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A one-pot selective synthesis of *N*-Boc protected secondary amines: tandem direct reductive amination/*N*-Boc protection

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ABSTRACT

A one-pot tandem direct reductive amination of aldehydes with primary amines resulting in *N*-Boc secondary amines using a $(Boc)_2O$/sodium triacetoxyborohydride (STAB) system is reported. The tandem procedure is efficient, selective, and versatile, giving excellent yields of *N*-Boc protected secondary amines even in those cases where the products are prone to intramolecular lactamization.

1. Introduction

Secondary amines are an important class of chemical compounds with a remarkable potential for industrial,[1] pharmaceutical,[2] and agrochemical[3] applications. Development of novel and efficient methods for synthesis of secondary amines is an active area of research in industry and academia.[4] The direct reductive amination (DRA) of aldehydes/ketones with amines is one of the most widely used methods for the synthesis of secondary amines.[5] The two most commonly used DRA methods are metal mediated catalytic hydrogenation[6] and reduction of imine intermediates by borohydride reagents such as $NaCNBH_3$.[7] In certain cases, the successful application of the former method may be limited due to its incompatibility with substrates having other reducible groups,[8] whereas the latter suffers from safety and environmental issues.[9] Among the several other alternative borohydride reagents developed recently, sodium triacetoxyborohydride (STAB) appears to be de facto the reagent of choice for DRA.[10]

Overalkylation of amines is a typical drawback in a majority of direct reductive amination protocols.[10,11] Despite the recent advancement in the form of new reagents[5a,12] to address this issue, further development of efficient and practical synthetic tools to extend the scope and improve the selectivity of reductive amination reactions is still highly desirable.

Recently, we have been involved in the design and synthesis of a series of photoreactive probes for histone deacetylases (HDAC)[13] that are now further extended to amine analogs of suberoylanilide hydroxamic acid (SAHA),[14] an FDA approved HDAC inhibitor. In this context we needed an efficient method for DRA of aromatic aldehydes with aliphatic amino esters of various chain lengths to synthesize the corresponding secondary benzylamino derivatives. We selected STAB considering its superior versatility for reductive amination over other traditionally used hydride reducing agents.[15] All our efforts on reductive amination of aromatic aldehydes with methyl 7-aminoheptanoate hydrochloride (**2**) using STAB resulted in 55–65% of desired monoalkylated products along with 20–25% of unwanted dialkylated products.[16] We also found that the reaction of benzaldehyde with shorter γ- or δ-amino esters in the same conditions resulted in the formation of *N*-benzylbutyro- and *N*-benzylvalerolactams, respectively, as the major products instead of the desired monoalkylated secondary amine derivatives. In fact, there is a literature precedence of exploring reductive amination/lactamization sequence, a.k.a. reductive lactamization[17] as an efficient synthetic route for γ- and δ-lactams.[18] To the best of our knowledge, the currently known approaches to overcome overalkylation and lactamization for this type of substrates would require multistep synthetic procedures.[19] Herein, we report a one-pot DRA of aldehydes with primary amines resulting in high yields of *N*-Boc protected secondary amines in a tandem reaction manner.

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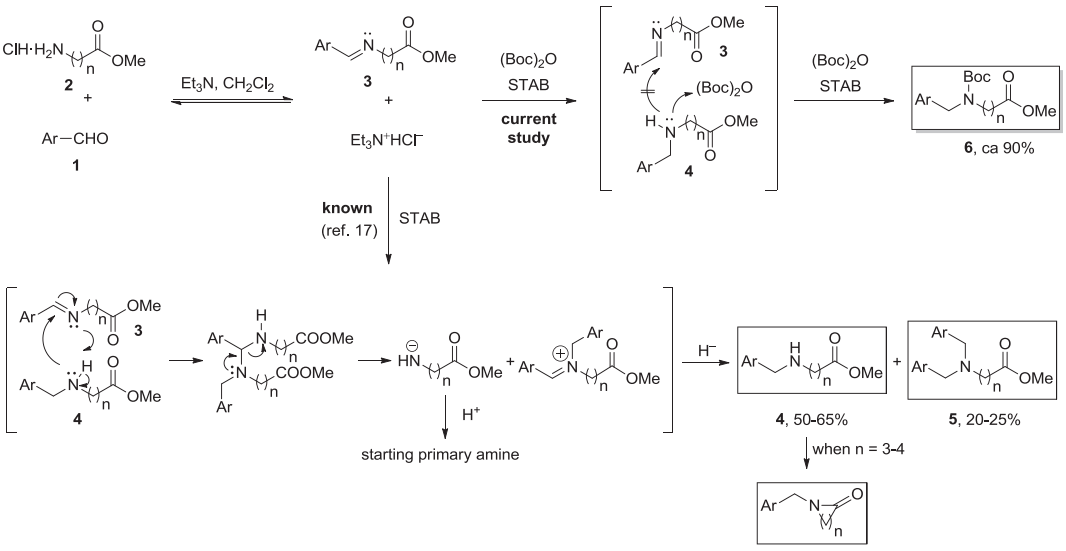
2. Results and discussion

It was proposed[17] that the formation of the tertiary amine **5** is a result of the nucleophilic addition of initially formed secondary amine **4** to the imine intermediate **3** followed by reduction. With this pathway in mind, we envisioned that addition of an electrophilic reagent such as $(Boc)_2O$ would trap the amine **4**, preventing it from further nucleophilic addition to the imine intermediate **3**, and eliminate the dialkylation or lactamization (Scheme 1). In addition, the versatility of the Boc protecting group may facilitate further functionalization,[20] otherwise the *N*-Boc group can be deprotected by the treatment with mild acids,[21] keeping the ester group intact. the corresponding *N*-Boc-benzylamino esters (Scheme 2).[19] To our delight, under the newly developed reaction settings, *N*-Boc-benzylamino esters **9** and **10** were obtained as a single product in 90% and 92% yields, respectively (Scheme 2).

As a demonstration of versatility of this approach, the tandem procedure was evaluated with a variety of aldehydes and amines shown in Table 2. Reaction of aromatic aldehydes **1a** and **1b** with aliphatic amines **17** and **19** gave the anticipated *N*-Boc amines **18** and **20** in 90% and 87% yields, respectively. The procedure was also successful with an aliphatic aldehyde–amine combination, giving the corresponding *N*-Boc amine **23** in high yield (80%, entry 3). The tandem DRA/*N*-Boc protection of benzylamine **24** with aliphatic



Scheme 1. Mechanism of the tandem DRA/*N*-Boc protection proposed in this study based on the known pathway.

To evaluate our concept, a mixture of benzaldehyde (**1a**), methyl 7-aminoheptanoate hydrochloride (**2**), and triethylamine in CH_2Cl_2 was stirred for 1 h to allow the imine formation. It was then treated with $(Boc)_2O$ and followed by addition of STAB at room temperature. The thin layer chromatographic analysis of the reaction mixture after 4 h showed formation of a single product that was confirmed to be *N*-Boc-benzylamino ester **6a** (Table 1).

To examine the effect of the aldehyde reactivity, a wide variety of aromatic aldehydes was subjected to the newly developed tandem DRA conditions with amine **2** (Table 1). Consistent with our hypothesis, the procedure worked well to give the corresponding *N*-Boc-benzylamino esters with excellent 78–95% yields. The reaction with both the benzaldehydes bearing electron donating (entries 2 and 3) and electron withdrawing substituents (entries 4 and 5) gave comparable yields >85%. The process was equally effective for heteroaromatic (entries 6–9) and polyaromatic (entry 10) systems as well. Although all the reactions in this study were carried out in CH_2Cl_2 as the solvent, the reaction proceeded equally well in dichloroethane, THF, and chloroform.

We also explored the synthetic utility of this procedure in case of the reaction between aromatic aldehydes and γ- and δ-amino esters, where the reductive lactamization was expected to be a competing event. A DRA reaction between benzaldehyde and methyl 4-aminobutyrate hydrochloride (**7**) or methyl 5-aminopentanoate hydrochloride (**8**) using only STAB produced *N*-benzylbutyro- and *N*-benzylvalerolactams **11** and **12** in 65% and 70% yields, respectively, along with 20% and 22% of dibenzylamino esters **13** and **14**, respectively. The yields are similar to those reported earlier.[17] The published synthesis of **9**[22] and **10** requires harsh conditions and three synthetic steps to convert the lactams to aldehydes **21**, **26**, and aromatic aldehyde **1h** resulted in the corresponding *N*-Boc secondary amines **25**, **27**, and **28**, respectively, in high yields (entries 4–6). A moderate yield (60%) was obtained when an aliphatic aldehyde **26** was reacted with benzyloxyaniline **29** (entry 7), whereas a high yield (85%) was observed in the reaction between cyclohexanal (**21**) and anisidine **31** (entry 8). The aromatic aldehyde **1c** was transformed to the corresponding *N*-Boc protected amine **33** in good yield (70%) in reaction with aromatic amine **31** (entry 9). However, the desired product **35** was not detected in reaction between aldehyde **1c** and nitroaniline **34** (entry 10). For entries 2, 3, and 7 small amounts (≤5%) of *N*-Boc protected starting amines were observed, slightly lowering the yields of the anticipated *N*-Boc protected products. In addition to the *N*-Boc protection of the starting amine, N-acetylation of the secondary amine product was found to be another side reaction for entries 7 and 9. Formation of small amounts of *N*-acetyl by-product was attributed to the nucleophilic attack of amines on STAB as suggested earlier.[15] The negative result obtained for aniline **34** is not surprising as the DRA of poorly nucleophilic arylamines is well known to give low yields.

We have performed a series of experiments to elucidate the proposed reaction pathway and also to inspect the possibility of other reaction pathways. A hypothetical alternative sequence where *N*-Boc protection would occur before DRA was ruled out after the reaction of benzaldehyde with *N*-Boc-methyl 7-aminoheptanoate **36** under the same DRA conditions using only STAB did not result in formation of **6a** (Scheme 3, Eq. 1). We also could not exclude another possible reaction pathway, where the imine intermediate would react with $(Boc)_2O$ resulting in a highly reactive acyliminium ion that can readily undergo reduction with