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Deprotection of a primary Boc group under basic conditions

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Abstract—Treatment of a primary *t*-butyl carbamate (Boc) group with excess sodium *t*-butoxide in slightly wet tetrahydrofuran or 2-methyltetrahydrofuran provides the corresponding primary amine in excellent yield. We believe the reaction proceeds through an isocyanate intermediate.

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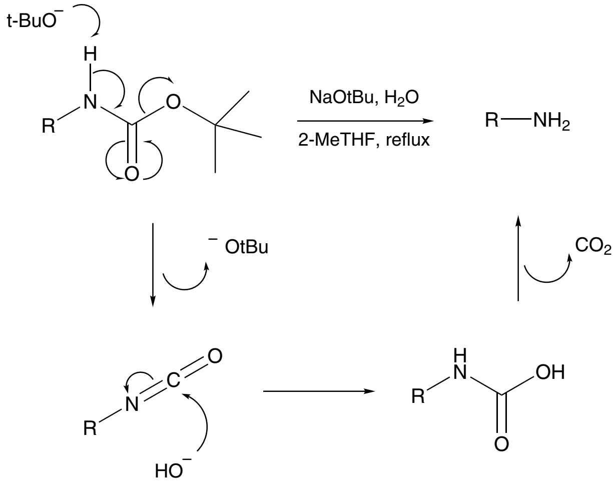
1. Introduction

A *t*-butyl carbamate (Boc) group is a common protecting group for amines. It is stable to hydrolysis under basic conditions and to many other nucleophilic reagents. Deprotection is generally achieved under acidic conditions, as extensively described in Greene's Protective Groups in Organic Synthesis.[1] Deprotection can be obtained under basic conditions only in special cases, where the amine is highly activated, such as a pyrrole.[2] Thermal deprotections have also been reported.[3,4] A basic deprotection would be advantageous if the molecule contains other acid-sensitive moieties. Herein, we report that unactivated primary Boc groups can be deprotected with sodium *t*-butoxide in slightly wet tetrahydrofuran or 2-methyltetrahydrofuran to provide the corresponding primary amines in excellent yield. We believe that this reaction proceeds through an isocyanate intermediate.

2. Discussions

As a part of an early pre-clinical program, we needed to develop a non-acidic method to deprotect a primary Boc group, due to the presence of an acid-sensitive moiety on the compound. A thermal deprotection was not an option and to the best of our knowledge, for a simple Boc group, there are no reported cases of deprotection under basic conditions. However, for an activated amine such as a pyrrole or indole, the Boc group can be cleaved under basic conditions.[1] Thus, we believed basic deprotection conditions were worth investigating. We are happy to report that treatment of the carbamate with excess sodium *t*-butoxide in tetrahydrofuran or 2-methyltetrahydrofuran did in fact provide the desired amine. It was found that addition of 1 equiv of water increased the rate of the reaction. Further experimentation showed that a strong base such as sodium *t*-butoxide was necessary as sodium or potassium hydroxide was not effective. Other strong bases such as sodium methoxide or sodium ethoxide could also be employed but for simplicity, all of our experiments were conducted with sodium *t*-butoxide as the base.



Scheme 1.

Keywords: *t*-Butyl carbamate; Boc; Sodium *t*-butoxide; Amine; Isocyanate.

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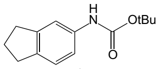
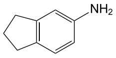
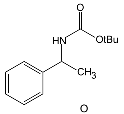
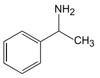
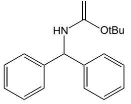
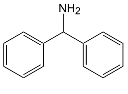
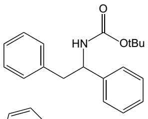
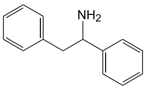
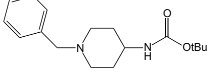
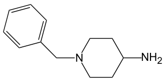
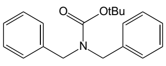
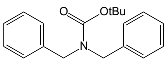
Table 1

Entry	Carbamate	Amine	Yield (%)
1			100
2			92
3			100
4			100
5			90
6			85 (recovered)

Based on these observations, we believe that the reaction proceeds through an isocyanate intermediate. We believe the carbamate is deprotonated by sodium *t*-butoxide (Scheme 1). Elimination of *t*-butoxide then provides the isocyanate intermediate, which is then hydrolyzed by water or sodium hydroxide formed from water and sodium *t*-butoxide to the carbamic acid. Finally, decarboxylation affords the free amine. The deprotection does not proceed with sodium or potassium hydroxide, which is not a strong enough base to deprotonate the carbamate. Additionally, the addition of 1 equiv of water increases the rate of reaction, presumably by enhancing the rate of hydrolysis of the isocyanate intermediate to the carbamic acid.

We decided to explore the scope of this reaction. The six Boc protected amines shown in Table 1 were obtained from the corresponding commercially available amines using standard conditions.[1] Each was subjected to the Boc deprotection conditions. Carbamates **1**–**5** were deprotected cleanly to provide the corresponding amines in 90% to quantitative yields. As further evidence of an isocyanate intermediate, carbamate **6**, which cannot form the isocyanate intermediate, was recovered unchanged in 85% yield.

We have developed a method for deprotecting primary Boc protected amines under basic conditions with sodium *t*-butoxide in wet tetrahydrofuran or 2-methyltetrahydrofuran in excellent yields. This method seems general for primary Boc protected amines that are stable to strongly basic conditions and provides a nice complement to the standard acidic deprotections.

3. General procedures

Sodium *t*-butoxide (2–4 equiv) was added to a solution of the Boc protected amine (1 equiv) in 2-methyltetrahydrofuran or tetrahydrofuran (10 vol). Volumes is defined as mL of solvent per gram of starting material. Water (1 equiv) was added and the reaction was heated at reflux for 2–12 h. The reaction was cooled to room temperature and quenched with 10% citric acid solution (10 vol). The resulting solution was stirred at room temperature for 30–60 min and then the pH was adjusted to 10–12 with 6 N NaOH solution. The layers were separated. The aqueous layer was further extracted with ethyl acetate (10 vol). The combined organic layers were dried and concentrated to afford the desired amine in 90% to quantitative yield. The crude amine was generally of excellent purity but the crude reaction can be purified by column chromatography or recrystallization if necessary.

References and notes

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