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Highly Chemoselective *O*-Ethylation of *N*-Boc Amino Alcohols Using Phase Transfer Catalysis

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ABSTRACT: A practical, highly selective *O*-ethylation method of *N*-Boc amino alcohols under phase-transfer catalyzed conditions is described. The *O*-ethylation was accomplished in heptanes or toluene using 50% aqueous sodium hydroxide as the base in the presence of a phase-transfer catalyst, tetrabutylammonium chloride. This method exclusively afforded the *O*-ethylated products in good yields.

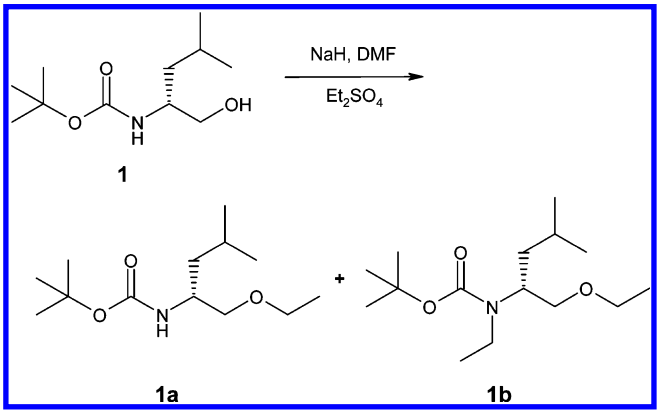
INTRODUCTION

Etherification is one of the basic transformations in organic chemistry. In spite of the many advances in organic chemistry since the discovery of the Williamson reaction, it is still the best general method for the preparation of unsymmetrical or symmetrical ethers.[1] In our effort to synthesize an active pharmaceutical ingredient, we needed to prepare the ethyl ether of *N*-Boc-D-leucinol (**1**). The traditional method involving deprotonation of the hydroxyl group using sodium hydride followed by reaction with diethyl sulfate gave a mixture of *O*-ethylated **1a** and *N*,*O*-diethylated **1b** products with poor selectivity, apparently due to the insufficient difference of the pK_a between the NH and the OH groups in the presence of a strong base (Scheme 1). Reactions with poor selectivity pose significant challenges in scale-up due to the fact that isolation of the desired isomer is not always straightforward, especially when the desired isomer is an oil which often has to be purified by column chromatography. It is of great interest that a highly selective method is used in such cases to provide crude product with sufficient purity, so that it can be carried directly to the next step without further purification. Quite surprisingly, methods for highly selective ethylation of *N*-Boc protected amino alcohols do not exist in the literature, even though poorly selective *O*-alkylation of unprotected amino alcohol was known.[2] In this communication, we wish to report a highly chemoselective *O*-ethylation of *N*-Boc amino alcohols under phase-transfer catalysis.

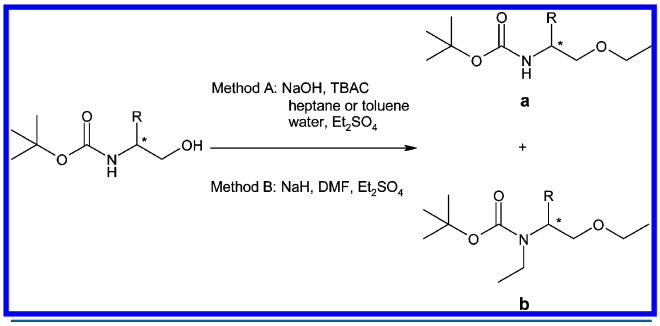
RESULTS AND DISCUSSION

Variants of the Williamson reaction using phase-transfer catalysis (PTC) have also been known for decades, including conditions that allow selective formation of mono ether from diols or triols.[3] In continuation of our interest in the application of PTC in the pharmaceutical industry,[4] and due to the fact that poor selectivity was observed above with NaH/DMF conditions which also posed significant safety hazard,[5] we reasoned that under PTC conditions the reactivity difference of the hydroxyl group and the BocNH group might be sufficient enough to allow preferential deprotonation of the hydroxyl group for its ethylation.

Scheme 1



Scheme 2



We investigated the ethylation of *N*-Boc-D-leucinol (**1**) in heptanes using 50% aqueous NaOH as the base and diethyl sulfate as the alkylating agent in the presence of 1.5 mol % of tetrabutylammonium chloride (TBAC). Under these PTC conditions, the desired isomer **1a** was formed exclusively, and the isolated yield was 70−75%. These new conditions (method A) are far superior when compared with the reaction using NaH in DMF (method B), where a mixture of *O*-ethylated isomers **1a** and bisethylated product **1b** was formed in a weight ratio of 65/35. To test the scope of this *O*-ethylation method under PTC, a variety of *N*-Boc amino alcohols were subjected to these conditions, which involved the addition of Et_2SO_4 to a biphasic mixture of substrate solution heptanes or toluene and 50% NaOH solution, in the presence of TBAC. The selection of heptanes or toluene as the solvent was based on the solubility of the substrate in each solvent and did not affect the outcome of the ethylation reaction (Scheme 2).

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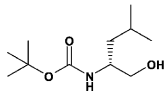
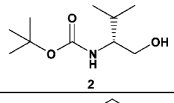
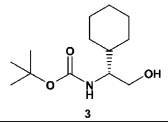
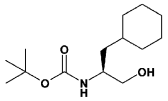
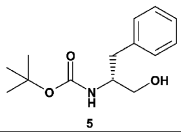
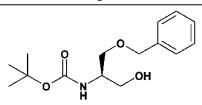
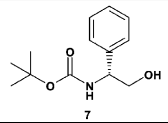
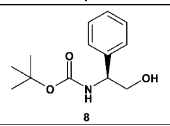
Table 1. Comparison of *O*-ethylation of *N*-Boc amino alcohols using methods A and B[d]

Entry	Substrate	Method A Yield, a/b[a]	Method A Solvent	Method B a/b
1	 1	75%	Heptanes	65/35 [b]
2	 2	70%	Heptanes	71/29[b]
3	 3	70%	Heptanes	73/27[b]
4	 4	73%	Heptanes	78/22 [b]
5	 5	84%	Toluene	56/44[c]
6	 6	90%	Toluene	55/45 [c]
7	 7	85%	Toluene	58/42[c]
8	 8	91%	Toluene	54/46[c]

[a]Isolated yield; a/b for Method A was 100/0 in all cases, ratio determination methods are described in footnotes b and c. [b]Weight ratio of isolated products obtained from silica gel chromatography (heptanes/ethyl acetate, 4:1 to 2:1). [c]Ratio of peak areas in HPLC at 254 nm. [d]Conditions: Method A: 3.75 mmol of Et_2SO_4 was added to a mixture of 2.5 mmol of substrate, 0.0375 mmol of TBAC, 3 mL of heptanes, and 6.5 mmol of NaOH (50 wt % aq. solution) at 20 °C; Method B: 3.75 mmol of NaH (60 wt % in mineral oil) was added to the solution of 2.5 mmol of substrate in 3 mL of anhydrous DMF at 0 °C followed by the addition of 3.75 mmol of Et_2SO_4. The reaction was allowed to warm to 20 °C.

In all cases using the PTC conditions, the selectivity was complete for the desired ethyl ether. The experimental results are summarized in Table 1 (for comparison, results using method B are also included). Ethylation of *N*-Boc amino alcohols **2**−**8** using method A gave exclusively *O*-ethylated compound **2a**−**8a** in 70−90% yield, whereas a mixture of *O*-ethylated and bisethylated products were obtained in the weight ratios as indicated in Table 1 when method B was used.[6] Either heptanes or toluene could be used as the solvent without any impact on the selectivity. Safety tests of the reaction mixture of the PTC procedure did not show much appreciable exotherm below 150 °C.

The ethylation of *N*-Boc-D-leucinol (**1**) using method A was scaled up to 53.8 kg in one batch, affording the desired *O*-ethylated product in 75% yield, same as obtained in the lab. The crude product was sufficiently pure based on ^{1}H NMR analysis. It was hydrolyzed directly using 6 N HCl in isopropanol to give the HCl salt of *O*-ethyl-D-leucinol as a crystalline material which was isolated by filtration in 99% yield. The purity assay of the HCl salt was 98.7% based on quantitative ^{1}H NMR analysis.

For lab scale reactions, the products were isolated by silica gel column purifications. The product purities ranged from 97 to 99%.

As one example of a methylation, the methylation of *N*-Boc-D-*α*-phenylglycinol (**7**) was successfully carried out with dimethyl sulfate using method A, and the reaction again produced only the *O*-methylated product in 85% isolated yield.

Interestingly, when we tried to expend the scope of the reaction using activated alkyl halides such as benzyl chloride, we observed the formation of a mixture of products.

In summary, we demonstrated that the selective *O*-ethylation of a wide range of *N*-Boc amino alcohols was effectively accomplished in heptanes or toluene using aqueous solution of NaOH in the presence of a phase-transfer catalyst and scaled the preparation of one compound to 54 kg.

EXPERIMENTAL SECTION

(*R*)-*tert*-Butyl-(1-ethoxy-4-methylpentan-2-yl)carbamate (1a). To a mixture of *N*-Boc-D-leucinol (**1**, 53.80 kg, 247.50 mol) and tetrabutylammonium chloride (1.03 kg, 3.71 mol) in heptanes (300 L) and 50% aq NaOH (51.4 kg, 643 mol) was added Et_2SO_4 (57.2 kg, 371.20 mol) over a period of 1 h while maintaining the internal temperature at 20−35 °C. The mixture was cooled to 20 °C over 30 min and stirred at this temperature for 14 h until TLC

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(heptanes−EtOAc = 2:1) indicated completion of the reaction. Aqueous NH_4OH solution (29 wt %, 19 L) was added, and the reaction mixture was stirred at 20−25 °C for 16 h. The organic layer was separated and washed with water (2 × 75 L). It was then concentrated under reduced pressure (90−30 mmHg) at 35−40 °C to afford **1a** in heptanes (~150 L, contains 45.6 kg of pure **2a**, 75% yield) which was used directly in the next step. Analytical data of a purified sample were consistent with those reported in the literature.[6]

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Notes

The authors declare no competing financial interest.

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