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Straightforward synthesis of orthogonally protected piperidin-3-ylmethanamine and piperidin-4-ylmethanamine derivatives

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ABSTRACT

The 1,3- and 1,4-disubstituted piperidines are important building blocks in medicinal chemistry and drug discovery. We present the synthesis of orthogonally protected piperidin-3-ylmethanamine and piperidin-4-ylmethanamine derivatives from commercially available nipecotamide, isonipecotamide, nipecotic acid and isonipecotic acid. This is a straightforward two-step procedure that gives high overall yields. Purification of the intermediates using this procedure is not necessary, and the final compounds are purified by simple flash column chromatography.

Piperidines are heterocyclic compounds that are found in numerous pharmacologically active compounds. For example, 1,3-disubstituted piperidines are used as anticonvulsant (tiagabine[1]) and antiplatelet (elarofiban[2]) drugs, and 1,4-disubstituted piperidines are utilized as analgesic (fentanyl[3]), antiallergic (fexofenadine[4]), antipsychotic (risperidone[5]), antidepressant (RS 67333[6]), antihypertensive (ketanserin[7]), anticholinergic (donepezil[8]), anti-andrenergic (indoramin[9]) and antineoplastic (irinotecan[10]) drugs. The high number of piperidine-containing drugs indicates that 1,3- and 1,4-disubstituted piperidine derivatives are important building blocks in drug discovery and development.

Convenient methods for preparing 1,3- and 1,4-disubstituted piperidines are thus highly desirable. As part of our studies of compounds related to the acetylcholinesterase inhibitor, donepezil (Fig. 1), we needed orthogonally protected piperidin-3-ylmethanamine and piperidin-4-ylmethanamine derivatives. Procedures to these types of structures are not well documented outside of the patent literature. Herein we describe a succinct procedure to produce these building blocks with orthogonal protection in high yields.

For the synthesis of the protected piperidin-3-ylmethanamine derivative **1**, nipecotamide was treated with benzoyl chloride in the presence of Et_3N in tetrahydrofuran (THF), to provide *N*-benzoyl derivative **2** in 98% yield. Compound **2** was then converted into orthogonally protected piperidin-3-ylmethanamine **1** in a procedure composed of two synthetic steps. First, five equivalents

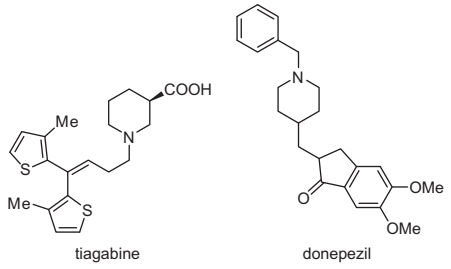
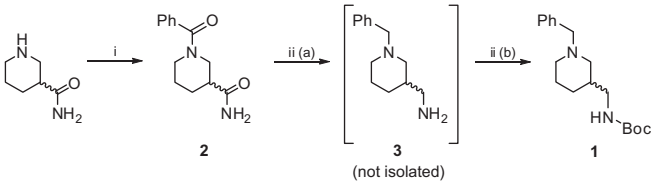


Figure 1. Example of piperidine-containing drugs.



Scheme 1. Reagents and conditions: (i) PhCOCl, Et_3N, THF, 0 °C to rt, 22 h, 98%; (ii) (a) $LiAlH_4$, anhydrous THF, rt to reflux, under argon, 3 h, (b) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 24 h, 49% (for step ii).

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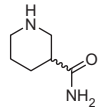
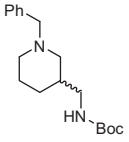
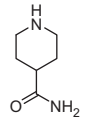
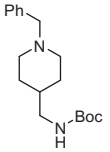
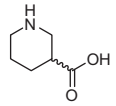
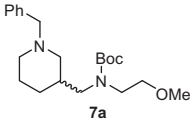
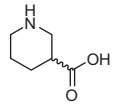
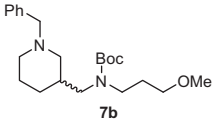
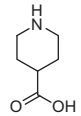
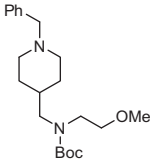
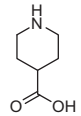
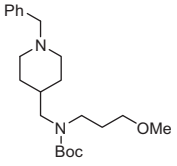
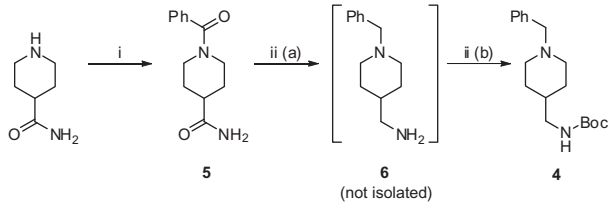
Table 1
Synthesized orthogonally protected piperidin-3-ylmethanamines (**1**, **7a** and **7b**) and piperidin-4-ylmethanamines (**4**, **8a** and **8b**)

Starting compound	Final compound	Overall yield[a] (%)
	 **1**	48
	 **4**	78
	 **7a**	74
	 **7b**	60
	 **8a**	56
	 **8b**	65

[a] Isolated yield of pure product.



Scheme 2. Reagents and conditions: (i) PhCOCl, Et_3N, THF, 0 °C to rt, 25 h, 95%; (ii) (a) $LiAlH_4$, anhydrous THF, rt to reflux, 2 h, under argon, (b) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 21 h, 82% (for step ii).

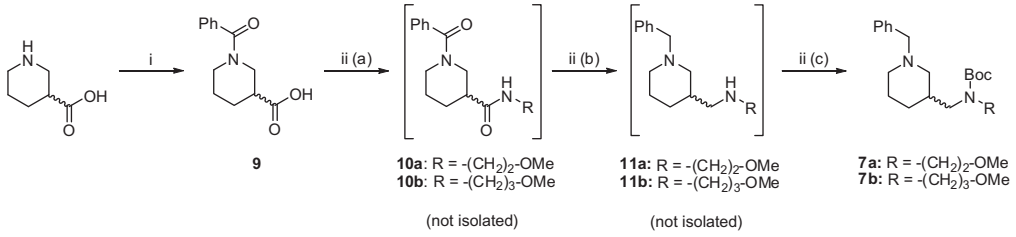
of $LiAlH_4$ in anhydrous THF was used to reduce both amide bonds:[11] the benzoyl amide on the piperidine nitrogen was reduced to a benzyl amine, and the primary amide on the piperidine side chain was reduced to an aminomethyl group to give compound **3**. Compound **3** was not isolated, but was immediately treated with Boc_2O in the presence of Et_3N in CH_2Cl_2. Thus, after flash column chromatography, this provided orthogonally protected piperidine **1** (Scheme 1). The overall isolated yield for the preparation of compound **1** from nipecotamide using this procedure comprising three synthetic steps was 48% (Table 1). As the starting nipecotamide was racemic, product **1** was also obtained as a racemic mixture.

The same procedure was then used to prepare the orthogonally protected piperidin-4-ylmethanamine **4** from isonipecotamide (Scheme 2). The overall isolated yield for these three steps was even higher than for the synthesis of compound **1** (78%, Table 1).

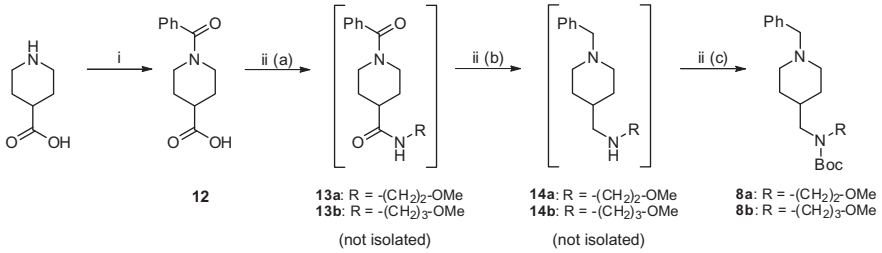
We were also interested in the derivatives of compounds **1** and **4** that have an *N*-alkyl group [$-(CH_2)_2-OMe$ or $-(CH_2)_3-OMe$] on the aminomethyl side chain. Using the principle of the procedure described above for the preparation of the parent compounds **1** and **4**, we also synthesized compounds **7a** and **7b** from nipecotic acid, and compounds **8a** and **8b** from isonipecotic acid. These syntheses confirm the general applicability of our procedure.

Here, nipecotic acid was treated with benzoyl chloride in the presence of K_2CO_3 in a THF–H_2O mixture, to provide, after acidification, carboxylic acid **9** in 95% yield (Scheme 3). Compound **9** was then converted into orthogonally protected piperidin-3-ylmethanamines **7a** or **7b** in a procedure composed of three reactions. Purification of the intermediates in these steps was not necessary. Carboxylic acid **9** was first treated with a primary amine (2-methoxyethylamine or 3-methoxypropylamine) in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) and Et_3N in CH_2Cl_2 at room temperature,[12] to provide the corresponding amides **10a** or **10b**. Treatment of **10a** or **10b** with five equivalents of $LiAlH_4$ in anhydrous THF under reflux[11] reduced both of the amide groups into their corresponding amines **11a** or **11b**. Compounds **11a** and **11b** were finally treated with Boc_2O in the presence of Et_3N in CH_2Cl_2. Flash column chromatography then provided orthogonally protected piperidines **7a** and **7b**. The overall yields for the preparation of compounds **7a** and **7b** from nipecotic acid using this procedure composed of four synthetic steps were 74% and 60%, respectively (Table 1). As the starting nipecotic acid was racemic, products **7a** and **7b** were also obtained as racemic mixtures. The overall yields for preparing compounds **8a** and **8b** from isonipecotic acid (Scheme 4) using the same procedure were 56% and 65%, respectively (Table 1).

In summary, we have developed convenient procedures for the synthesis of orthogonally protected piperidin-3-ylmethanamine and piperidin-4-ylmethanamine derivatives that start from commercially available nipecotamide, isonipecotamide, nipecotic acid, and isonipecotic acid. No purification of the intermediates was necessary, which helps maintain the high overall yields for our syntheses. The synthesized 1,3- and 1,4-disubstituted piperidines



Scheme 3. Reagents and conditions: (i) (a) PhCOCl, K_2CO_3, THF–H_2O, 0 °C to rt, 22 h, (b) 6 M HCl (aq), 0 °C, 95%; (ii) (a) H_2N-R, TBTU, Et_3N, CH_2Cl_2, rt, 22 h for **10a** and 21 h for **10b**, (b) $LiAlH_4$, anhydrous THF, rt to reflux, under argon, 3 h for **11a** and 2.5 h for **11b**, (c) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 20 h for **7a** and 17 h for **7b**, 78% for **7a** from **9**, and 63% for **7b** from **9**.



Scheme 4. Reagents and conditions: (i) (a) PhCOCl, K_2CO_3, THF–H_2O, 0 °C to rt, 22 h, (b) 6 M HCl (aq), 0 °C, 85%; (ii) (a) H_2N-R, TBTU, Et_3N, CH_2Cl_2, rt, 23 h for **13a** and 22 h for **13b**; (b) $LiAlH_4$, anhydrous THF, rt to reflux, under argon, 2 h for **14a** and 2.5 h for **14b**; (c) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 22 h for **8a** and 18 h for **8b**, 65% for **8a** from **12**, and 77% for **8b** from **12**.

are new building blocks with potential use in medicinal chemistry and drug discovery.

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Supplementary data

Supplementary data (general methods and experimental procedures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.034.

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