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A One-Pot Selective Synthesis of *N*-Boc Protected Secondary Amines: Tandem Direct Reductive Amination/*N*-Boc Protection

Raghupathi Neelarapu and Pavel A. Petukhov*

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, 833, S. Wood Street, Chicago, IL-60612, USA

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

Keywords

Direct reductive amination; secondary amines; *N*-Boc protection; sodium triacetoxyborohydride; tandem reaction

Introduction

Secondary amines are an important class of chemical compounds with a remarkable potential for industrial,¹ pharmaceutical,² and agrochemical³ 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 hydrogenation⁶ and reduction of imine intermediates by borohydride reagents such as NaCNBH₃.⁷ 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.

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*Tel: 312-996-4174; fax: 312-996-7107; pap4@uic.edu.

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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 (**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 -aminoesters in the same conditions resulted in the formation of *N*-benzylbutyro- and *N*-benzyl valerolactams, 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. reductivelactamization¹⁷ 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.

Results and discussion

It was proposed¹⁷ 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.

To evaluate our concept, a mixture of benzaldehyde (**1a**), methyl 7-aminoheptanoate hydrochloride (**2**), and triethylamine in CH₂Cl₂ 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 (entry 6–9) and polyaromatic (entry 10) systems as well. Although all the reactions in this study were carried out in CH₂Cl₂ 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 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 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 benzyloxylaniline **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 STAB. Such a reaction between imines and carbonyl-containing electrophiles is well documented,²³ and the resulting acyliminium intermediates have been widely utilized as high-value building blocks in organic synthesis for construction of various biologically active compounds.²⁴ We have carried out NMR spectroscopic experiments to investigate this option. A solution of benzaldehyde (1 equiv.) in CDCl₃ was treated with **2** (*n* = 6, 1 equiv.) and Et₃N (2.2 equiv.) at the same concentrations and in the same conditions as above. The ¹H and ¹³C NMR spectra acquired after 1 h revealed the disappearance of the peaks corresponding to the aldehyde and the amine and appearance of the imine proton as singlet at 8.06 ppm and the corresponding imine carbon at 160.3 ppm. When the mixture in the NMR tube was treated with (Boc)₂O (1 equiv.), there was no significant change in the chemical shifts of the peaks corresponding to the imine, in both the ¹H and ¹³C NMR spectra recorded at 0 min, 5 min, 15 min, 1 h, and 5 h time intervals. Further, addition of STAB (2.5 equiv.) to the mixture in NMR tube resulted in an exclusive formation of **6a** after 4 h, as confirmed by NMR after purification. The control experiments did not offer any evidence for the formation of the *N*-acyliminium ion, suggesting that the imine **3** undergoes reduction by STAB, followed by the *N*-Boc protection of secondary aryl amine **4** as proposed in Scheme 1. Next, we addressed the question whether other carbamate-based protecting groups could be employed in the same reaction settings. We observed the

formation of tertiary amine derivative as the major product in the tandem DRA using dibenzylidicarbonate, CbzCl, whereas reaction in the presence of FmocCl resulted in the mixture of compounds. The outcomes of these experiments suggested that the ability of the protecting group to trap the initially formed secondary amine is the key to the exclusive formation of *N*-Boc protected secondary amine and to avoid the dialkylation and lactamization. To further investigate this aspect, we compared the rates of protection of the amino group of benzylamino ester **37**, which was prepared from **6a**, with Boc₂O and CbzCl. The reaction of **37** with (Boc)₂O and Et₃N in CH₂Cl₂ led to the rapid *N*-Boc protection to give **6a** within few seconds, whereas the reaction with CbzCl under the same conditions took at least 10 min to give **38** (Scheme 3, eq. 2). A similar comparison of the reactivity of Boc₂O and CbzCl in reaction with amine **39** in CH₂Cl₂ in the presence of Et₃N showed that CbzCl was much less reactive (Scheme 3, eq. 3). These observations indicate that if the formation of the secondary aryl amine **4** takes place as suggested in Scheme 1, *N*-Boc protection of amine **4** would outcompete dialkylation and lactamization. In the case of the other protecting agents, dibenzylidicarbonate, CbzCl, and FmocCl, the rates of the side-reactions appear to be comparable or faster than the protection of the secondary amine **4**, which is also consistent with the proposed mechanism. Next, we explored whether the presence of Et₃N is only required to neutralize the hydrochloride salts of the primary amines and the imine formation step or it is also required for the subsequent transformations. The reduction of imine **41** with (Boc)₂O (1.1 equiv.), STAB (2.5 equiv.) in the presence of Et₃N (1.5 equiv.) in CH₂Cl₂ followed by the standard reaction work-up employed for all the reactions afforded *N*-Boc-amine **26** as the sole product. A mixture of tertiary amine derivative **42** and *N*-Boc-amine **26** was obtained without Et₃N (Scheme 4). Although the exact role that the triethylamine may play in this reaction is unclear, its presence during reduction of the imine intermediate is certainly required. In our opinion, one of the plausible explanations is that it may facilitate decomposition of the complex between the secondary amine and the boron triacetate and, therefore, accelerating the nucleophilic attack of the resulting secondary amine on (Boc)₂O.

Conclusion

An operationally simple, selective, efficient, and versatile one-pot tandem DRA/*N*-Boc protection procedure has been developed. It offers three powerful advantages over traditional approaches. First, this procedure eliminates commonly encountered overalkylation resulting in tertiary amines as major by-products. Second, it avoids reductive lactamization in case of γ - or δ -amino esters. Third, it allows a step-economic synthesis of monoalkylated *N*-Boc protected secondary amines in high yields using inexpensive and well-tolerated reaction conditions. The procedure is applicable to a wide variety of primary amines and aldehydes with the exception of weakly nucleophilic arylamines. Multiple lines of evidence presented in the paper support the mechanism of the tandem DRA/*N*-Boc protection procedure shown in Scheme 1. Further exploration of this synthetic approach and its mechanism is underway.

Experimental section

General information

All the reagents and solvents were obtained from commercial sources and used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on Bruker spectrometers at 300/400 MHz and 75/100 MHz, respectively. Chemical shifts were reported on δ scale in ppm with solvent indicated as the internal reference. Coupling constants were reported in Hz and the standard abbreviations indicating multiplicity were used as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectrometry

experiment was carried out on Agilent1100-MSD instrument. The IR spectra were recorded on a JASCO FT-IR 4100 spectrophotometer. High-resolution mass spectra (HRMS) were recorded with Electrospray Ionization (ESI) on a Waters Micromass Q-ToF Ultima API in the Mass Spectrometry Lab of School of Chemical Sciences, University of Illinois at Urbana-Champaign. TLC was performed with Merck 60F₂₅₄ silica gel plates. Chromatography purification was performed on Biotage-Isolera four instrument using pre-filled KP-Sil (normal phase) SNAP cartridges with UV detection at 254 and 280 nm. Hexane–ethyl acetate solvent system was used as eluent for chromatography unless otherwise mentioned. Products were visualized using ninhydrin (1% w/v in EtOH) with heating for 2 min, UV irradiation at 254 nm, or iodine oxidation.

General procedure for tandem DRA/*N*-Boc protection

To a mixture of aldehyde (1 mmol) and amine/amine hydrochloride (1 mmol) in anhydrous CH₂Cl₂ (10 mL) was added triethylamine (2.5 mmol) at rt, and the resulting solution was stirred vigorously for 1 h. To this was then added (Boc)₂O (1.2 mmol) followed by sodium triacetoxyborohydride (2 mmol). The reaction was stirred for an additional 4 h at rt, quenched with saturated NaHCO₃ solution, and extracted with CH₂Cl₂. The combined organic fractions were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (95:05 → 50:50, hexanes:EtOAc) to afford the *N*-Boc secondary amine. Most of the title compounds were present as a mixture of rotational isomers in their ¹H and ¹³C NMR spectra.

Compound characterization data

7-(Benzyl-*tert*-butoxycarbonylamino)heptanoic acid methyl ester (6a)

Colorless oil, 88% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.33–7.22 (m, 5H), 4.42 (br d, *J* = 8.0 Hz, 2H), 3.63 (s, 3H), 3.20–3.13 (m, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 1.63–1.28 (m, 17H). ¹³C NMR (100 MHz, CDCl₃): δ 174.0, 155.8, 138.7, 128.4 (2C), 127.6, 127.4, 79.5, 50.3, 46.4, 33.9 (2C), 27.7, 28.8, 28.6, 27.7, 26.5, 24.8. IR (Neat) cm⁻¹: 2937, 1736, 1689, 1414, 1358, 1243, 1167, 699 cm⁻¹. HRMS (ESI) *m/z* [M + Na]⁺ calcd for C₂₀H₃₁NO₄Na 372.2151, found 372.2153.

7-[*tert*-Butoxycarbonyl-(3-methoxybenzyl)amino]heptanoic acid methyl ester (6b)

Colorless oil, 90% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.22 (t, *J* = 7.6 Hz, 1H) 6.78 (d, *J* = 7.2 Hz, 3H), 4.39 (m, 2H), 3.78 (s, 3H), 3.65 (s, 3H), 3.15 (m, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.63–1.56 (m, 2H), 1.49–1.44 (m, 11H), 1.28 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 174.1, 159.7, 155.5, 140.4, 129.4, 119.6, 113.0, 112.5, 79.5, 55.1, 51.4, 50.0, 46.4, 33.9, 28.6, 27.7, 26.4, 24.8. IR (Neat) cm⁻¹: 2933, 1736, 1688, 1413, 1257, 1164, 875, 773, 404. HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₁H₃₄NO₅ 380.2437, found 380.2429.

7-(Benzo[1,3]dioxol-5-ylmethyl-*tert*-butoxycarbonylamino)heptanoic acid methyl ester (6c)

Pale yellow oil, 92% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, *J* = 8.0 Hz, 2H) 6.68 (bs, 1H), 5.93 (s, 2H), 4.23 (bs, 2H), 3.66 (s, 3H), 3.10 (m, 2H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.63–1.56 (m, 2H), 1.47–1.44 (m, 11H), 1.32–1.25 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 174.1, 155.9, 147.8, 146.6, 132.5, 121.5, 108.0 (2C), 100.9, 79.5, 51.4, 46.1, 33.9, 28.8, 28.7, 28.5 (3C), 28.4, 26.4, 24.8. IR (Neat) cm⁻¹: 2929, 1737, 1688, 1489, 1245, 1166, 1037, 927, 774. HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₁H₃₂NO₆ 394.2230, found 394.2226.

7-[*tert*-Butoxycarbonyl(4-fluorobenzyl)amino]heptanoic acid methyl ester (6d)

Colorless oil, 85% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.13 (bs, 2H), 6.94–6.90 (m, 2H), 4.32 (bs, 2H), 3.58 (s, 3H), 3.12–3.05 (m, 2H), 2.21 (m, 2H), 1.57–1.50 (m, 2H), 1.41 (m, 1H), 1.22 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 173.5, 162.7, 160.3, 155.3, 134.0, 128.8, 128.2, 114.8, 114.6, 79.1, 50.9, 49.0, 46.0, 33.4, 28.3, 27.9 (3C), 27.4, 26.0, 24.3. IR (Neat) cm^{-1} : 2929, 1736, 1688, 1509, 1410, 1221, 1149, 820. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_4\text{F}$ 368.2237, found 368.2240.

7-[*tert*-Butoxycarbonyl(4-nitrobenzyl)amino]heptanoic acid methyl ester (6e)

Pale yellow oil, 95% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.16 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 6.8 Hz, 2H), 4.49 (bs, 2H), 3.63 (s, 3H), 3.23–3.14 (m, 2H), 2.27 (t, J = 7.6 Hz, 2H), 1.62–1.27 (m, 17H). ^{13}C NMR (100 MHz, CDCl_3): δ 174.0, 155.8, 147.08, 128.0, 127.4, 123.7 (2C), 80.4, 51.4, 49.7, 47.2, 33.9, 33.8, 28.7, 28.4, 28.3, 28.0, 26.4, 24.7. IR (Neat) cm^{-1} : 2967, 1737, 1688, 1520, 1409, 1344, 1252, 856, 733. HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_6\text{Na}$ 417.2002, found 417.2014.

7-(*tert*-Butoxycarbonylpyridin-3-ylmethylamino)heptanoic acid methyl ester (6f)

Pale yellow oil, 78% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.48 (m, 2H), 7.57 (bs, 1H), 7.28–7.22 (m, 1H), 4.40 (bs, 2H), 3.63 (s, 3H), 3.18–3.11 (m, 2H), 2.26 (t, J = 7.6 Hz, 2H), 1.60–1.26 (m, 17H). ^{13}C NMR (100 MHz, CDCl_3): δ 174.0, 155.7, 148.8, 148.5, 135.1, 134.2, 123.4, 79.9, 51.4, 47.6, 46.8, 33.8, 28.7, 28.4 (3C), 27.9, 26.4, 24.7. IR (Neat) cm^{-1} : 2933, 1737, 1689, 1410, 1365, 1247, 1163, 768. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_4$ 351.2284, found 351.2279.

7-[*tert*-Butoxycarbonyl(4-pyridin-2-ylbenzyl)amino]heptanoic acid methyl ester (6g)

Colorless oil, 85% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.65 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.72–7.69 (m, 2H), 7.19–7.16 (m, 3H), 4.44 (bs, 2H), 3.61 (s, 3H), 3.22–3.11 (m, 2H), 2.25 (t, J = 7.2 Hz, 2H), 1.61–1.42 (m, 13H), 1.26 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 174.0, 157.0, 155.9, 149.5, 139.6, 138.1, 136.7, 128.1, 127.3, 126.9 (2C), 122.0, 120.3, 79.5, 51.3, 49.9, 46.7, 33.9, 28.8, 28.4 (3C), 27.8, 26.4, 24.8. IR (Neat) cm^{-1} : 2929, 1736, 1687, 1466, 1242, 1165, 774. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_4$ 427.2597, found 427.2589.

7-{*tert*-Butoxycarbonyl[5-(4-nitrophenyl)furan-2-ylmethyl]amino}heptanoic acid methyl ester (6h)

Orange oil, 92% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.22 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 3.6 Hz, 1H), 6.35 (m, 1H), 4.47–4.42 (m, 2H), 3.65 (s, 3H), 3.27 (m, 2H), 2.27 (t, J = 7.6 Hz, 2H), 1.63–1.56 (m, 4H), 1.48 (s, 9H), 1.31–1.25 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 174.0, 155.7, 154.9, 150.9, 146.2, 136.3, 124.3 (2C), 123.6 (2C), 110.4, 109.9, 79.9, 51.4, 47.1, 43.5, 33.9, 28.8, 28.7 (3C), 28.4, 26.4, 24.8. IR (Neat) cm^{-1} : 2933, 1736, 1688, 1521, 1333, 1247, 1160, 852. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_7$ 461.2288, found 461.2292.

7-[*tert*-Butoxycarbonyl(5-phenylthiophen-2-ylmethyl)amino]heptanoic acid methyl ester (6i)

Pale yellow oil, 85% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.57 (d, J = 7.6 Hz, 2H), 7.36–7.26 (m, 3H), 7.14–7.13 (m, 1H), 6.89 (br s, 1H), 4.52 (bs, 2H), 3.66 (s, 3H), 3.24 (m, 2H), 2.30 (t, J = 7.6 Hz, 2H), 1.64–1.45 (m, 13H), 1.32 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 174.1, 155.5, 143.9, 141.2, 134.4, 128.8 (2c), 127.3, 126.8, 125.7, 125.6, 122.3, 80.0, 51.4, 46.4, 45.5, 33.9, 28.8, 28.7 (3C), 27.9, 26.5, 24.8. IR (Neat) cm^{-1} : 2929, 1736, 1689, 1492,

1364, 1240, 1155, 756. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{34}NO_4S$ 432.2209, found 432.2210.

7-(*tert*-Butoxycarbonylnaphthalen-2-ylmethylamino)heptanoic acid methyl ester (6j)

Colorless oil, 95% yield. 1H NMR (400 MHz, $CDCl_3$): δ 7.85–7.81 (m, 3H), 7.66 (bs, 1H), 7.51–7.40 (m, 3H), 4.61 (br s, 2H), 3.67 (s, 3H), 3.27–3.16 (m, 2H), 2.28 (t, J = 7.6 Hz, 2H), 1.64–1.48 (m, 13H), 1.30 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 156.0, 136.1, 133.3, 132.7, 128.3, 127.6 (3C), 126.1, 125.6 (2C), 79.6, 51.4, 50.3, 46.4, 33.9, 28.8, 28.5 (3C), 27.7, 26.5, 24.8. IR (Neat) cm^{-1} : 2929, 1736, 1688, 1413, 1364, 1240, 1164, 749. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{34}NO_4$ 400.2488, found 400.2488.

4-(Benzyl-*tert*-butoxycarbonylamino)butyric acid methyl ester (9)

Colorless oil, 90% yield. 1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.24 (m, 5H), 4.43 (br s, 2H), 3.65 (s, 3H), 3.25–3.18 (m, 2H), 2.29 (m, 2H), 1.83 (m, 2H), 1.49–1.45 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 155.7, 138.3, 128.5 (2C), 127.8, 127.1, 79.7, 51.5, 50.0, 45.6, 31.2, 28.4 (3C), 23.3. IR (Neat) cm^{-1} : 2936, 1735, 1688, 1414, 1358, 1243, 1167, 1118, 698. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{26}NO_4$ 308.1862, found 308.1856.

5-(Benzyl-*tert*-butoxycarbonylamino)pentanoic acid methyl ester (10)

Colorless oil, 92% yield. 1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.24 (m, 5H), 4.43 (br s, 2H), 3.67 (s, 3H), 3.23–3.15 (m, 2H), 2.31 (m, 2H), 1.58–1.45 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 155.9, 138.8, 128.8 (2C), 127.6, 127.4, 80.1, 51.9, 50.6, 46.8, 34.1, 28.8 (3C), 28.6, 22.6. IR (Neat) cm^{-1} : 2937, 1736, 1689, 1413, 1243, 1157, 732, 699. HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{27}NO_4Na$ 344.1838, found 344.1826.

Benzyl(4-*tert*-butoxycarbonylamino)butyl)carbamic acid *tert*-butyl ester (18)

Colorless oil, 90% yield. 1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.21 (m, 5H), 4.70 (br s, 1H), 4.39 (br s, 2H), 3.19 (m, 2H), 3.05 (m, 2H), 1.46–1.41 (m, 22H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (2C), 138.8, 128.4 (2C), 127.6, 127.1, 79.5, 78.8, 50.5, 46.1, 40.1, 28.8 (6C), 27.3, 25.3. IR (Neat) cm^{-1} : 3356, 2933, 1689, 1452, 1364, 1246, 1165, 732. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{35}N_2O_4$ 379.2597, found 379.2603.

(3-Methoxybenzyl)-(4-phenylbutyl)carbamic acid *tert*-butyl ester (20)

Colorless oil, 87% yield. 1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.18 (m, 6H), 6.84–6.82 (m, 3H), 4.42 (br s, 2H), 3.82 (s, 3H), 3.28–3.19 (m, 2H), 2.63 (t, J = 6.8 Hz, 2H), 1.61–1.56 (m, 4H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 155.6, 142.3, 140.4, 129.4, 128.4 (2C), 128.3 (2C), 125.7, 119.6, 113.0, 112.5, 79.6, 55.1, 50.0, 46.4, 35.6, 28.6, 28.5, 27.7. IR (Neat) cm^{-1} : 2933, 1688, 1413, 1257, 1164, 775, 404. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{32}NO_3$ 370.2382, found 370.2380.

Cyclohexylmethylcyclopropylcarbamic acid *tert*-butyl ester (23)

Colorless oil, 80% yield. 1H NMR (400 MHz, $CDCl_3$): δ 3.01 (d, J = 6.9 Hz, 2H), 2.46–2.44 (m, 1H), 1.71–1.62 (m, 6H), 1.43 (bs, 9H), 1.21–1.14 (3H), 0.91–0.88 (m, 2H), 0.71–0.69 (m, 2H), 0.56–0.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 78.7, 52.9, 36.4, 30.4 (2C), 28.5, 28.0 (3C), 26.1, 25.5 (3C), 7.7. IR (Neat) cm^{-1} : 2923, 1695, 1393, 1149, 770. HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{27}NO_2Na$ 276.1939, found 276.1941.

Benzylcyclohexylmethylcarbamic acid *tert*-butyl ester (25)

Colorless oil, 95% yield. 1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.24 (m, 5H), 4.49–4.43 (m, 2H), 3.09–3.00 (m, 2H), 1.74–1.68 (m, 4H), 1.54 (br s, 9H), 1.44–1.38 (m, 2H), 1.27–1.14

(m, 3H), 0.92 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 156.2, 138.6, 128.4 (2C), 127.6, 127.0 (2C), 79.4, 52.6, 50.5, 36.7, 30.9, 28.4 (2C), 27.4 (3C), 26.5, 25.9. IR (Neat) cm^{-1} : 2926, 1690, 1413, 1168, 1069, 875, 698. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{30}\text{NO}_2$ 304.2277, found 304.2285.

2-[(*tert*-Butoxycarbonylcyclopropylamino)methyl]cyclopropanecarboxylic acid ethyl ester (27)

Colorless oil, 91% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.33–7.23 (m, 5H), 4.53 (s, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.21–3.04 (m, 2H), 1.52 (bs, 9H), 1.46 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.14–1.12 (m, 1H), 0.78–0.72 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 173.6, 155.7, 138.1, 128.5 (2C), 127.8, 127.6, 127.2, 79.8, 60.4, 50.2, 48.6, 28.4 (3C), 21.1, 19.2, 14.9, 13.6. IR (Neat) cm^{-1} : 2978, 1721, 1689, 1412, 1248, 1166, 868, 731, 407. HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_4\text{Na}$ 356.1838, found 356.1829.

Benzyl[5-(4-nitrophenyl)furan-2-ylmethyl]carbamic acid *tert*-butyl ester (28)

Pale yellow semi-solid, 83% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.24 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.34–7.29 (m, 5H), 6.80 (d, J = 3.2 Hz, 1H), 6.37–6.28 (m, 1H), 4.56–4.38 (m, 4H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 155.1, 153.4, 150.7, 145.9, 137.4, 135.9, 128.2 (2C), 127.6 (2C), 127.0, 123.9 (2C), 123.3 (2C), 110.5, 109.4, 80.1, 59.7, 42.4, 28.0 (3C). HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_5$ 409.1763, found 409.1759.

2-[[4-Benzoyloxyphenyl)-*tert*-butoxycarbonylamino]methyl]cyclopropanecarboxylic acid ethyl ester (30)

White semi-solid, 60% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.46–7.32 (m, 5H), 7.10 (br s, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.07 (s, 2H), 4.16–4.10 (m, 2H), 3.61–3.51 (m, 2H), 1.66–1.47 (m, 2H), 1.44 (bs, 9H), 1.25 (t, J = 7.2 Hz, 3H), 1.19–1.16 (m, 1H), 0.80–0.78 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 173.7, 157.2, 155.0, 136.8, 135.4, 128.7, 128.6, 128.0, 127.5, 115.0, 114.7, 80.1, 70.2, 60.4, 52.5, 28.3 (3C), 21.7, 19.2, 14.3, 13.7. IR (Neat) cm^{-1} : 2982, 1723, 1691, 1510, 1366, 1237, 1163, 1007, 736. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{32}\text{NO}_5$ 426.2280, found 426.2274.

Cyclohexylmethyl(4-methoxyphenyl)carbamic acid *tert*-butyl ester (32)

Pale yellow semi-solid, 85% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.09 (br s, 2H), 6.86 (m, 2H), 3.81 (s, 3H), 3.45 (d, J = 7.3 Hz, 2H), 1.71–1.62 (m, 6H), 1.42 (bs, 9H), 1.12–1.15 (m, 3H), 0.97–0.93 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 157.5, 155.6, 135.4, 128.3 (2C), 113.8 (2C), 79.8, 56.1, 55.2, 36.4, 30.6 (2C), 28.2 (3C), 26.4, 25.7 (2C). IR (Neat) cm^{-1} : 2922, 1692, 1510, 1244, 1147, 1037, 832. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{30}\text{NO}_3$ 320.2226, found 320.2224.

Benzo[1,3]dioxol-5-ylmethyl(4-methoxyphenyl)carbamic acid *tert*-butyl ester (33)

Pale yellow semi-solid, 70% yield. ^1H NMR (400 MHz, CDCl_3): δ 6.99 (bs, 2H), 6.84–6.51 (m, 5H), 5.92 (s, 2H), 4.68 (s, 2H), 3.77 (s, 3H), 1.44 (bs, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 157.2, 154.7, 147.2, 146.2, 135.0, 132.1, 127.8 (2C), 120.8, 113.7, 113.4, 108.1, 107.6, 100.5, 79.8, 54.9, 53.4, 28.0 (3C). IR (Neat) cm^{-1} : 2978, 1689, 1512, 1410, 1390, 1243, 1160, 1025, 834, 734. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_5$ 358.1654, found 358.1658.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

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

Scheme 2. Investigation of the tandem DRA/*N*-Boc protection procedure with γ - or δ -amino esters

Scheme 3.

Control experiments to elucidate the proposed reaction pathway

Scheme 4. Control experiments to elucidate the role of Et_3N

Table 1Investigation of the scope of tandem DRA/*N*-Boc protection of aromatic aldehydes with amino ester **2** (*n* = 6)^a

$ \begin{array}{c} \text{Ar-CHO} + \text{ClH} \cdot \text{H}_2\text{N} \left(\text{CH}_2 \right)_n \text{C(=O)OMe} \xrightarrow[\text{STAB, CH}_2\text{Cl}_2]{\text{Et}_3\text{N, (Boc)}_2\text{O}} \text{Ar-CH}_2\text{-N(Boc)CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C(=O)OMe} \\ \mathbf{1} \qquad \qquad \mathbf{2} \ (n = 6) \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \mathbf{6} \ (n = 6) \end{array} $				
entry	aldehyde	Ar	product	Yield
1	1a		6a	88%
2	1b		6b	90%
3	1c		6c	92%
4	1d		6d	85%
5	1e		6e	95%
6	1f		6f	78%
7	1g		6g	85%
8	1h		6h	92%

$ \begin{array}{c} \text{Ar-CHO} + \text{ClH} \cdot \text{H}_2\text{N} \left(\text{CH}_2 \right)_n \text{C(=O)OMe} \xrightarrow[\text{STAB, CH}_2\text{Cl}_2]{\text{Et}_3\text{N, (Boc)}_2\text{O}} \text{Ar-CH}_2\text{-N(Boc)CH}_2\text{C(=O)OMe} \\ \mathbf{1} \qquad \qquad \mathbf{2 \ (n = 6)} \qquad \qquad \qquad \qquad \mathbf{6 \ (n = 6)} \end{array} $				
entry	aldehyde	Ar	product	Yield
9	1i		6i	85%
10	1j		6j	95%

^aUnless otherwise indicated, all the reactions were carried out in CH₂Cl₂ (10 mL) at rt using 1 mmol of aldehyde, 1 mmol of amine, 2.5 equiv. of NEt₃, 1.2 equiv. of (Boc)₂O, and 2.5 equiv. of STAB for 5 h.

Table 2

Further investigation of the scope of tandem DRA/*N*-Boc protection^a

$\text{R}^1\text{-CHO} + \text{R}^2\text{-NH}_2 \xrightarrow[\text{STAB, CH}_2\text{Cl}_2]{\text{Et}_3\text{N, (Boc)}_2\text{O}} \text{R}^1\text{-CH}_2\text{-N}^{\text{Boc}}\text{-R}^2$				
entry	R ¹ -CHO	R ² -NH ₂	product	Yield
1	1a	17	18	90%
2	1b	19	20	87%
3		22		80%
	21		23	
4	21	24	25	95%
5	26	24	27	91%
6	1h	24	28	83%
7	26	29	30	60%
8	21	31	32	85%
9	1c	31	33	70%

$\text{R}^1\text{-CHO} + \text{R}^2\text{-NH}_2 \xrightarrow[\text{STAB, CH}_2\text{Cl}_2]{\text{Et}_3\text{N, (Boc)}_2\text{O}} \text{R}^1\text{-CH}_2\text{-N}(\text{Boc})\text{R}^2$				
entry	R ¹ -CHO	R ² -NH ₂	product	Yield
10	1c	34	35	no reaction

^aUnless otherwise indicated, all the reactions were carried out in CH₂Cl₂ (10 mL) at rt using 1 mmol of aldehyde, 1 mmol of amine, 2.5 equiv. of NEt₃, 1.2 equiv. of (Boc)₂O, and 2.5 equiv. of STAB for 5 h.