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# A Simple and Efficient Access to α-Amino Phosphonates from *N*-Benzyloxycarbonylamino Sulfones Using Indium(III) Chloride†

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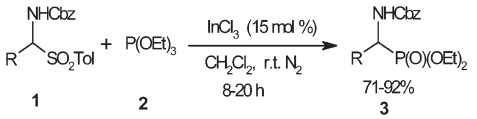
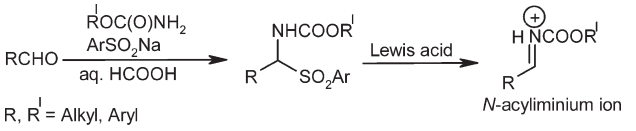



Treatment of *N*-benzyloxycarbonylamino sulfones with triethyl phosphite catalyzed by $InCl_3$ produces the corresponding protected α-amino phosphonates in high yields (71−92%).

α-Amino phosphonic acids and their derivatives exhibit various important biological properties[1] and can serve as structural analogues of the corresponding α-amino acids.[2] They are used as antibacterial,[3a,3b] anticancer,[3c] and anti-HIV agents.[3d] These compounds are also utilized as peptide mimics[4a] and enzyme inhibitors.[4b−4d] Several medicinally important compounds such as alafosfalin and (*R*)-phosphotyrosin possess an α-amino phosphonate moiety as their structural unit.[5] In addition, α-amino phosphonates have been employed as insecticides,[6a] herbicides,[6b,6c] and fungicides.[6d] Due to their interesting biological properties, various methods have been developed for the synthesis of these compounds.[7] The optically active forms of these molecules have also been synthesized.[3a,5,8] Generally, the carbonyl compound and amines or directly the imines have been utilized in these synthetic methods. However, many of these methods are associated with different drawbacks such as high temperature, long reaction time, application of costly reagents, and tedious experimental procedure. Recently, $ZrOCl_2 \cdot 8H_2O$ has been introduced as an efficient catalyst for one-pot reaction of amines, aldehydes, and diethyl phosphite to form α-amino phosphonates in excellent yields under solvent-free conditions.[9] The three-component reaction of aldehydes, 2-aminophenol, and diphenyl phosphite catalyzed by chiral scandium(III)-*N*,*N*′-dioxide complexes afforded the corresponding α-amino phosphonates with high diastereoselectivity.[10] A four-component reaction for the preparation of α-amino phosphonates has also been developed by treatment of methyleneaziridines with Grignard reagents, alkyl halides, and dialkyl phosphites.[11] Herein, we wish to report the application of *N*-benyloxycarboxylamino sulfones for a simple and efficient synthesis of α-amino phosphonates.

**SCHEME 1. *N*-Benzyloxycarbonylamino Sulfones as Precursors of *N*-Acyliminium Ions**




*N*-Benyloxycarbonylamino sulfones, generally referred to as α-amido sulfones, can be conveniently prepared[12] from aldehydes and are generally stable solids which can be stored for prolonged times. It is known that they can be converted into the corresponding protected imines (*N*-acyliminium ions) on treatment with an appropriate Lewis acid (Scheme 1).[13] These imine derivatives contain a positively charged nitrogen atom and are thus highly suitable for nucleophilic addition.

† Studies on Novel Synthetic Methodologies. 188.

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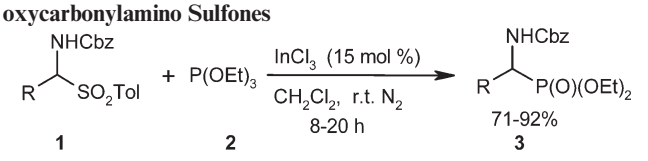
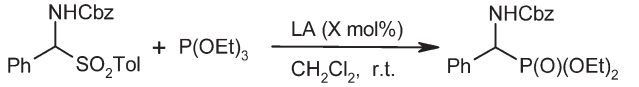
**SCHEME 2. Synthesis of α-Amino Phosphonates from *N*-Benyloxycarbonylamino Sulfones**




R = alkyl, aryl

**TABLE 1. Synthesis of α-Amino Phosphonates from *N*-Benzyloxycarbonylamino Sulfone, 1a, Using Different Lewis Acids at Room Temperature[a]**




LA = Lewis Acid

| entry | Lewis acid | X (mol %) | time (h) | yield[b] (%) |
|---|---|---|---|---|
| 1 | $CeCl_3 \cdot 7H_2O$ | 15 | 10 | 10 |
| 2 | $CeCl_3 \cdot 7H_2O$ | 15 | 24 | 15 |
| 3 | $ZrCl_4$ | 15 | 10 | 25 |
| 4 | $ZrCl_4$ | 15 | 24 | 30 |
| 5 | $VCl_3$ | 15 | 10 | 25 |
| 6 | $VCl_3$ | 15 | 24 | 35 |
| 7 | $CuBr_2$ | 15 | 10 | 30 |
| 8 | $CuBr_2$ | 15 | 24 | 45 |
| 9 | $InCl_3$ | 10 | 10 | 50 |
| 10 | $InCl_3$ | 10 | 24 | 65 |
| 11 | $InCl_3$ | 15 | 10 | 88 |
| 12 | $InCl_3$ | 15 | 24 | 90 |

[a]Reaction conditions: *N*-benzyloxycarbonylamino sulfone, **1a** (1 mmol), triethyl phosphite (1.5 mmol), and $CH_2Cl_2$ (10 mL). [b]Yields of isolated pure compound after column chromatography.

In continuation of our work[14] on the development of useful synthetic methodologies, we have observed that the treatment of *N*-benzyloxycarbonylamino sulfones with triethyl phosphite in the presence of $InCl_3$ as a catalyst yielded the corresponding α-amino phosphonates at room temperature (Scheme 2).

Initially, the reaction of *N*-benzyloxycarbonylamino sulfone, **1a** (R = Ph), with triethyl phosphite was carried out at room temperature using various Lewis acids (Table 1). Considering the reaction time and yield, $InCl_3$ (15 mol %) was found to be the most effective. The reaction of **1a** was also studied with different phosphites in the presence of $InCl_3$ at room temperature (Table 2). Triethyl phosphite was found to afford the product in highest yield. However, with diethyl phosphite only a trace amount of the product was obtained. Thus, the reaction of *N*-benyloxycarbonylamino sulfones with triethyl phosphite using $InCl_3$ as a catalyst was subsequently employed for the preparation of a series of protected α-amino phosphonates (Table 3).

*N*-Benzyloxycarbonylamino sulfones derived from various aldehydes (aromatic and aliphatic) underwent the present conversion smoothly. Aromatic aldehydes having electron-donating as well as electron-withdrawing groups were used to prepare the sulfones. The reaction was completed within 8−13 h except for the α-amido sulfones containing an aromatic ring with an electron-withdrawing substrate (e.g., Table 3, entries 15 and 16). In the latter case, the reaction times were somewhat longer (15−20 h). The reaction conditions were mild, and the products were formed in high yields (71−92%). Various functionalities such as ether, hydroxyl, halogen, and nitro groups remained unchanged. The sulfone derived from an acid-sensitive aldehyde such as furfuraldehyde (Table 2, entry 18) and the sulfone derived from a sterically hindered aldehyde such as 2-naphthaldehyde (Table 2, entry 17) also afforded the corresponding protected α-amino phosphonates in good yields. The structures of the products were established from their spectroscopic (IR, $^1$H and $^{13}$C NMR, ESIMS, and HRMS) data.

Recently, there is only one report of the reaction of *N*-benzyloxycarboxylamino sulfones with dialkyl phosphites

**TABLE 2. Reactivity of Phosphite Reagents for the Synthesis of α-Amino Phosphonates from *N*-Benzyloxycarbonylamino Sulfone, 1a, at Room Temperature[a]**

| entry | phosphite reagent | yield[b,c] (%) |
|---|---|---|
| 1 | $P(OMe)_3$ | 66 |
| 2 | $HP(O)(OMe)_2$ | trace |
| 3 | $P(OEt)_3$ | 88 |
| 4 | $HP(O)(OEt)_2$ | trace |
| 5 | $P(OPh)_3$ | 59 |
| 6 | $HP(O)(OPh)_2$ | trace |

[a]Reaction conditions: *N*-benzyloxycarbonylamino sulfone, **1a** (1 mmol), phosphite reagent (1.5 mmol), and $CH_2Cl_2$ (10 mL); the reaction was stirred at rt for 10 h. [b]Yields of isolated pure compound after column chromatography. [c]The products were characterized from their IR, $^1$H and $^{13}$C NMR, and MS spectra.

**TABLE 3. $InCl_3$-Catalyzed Synthesis of α-Amino Phosphonates from *N*-Benzyloxycarbonylamino Sulfones and Triethyl Phosphite (Scheme 2)[a]**

| entry | R | product | time (h) | yield[b] (%) |
|---|---|---|---|---|
| 1 | $C_6H_5$ | **3a** | 10 | 88 |
| 2 | $4\text{-}MeC_6H_4$ | **3b** | 9 | 90 |
| 3 | $4\text{-}(CH_3)_2CHC_6H_4$ | **3c** | 9 | 91 |
| 4 | $4\text{-}ClC_6H_4$ | **3d** | 9 | 89 |
| 5 | $3\text{-}ClC_6H_4$ | **3e** | 10 | 88 |
| 6 | $2,4\text{-}(Cl)_2C6H_3$ | **3f** | 9 | 88 |
| 7 | $4\text{-}BrC_6H_4$ | **3 g** | 9 | 89 |
| 8 | $4\text{-}FC_6H_4$ | **3 h** | 12 | 86 |
| 9 | $3\text{-}Cl,4\text{-}FC_6H_3$ | **3i** | 12 | 87 |
| 10 | $2,4,6\text{-}(F)_3C_6H_2$ | **3j** | 12 | 84 |
| 11 | $4\text{-}MeOC_6H_4$ | **3k** | 8 | 92 |
| 12 | vanilyl | **3l** | 9 | 86 |
| 13 | $3,4\text{-}(\text{-}OCH_2O\text{-})C_6H_3$ | **3m** | 8 | 91 |
| 14 | $3,4,5\text{-}(MeO)_3C_6H_3$ | **3n** | 9 | 89 |
| 15 | $4\text{-}NO_2C_6H_4$ | **3o** | 20 | 79 |
| 16 | $3\text{-}NO_2C_6H_4$ | **3p** | 16 | 81 |
| 17 | 2-naphthyl | **3q** | 13 | 87 |
| 18 | 2-furyl | **3r** | 13 | 71[c] |
| 19 | 2-thienyl | **3s** | 11 | 90 |
| 20 | $C_6H_5CH_2$ | **3t** | 11 | 86 |
| 21 | $CH_3CH_2CH_2$ | **3u** | 12 | 83 |
| 22 | $CH_3(CH_2)_3CH_2$ | **3v** | 11 | 85 |
| 23 | $(CH_3)_2CHCH_2$ | **3w** | 11 | 84 |

[a]Reaction conditions: *N*-benyloxycarbonylamino sulfone, **1** (1 mmol), triethyl phosphite, **2** (1.5 mmol), $InCl_3$ (15 mmol %), and $CH_2Cl_2$ (10 mL); the reaction was carried out at room temperature. [b]Yields of pure isolated compounds after column chromatography. [c]Reaction was carried out with 2.0 mmol of triethyl phosphite.

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using a phase-transfer catalyst to form the protected chiral α-amino phosphonates.[15] The reaction was conducted in the presence of a base and required a long time (60 h). Moreover, α-amido sulfones generated from aromatic aldehydes have not been examined.

In conclusion, we have demonstrated here a simple, mild, and efficient protocol for the synthesis of protected α-amino phosphonates at room temperature and in high yields by applying the reaction of *N*-benzyloxycarbonylamino sulfones (derived from both aromatic and aliphatic aldehydes) with $P(OEt)_3$ using indium(III) chloride as a catalyst.

## Experimental Section

**General Experimental Procedure.** Triethyl phosphite, **2** (249.2 mg, 1.5 mmol), was added dropwise to a solution of *N*-benzyloxycarbonylamino sulfone, **1** (1 mmol), and $InCl_3$ (15 mol %) in $CH_2Cl_2$ (10 mL) under nitrogen atmosphere. The mixture was stirred at room temperature, and the reaction was monitored by TLC. After completion, distilled water (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic portions were washed with water (2 × 10 mL), dried over anhydrous $Na_2SO_4$, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (20−35% EtOAc/hexane) to obtain pure protected α-amino phosphonate **3**.

**Benzyl (Diethoxyphosphoryl)(phenyl)methylcarbamate (3a).** Following the general experimental procedure, **1a** (395 mg, 1 mmol) produced, after column chromatography (20% EtOAc/hexane), the α-amino phosphonate **3a** (331.8 mg, 88%) as a white solid: mp = 111−113 °C; IR $\nu_{max}$ (KBr)/cm$^{-1}$ 3241, 1716, 1548, 1252, 1030; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ ppm 7.51−7.23 (10H, m), 6.07(1H, brs), 5.23−5.01(3H, m), 4.28−4.03(2H, m), 3.91(1H, m), 3.66(1H, m), 1.30 (3H, t, $J$ = 7.0 Hz), 1.10 (3H, t, $J$ = 7.0 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ ppm 156.0 (d, $J$ = 10.0 Hz), 137.2, 135.2, 129.1, 128.8, 128.5, 127.8, 67.3, 63.9 (d, $J$ = 6.5 Hz), 63.3 (d, $J$ = 6.5 Hz), 52.8 (d, $J$ = 156.6 Hz), 16.2 (d, $J$ = 6.0 Hz), 16.1 (d, $J$ = 6.0 Hz); ESIMS $m/z$ 378 $[M + H]^+$, 400 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{25}NO_5P$ $[M + H]^+$ 378.1470, found 378.1478.

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**Supporting Information Available:** General experimental information, characterization data of products **3b**−**w**, products obtained with trimethyl phosphite and triphenyl phosphite (Table 2, entries 1 and 5), and copies of NMR ($^1$H and $^{13}$C) and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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