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# An expeditious one-pot synthesis of diethyl *N*-Boc-1-aminoalkylphosphonates

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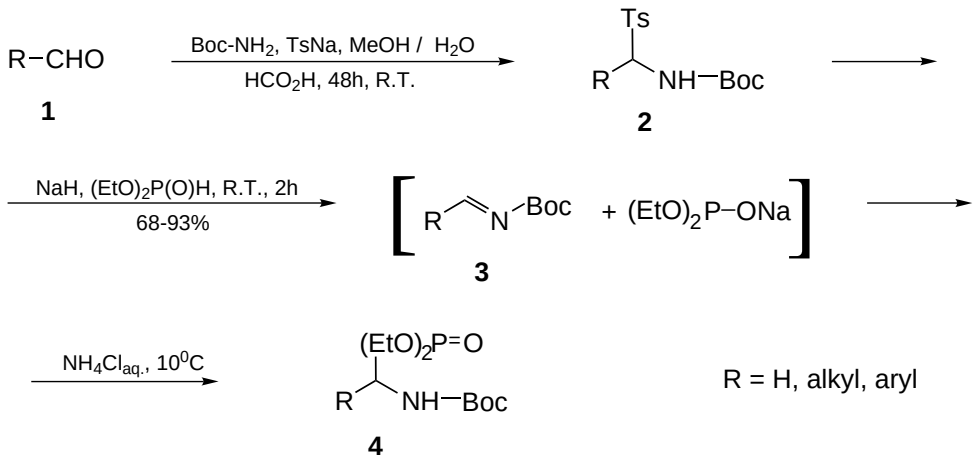
**Abstract**—A general one-pot, purification-free synthesis of diethyl *N*-Boc-1-aminoalkylphosphonates has been developed. The procedure involves base-catalyzed Michael-type addition of sodium diethyl phosphite to *N*-Boc imines generated in situ by the action of sodium hydride on α-amidoalkyl-*p*-tolyl sulfones in tetrahydrofuran. © 2002 Elsevier Science Ltd. All rights reserved.

1-Aminoalkylphosphonic and phosphinic acids and the corresponding phosphono- and phosphinopeptides can interfere in biological mechanisms inducing enzyme inhibitor properties.[1] Consequently, their synthesis has recently received an increasing amount of attention.[2–5] Phosphonamidate peptides are most often prepared from monoalkyl or monoaryl *N*-protected aminoalkylphosphonochloridates by coupling them with an appropriate amino acid ester or suitably protected peptide.[6] *N*-Protected diethyl 1-aminoalkylphosphonates can also be considered as possible alternative substrates for the synthesis of phosphonamidate peptides.

In the course of our studies on potential applications of α-amidoalkyl-*p*-tolyl sulfones **2** as *N*-Boc imine **3** equivalents, we found that sodium hydride can be employed for base-induced elimination of *p*-toluenesulfinic acid from **2**. Trapping of *N*-Boc imines **3** thus formed by Michael-type addition of sodium diethyl phosphite affords diethyl *N*-Boc-1-aminoalkylphosphonates **4** in high yields and excellent purity (Scheme 1).

Two possible alternative mechanisms to account for the formation of **4** are: (a) an elimination of *p*-toluenesulfinic acid giving *N*-Boc imine **3**, which is then trapped by




**Scheme 1.**

*Keywords*: α-amidoalkyl-*p*-tolyl sulfones; *N*-Boc imines; diethyl phosphite.

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**Table 1.** α-Amidoalkyl-*p*-tolyl sulfones **2** and diethyl *N*-Boc 1-aminoalkylphosphonates **4**[a]

| Entry | R | **2** Yield (%)[b] | **2** Mp (°C) | **4** Yield (%)[b] | **4** Mp (°C)[c] |
|---|---|---|---|---|---|
| a | H | 55[d] | 116–118 | 68 | Oil |
| b | Me | 76 | 104–106 | 90 | 54–56 (55) |
| c | Et | 74 | 114–116 | 83 | 39–41 |
| d | Pr | 74 | 120–122 | 82 | 55–57 |
| e | *i*-Pr | 76 | 127–129 | 78 | 52–55 (52–54) |
| f | Bu | 82 | 110–111 | 77 | 36–38 |
| g | *i*-Bu | 82.5 | 122–124 | 82 | 58–60 (60) |
| h | Ph | 65 | 182–184 (dec.) | 87 | 116–118 (116–118) |
| i | *p*-MeO-$C_6H_4$ | 68 | 174–176 (dec.) | 93 | 78–80 |

[a] All compounds were fully characterized by MS, IR and 1H NMR spectroscopy.
[b] Yields of crude, analytically pure products.
[c] Mps of crude, analytically pure products. Mps of the same compounds obtained by an independent procedure[10] are given in parentheses.
[d] 30% aqueous solution of formaldehyde (formalin) was used for the preparation of **2a**.

sodium diethyl phosphite to form the final product **4**; (b) a direct $S_N2$ sulfinate displacement leading directly to **4**. We have not investigated which of these two mechanisms is operating. However, the following observation is relevant. When sulfone **2** was treated with 1 equiv. of sodium diethyl phosphite, the desired product **4** was formed in 25% yield only; the remainder contained 55% of unreacted **2** together with some diethyl phosphite. This result shows that direct nucleophilic displacement of a sulfinate anion by means of sodium diethyl phosphite is highly improbable and, in contrast to literature suggestions,[7] supports the alternative elimination–addition route via *N*-Boc imine **3**.

The following typical experimental conditions were used. Sodium hydride (0.24 g, 10 mmol) was suspended in THF (25 ml). Crude, finely powdered α-amidoalkyl-*p*-tolyl sulfone **2**[8] (5 mmol) was added portionwise with stirring at room temperature over ca. 5 min. A solution of diethyl phosphite (0.69 g, 5 mmol) in THF (5 ml) was then added dropwise over ca. 10 min. The reaction was slightly exothermic. The resulting mixture was stirred at room temperature for 2 h, cooled to 10°C and quenched with satd aq. $NH_4Cl$ (15 ml). Water (10 ml) was added, the organic layer was separated and the aqueous phase extracted with $CH_2Cl_2$ (2×20 ml). All impurities were water soluble and remained in the aqueous phase. The combined extracts and organic phase were dried over $MgSO_4$ and evaporated to give analytically pure **4** ($^1$H NMR, MS). Yields and mps of **2** and **4** are compiled in Table 1.

The outlined method for the synthesis of diethyl *N*-Boc 1-aminoalkylphosphonates **4** represents a versatile and economic approach to these compounds from easily available starting materials.

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8. Bernacka, E.; Klepacz, A.; Zwierzak, A. *Tetrahedron Lett*. **2001**, *42*, 5093–5094. Slightly modified experimental procedure for the preparation of **2**: A mixture of aldehyde **1** (20 mmol), crude *t*-butyl carbamate[9] (2.34 g, 20 mmol), anhydrous sodium *p*-toluenesulfinate (3.57 g, 20 mmol), water (40 ml), methanol (20 ml) and formic acid (5 ml) was stirred for ca. 15 min until it became homogeneous and then left for 48 h at room temperature. The crystalline sulfone **2** was filtered off with suction, washed with water (30 ml) and dried in an oven at ca. 70°C. Sulfones **2h** and **2i** were washed successively with water (30 ml) and ether (15 ml) and dried over $P_2O_5$. Crude **2** were analytically pure and their mps were virtually unchanged after crystallization. All other components of the reaction mixture were water soluble and could be removed during washing of crude **2**.
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