points for new pharmaceuticals or the building blocks for biologically active compounds. We thus became interested in developing a general and efficient approach to these novel amino phosphinate derivatives. To our knowledge, there is no literature concerning the synthesis of this type compounds.

Results and Discussion

In this paper, we wish to describe an effective strategy for the preparation of ethyl 4-(aminomethyl) benzyl (methyl) phosphinate (**1**), which was selected as the representative compound (Scheme 1). Its structure

Scheme 1 Structure of aminomethylarylphosphinate analogues



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features the monomethyl connecting the phosphorous atom directly and the aminomethyl group binding to the phenyl ring. The key step to the overall plan involves the P-chlorination of phosphonic ester with phosphorus oxychloride, then followed by nucleophilic addition reaction with methylmagnesium bromide and the monophosphate chloride and afforded the monomethylphosphinate. After that, the Mitsunobu reaction was applied to introduce the amino group. It should be mentioned that, there are several common methods to introduce the amino group into the phosphinate analogs. For example, nitrile group was introduced and then was reduced into amino group by Raney-Ni under hydrogen;[5] azide group is another amino resource;[6] also, the phosphinate intermediate was added to the imines and then removed the protective group to provide the amino group.[7] All of these methods had more or less shortcomings under the reaction conditions during the course of this methodology described in this report. However, the Mitsunobu reaction can smoothly provide the amino group under these mild conditions.

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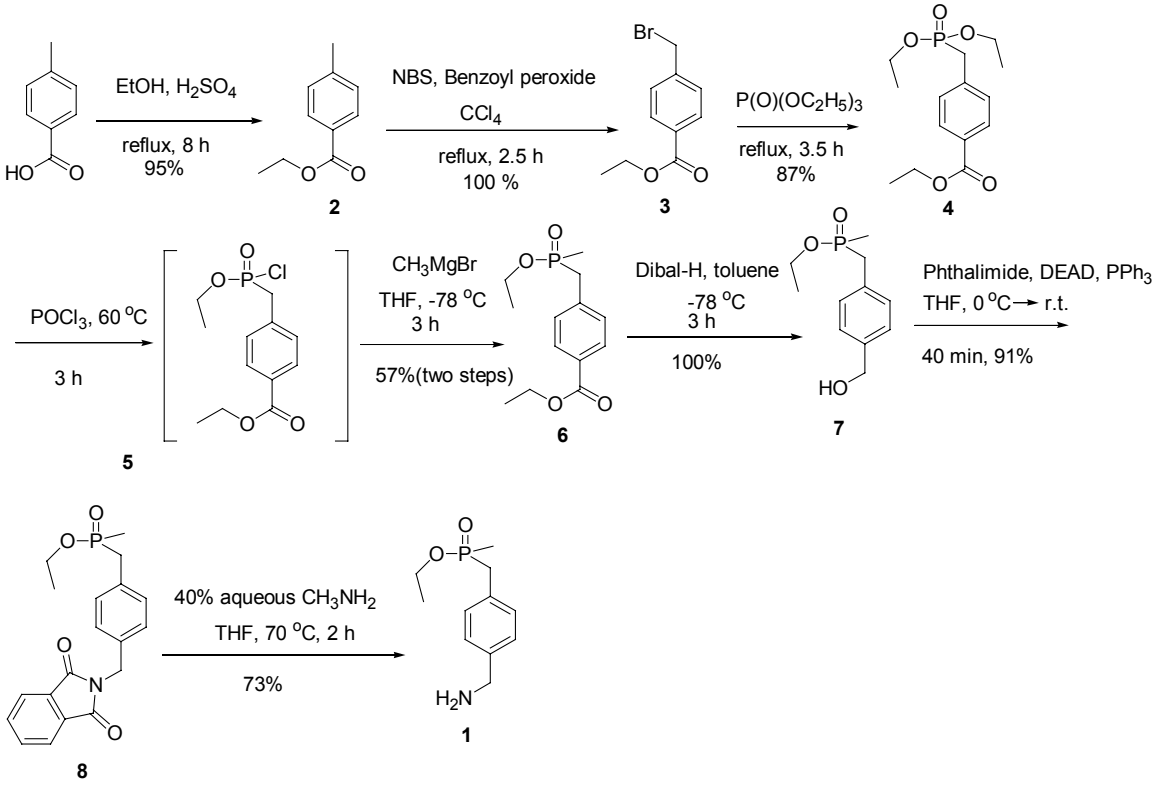
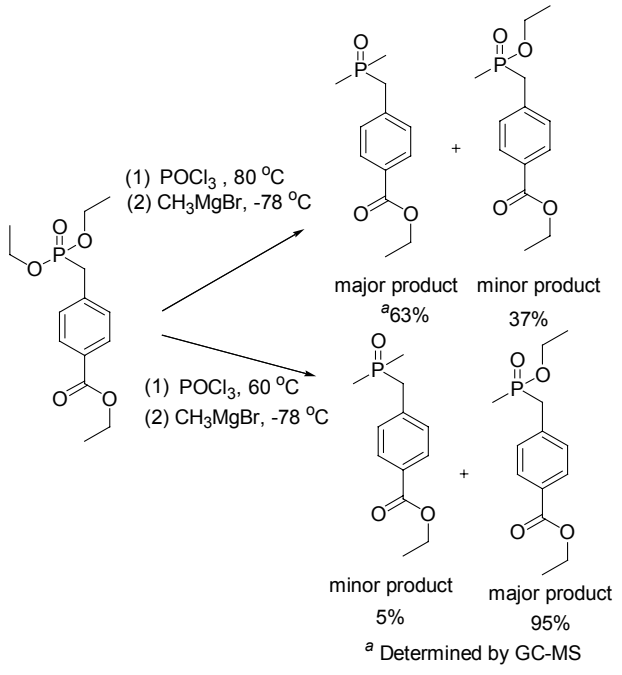
Scheme 2 Synthetic route to compound **1**



Scheme 3 The effect of temperature towards chlorination



As depicted in Scheme 2, the bromide **3**[8] was obtained through bromination of the ester **2**[9] under reflux in the presence of NBS and benzoyl peroxide. The subsequent Arbuzov reaction of triethylphosphite with the bromide **3** afforded the corresponding ethyl phosphonate **4**[10] in high yield. With the access to **4**, we were poised to study the chlorination step. Compound **4** was then treated with $POCl_3$ followed by alkylation reaction and provided the key intermediate **6**.[11] It should be pointed out that this step is crucial to the synthetic strategy. Phosphorus oxychloride was used to chlorinate the phosphate **4** at 60 ℃ followed by the nucleophilic addition with CH_3MgBr and the major product, monomethyl phosphinate **6**, was generated in good yield. However, when the reaction was carried out at higher temperature (80 ℃), the phosphonate **4** was prominently turned into the phosphonic dichloride and the major product was dimethylphosphinate (63%, determined by GC-MS, Scheme 3). In addition, to effect the monochlorination , different ratios (1∶1.05, 1∶1.25 and 1∶1.5) of phosphinate to $POCl_3$ were also screened and the results indicated there was not much difference among them although a slightly better result was observed for the ratio of 1∶1.05. These results indicated that the reaction temperature played a key role in the selectivity of chlorination.

With the desired **6** in hand, we turned our attention to the conversion of **6** into alcohol **7**. At first, compound **6** was treated with $NaBH_4$ in THF, several products were detected through TLC analysis, making it difficult to obtain the pure alcohol **7**. However, excess DIBAl-H performed very well under −78 ℃ furnishing alcohol **7** in quantitative yield. Of note, if the DIBAL-H was not used in excess and the reaction time was not enough (less than 3 h), it would produce a mixture of alcohol and aldehyde, rendering purification difficult. Subse-

quently, alcohol **7** was transformed via the Mitsunobu reaction[12] at 0 ℃ to room temperature into phthalimide derivative **8**. Finally, removal of the phthalimide protecting group was achieved via treatment with 40% aqueous methylamine to afford the desired compound **1** with good yield.

Conclusions

In conclusion, this is the first time that the synthetic sequence to new aminomethylmonoalkylphosphinate analogs with the total yield 31.3% has been reported, which was developed from a simple starting material. At the same time, the key factor concerning the problem of possible competitive side reactions was discussed. The reported synthetic strategy in this communication is explored for a general access to those analogs.

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[11] **The procedure for the preparation of compounds 6, 7, 8 and 1. (1) Synthesis of compound 6**: Compound **4** (1.50 g, 5 mmol) and $POCl_3$ (0.80 g, 5.125 mmol) were heated at 60 ℃ for 3 h, then the mixture was connected with a receiver flask which was cooled with dry ice and excess $POCl_3$ was vacuum transferred at r.t. After 40 min, the receive flask was disconnected and the crude ethyl 4-((chloro-(ethoxy)phosphoryl)methyl)benzoate (**5**) was used in the next step immediately without purification. A solution of the above compound **5** in anhydrous THF was cooled to −78 ℃ and CH_3MgBr (1.5 mol/L in THF, freshly made, 3.33 mL, 5 mmol) was then added slowly. The solution was stirred at −78 ℃ for 3 h then poured into cold saturated NH_4Cl solution. The mixture was extracted with ether, dried over anhydrous Na_2SO_4 and concentrated in vaccum. Purification of this residue by column chromatography (DCM/MeOH, 50∶1, *V*/*V*) allowed the isolation of viscous liquid **6** (0.71 g, 57% yields over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, J=7.5 Hz, 2H), 7.36 (dd, J_1=2.5 Hz, J_2=8.5 Hz, 2H), 4.38 (q, J=7.0 Hz, 2H), 4.01—4.06 (m, 2H), 3.22 (d, J=17.5 Hz, 2H), 1.37—1.41 (m, 6H), 1.29 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3, 137.4 (d, J=7.50 Hz), 129.9 (d, J=2.50 Hz), 129.6 (d, J=6.25 Hz), 129.2 (d, J=3.75 Hz), 61.0, 60.7 (d, J=6.25 Hz), 38.2 (d, J=86.25 Hz), 16.6 (d, J=6.25 Hz), 14.3, 13.5 (d, J=93.75 Hz); ^{31}P NMR ($CDCl_3$) δ: 49.68. HRMS (EI) calcd for $C_{13}H_{19}O_4P$ 270.1021, found 270.1025. **(2) Synthesis of compound 7**: 100 mL round-bottom flask was charged with 50 mL anhydrous CH_2Cl_2 and compound **6** (1.0 g, 3.704 mmol) at −78 ℃, Dibal-H (11.1 mL, 11.10 mmol) was added drop-wise to the above mixture. After stirred for 3 h at the same temperature, the mixture was quenched by saturated NH_4Cl. The aqueous phase was extracted with ether for 3 h and the organic layers were combined. Then the organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (DCM/MeOH, 40∶1, *V*/*V*) and gave the alcohol **7** in 100% yield (0.84 g); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (d, J=8.0 Hz, 2H), 7.24 (dd, J_1=2.0 Hz, J_2=8.0 Hz, 2H), 4.66 (s, 2H), 3.99—4.05 (m, 2H), 3.13 (dd, J_1=3.0 Hz, J_2=18.0 Hz, 2H), 2.77 (br, 1H), 1.35 (d, J=14.0 Hz, 3H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.1 (d, J=3.8 Hz), 131.0 (d, J=7.5 Hz), 129.7 (d, J=5.0 Hz), 127.4 (d, J=2.5 Hz), 64.6, 60.6 (d, J=6.25 Hz), 37.5 (d, J=87.5 Hz), 16.6 (d, J=6.25 Hz), 13.2 (d, J=93.75 Hz); ^{31}P NMR ($CDCl_3$) δ: 51.29. HRMS (EI) calcd for $C_{11}H_{17}O_3P$ 228.0915, found 228.0910. **(3) Synthesis of compound 8**: DEAD (1.95 g, 11.2 mmol) was added drop-wise via syringe to a solution of alcohol **7** (0.84 g, 3.68 mmol), phthalimide (1.65 g, 11.2 mmol), and PPh_3 (2.93 g, 11.2 mmol) in THF at 0 ℃. The mixture was allowed to room temperature and stirred for 40 min. Then the solvent was evaporated and the crude material was purified by column chromatography (DCM/MeOH, 60∶1, *V*/*V*) and afforded the phthalimide **8** as a viscous liquid (1.20 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83—7.85 (m, 2H), 7.70—7.72 (m, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.21 (dd, J_1=2.0 Hz, J_2=8.0 Hz, 2H), 4.82 (s, 2H), 3.98—4.06 (m, 2H), 3.10 (d, J=17.5 Hz, 2H), 1.34 (d, J=13.5 Hz, 3H), 1.28 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.0, 135.1 (d, J=3.75 Hz), 134.0, 132.1, 131.7 (d, J=7.5 Hz), 129.9 (d, J=5.0 Hz), 129.0 (d, J=3.75 Hz), 123.4, 60.5 (d, J=7.5 Hz), 41.2, 37.6 (d, J=87.5 Hz), 16.6 (d, J=6.25 Hz), 13.3 (d, J=93.75 Hz); ^{31}P NMR ($CDCl_3$) δ: 50.70. HRMS (EI) calcd for $C_{19}H_{20}NO_4P$ 357.1130, found 357.1138. **(4) Synthesis of compound 1**: Phthalimide derivative **8** (0.60 g, 1.68 mmol) was dissolved in 20 mL THF. 5 mL 40% aqueous methylamine was added to the reaction mixture. The solution was heated at 70 ℃ for 2 h and then diluted with ethyl acetate. The organic layer was washed with saturated NH_4Cl. Then, The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (DCM/MeOH, 35∶1, *V*/*V*) and compound **1** was obtained as an oil (278.4 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24—7.27 (m, 2H), 7.18—7.20 (m, 2H), 3.95—4.04 (m, 2H), 3.82 (s, 2H), 3.10 (d, J=17.6 Hz, 2H), 2.03 (br, 2H), 1.32 (d, J=13.6 Hz, 3H), 1.26 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.5 (d, J=4.0 Hz), 130.6 (d, J=7.0 Hz), 129.8 (d, J=5.0 Hz), 127.7 (d, J=3.0 Hz), 60.5 (d, J=6.0 Hz), 46.0, 37.6 (d, J=88.0 Hz), 16.7 (d, J=6.0 Hz), 13.4 (d, J=94.0 Hz); ^{31}P NMR ($CDCl_3$) δ: 53.09. HRMS (EI) calcd for $C_{11}H_{18}NO_2P$ 227.1075, found 227.1069.

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