Heterocycles

DOI: 10.1002/anie.200800404

An Expedient Strategy for the Synthesis of Tryptamines and Other Heterocycles**

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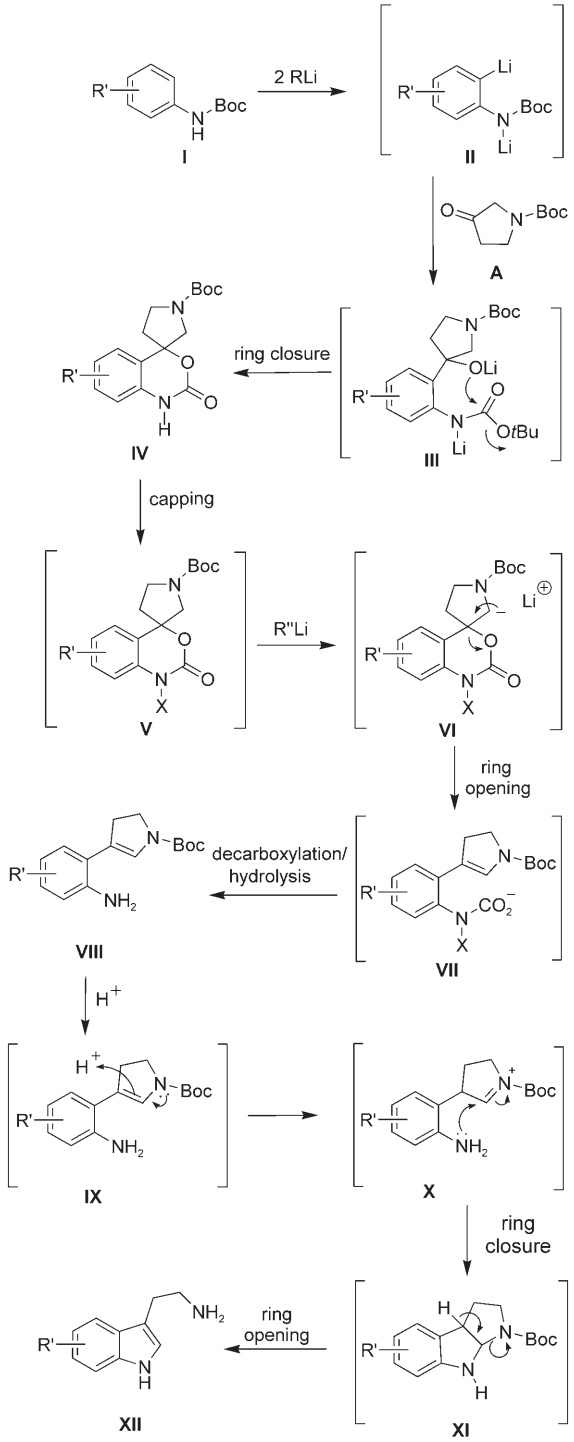
The increasing number of heterocyclic natural products and the well known applications of heterocyclic chemistry to pharmaceutical research dictate the development of new synthetic methods for accessing heterocycles. Novel cascade reactions offer rapid assembly of molecular frameworks and have been employed in natural product and other complex molecule construction with impressive results.[1] In this communication, we report an expedient, cascade-based strategy for the construction of novel heterocyclic systems, including spiro-heterocycles, *ortho*-substituted anilines, and tryptamines.

Scheme 1 depicts the general concepts for the construction of spiro-heterocycles (**IV**), *ortho*-substituted anilines (**VIII**), and tryptamines (**XII**) starting with readily available aniline derivatives (**I**). Thus, bis-metalation of aniline **I** to form reactive intermediate **II**,[2] and subsequent addition of *N*-Boc pyrrolidin-3-one (**A**) should lead to species **III**, whose ring closure as shown should offer an entry into spirocyclic system **IV** and derivatives thereof as stable chemical entities. Temporary capping of the active NH functionality within **IV** should allow a second cascade sequence initiated by regioselective base-induced deprotonation of intermediate **V**[3] to afford anionic species **VI**, whose collapse as shown should lead, sequentially, to intermediates **VII** (ring opening) and **VIII** (extrusion of CO_2 and hydrolysis of the N–X bond). The latter species represents a reactive class of *ortho*-substituted anilines whose potential remains relatively unexplored.[4]



Scheme 1. General, cascade-based strategy for the construction of novel spiro-heterocycles (**IV**), *ortho*-substituted anilines (**VIII**), and tryptamines (**XII**). X = capping group; Boc = *tert*-butoxycarbonyl.

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[**] We thank Doris Tan (ICES) for high-resolution mass spectrometry (HRMS) assistance and Dr. T. W. C. Hoe (Institute of Molecular and Cell Biology (IMCB), A*STAR) for X-ray crystallographic analysis. Financial support for this work was provided by A*STAR.

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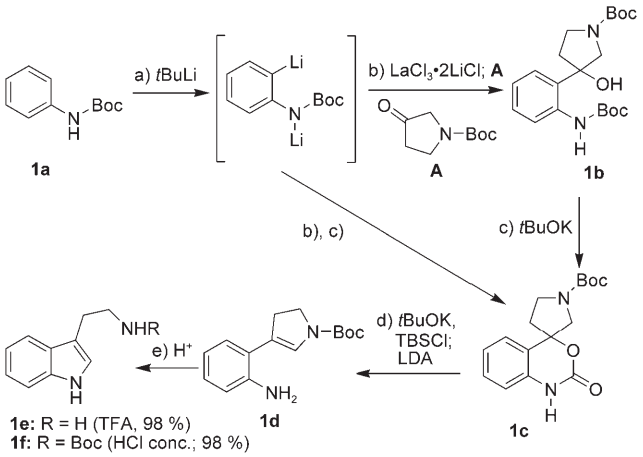
Finally, a third cascade sequence may be initiated from *ortho*-substituted aniline system **VIII** by acid catalysis, leading, through fleeting intermediates **IX**–**XI**, to tryptamine **XII**, a well known building block for many intents and purposes.[5]

The implementation of this plan by using *N*-Boc aniline (**1a**) as a starting material is shown in Scheme 2. Thus,



Scheme 2. Synthesis of *ortho*-substituted anilines **1b** and **1d**, spiro-heterocycle **1c**, and tryptamines **1e** and **1f**. Reagents and conditions: a) *t*BuLi (2.4 equiv), Et_2O, −10 °C, 4 h; b) $LaCl_3$·2 LiCl (0.33 M in THF, 1.3 equiv), −70 °C, 5 min; then **A** (1.0 M in THF, 1.2 equiv), −70→25 °C, 1 h, **1b** (75 %); c) *t*BuOK (0.1 equiv), THF, 70 °C, 4 h, **1c** (90 % from **1b**; 72 % from **1a**); d) *t*BuOK (1.2 equiv), TBSCl or TIPSCl (1.2 equiv), THF, 25 °C, 1 h; then LDA (1.0 M in THF, 5.0 equiv), −50→−30 °C, 2 h, **1d** (77 %); e) TFA/CH_2Cl_2 (1:10), 0→25 °C, 2 h, **1e** (98 %) or HCl (conc., 1 drop), CH_2Cl_2, 0→25 °C, 2 h, **1f** (98 %). TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl; TFA = trifluoroacetic acid.

treatment of **1a** with *t*BuLi in ether (−10 °C, 4 h) and subsequent sequential addition of $LaCl_3$·2 LiCl (−70 °C, 5 min)[6] and *N*-Boc pyrrolidin-3-one (**A**)[7] (−70 °C) furnished, upon warming to room temperature and aqueous workup, aniline derivative **1b** in 75 % yield. The latter compound was converted into spiro-heterocycle **1c** in 90 % yield upon exposure to catalytic amounts of *t*BuOK (10 mol %; THF, 70 °C, 4 h). Alternatively, spiro-heterocycle **1c** could be directly obtained from intermediate **1a** in 72 % yield upon addition of catalytic amounts of *t*BuOK (10 mol %; THF, 70 °C, 4 h) to the reaction mixture prior to the workup. The latter observation elevates the cascade sequence from **1a** to a convenient, one-pot operation for the preparation of spirocycle **1c**. Exposure of carbamate **1c** to *t*BuOK and TBSCl (or TIPSCl)[8] with subsequent addition of LDA gave, after work up with aqueous NH_4Cl, *ortho*-substituted aniline **1d** in 77 % yield. Finally, treatment of the labile *ortho*-substituted aniline **1d** with TFA in CH_2Cl_2 afforded tryptamine **1e** in 98 % yield, whereas the use of concentrated HCl, instead of TFA, led to the N-Boc protected tryptamine derivative **1f** (98 % yield).

Heterocycles **1c** (m.p. 176–177 °C, EtOAc) and **1d** (m.p. 124–125 °C, EtOAc) afforded crystals suitable for X-ray crystallographic analysis that proved their structure beyond question[9] (see ORTEP drawings, Figure 1).

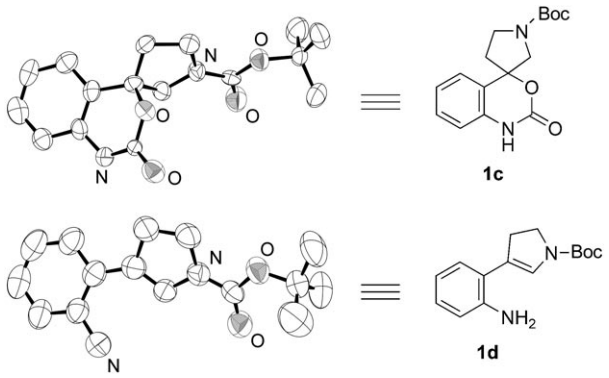
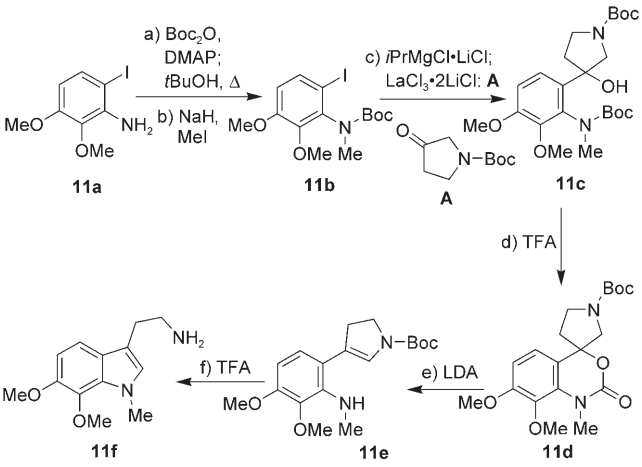


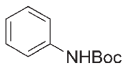
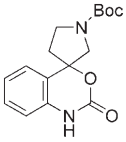
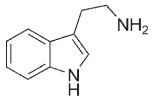
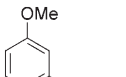
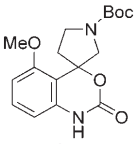
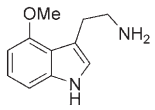
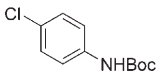
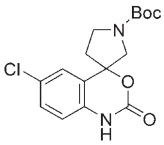
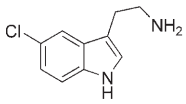
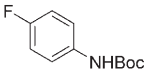
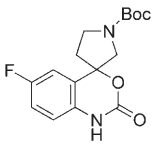
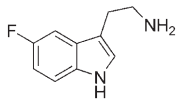
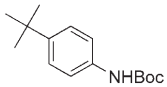
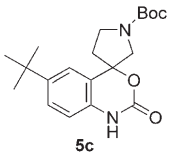
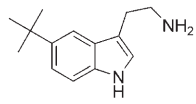
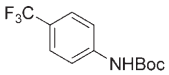
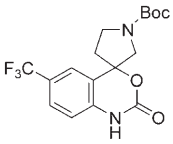
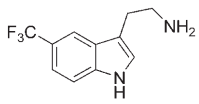
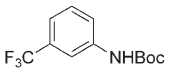
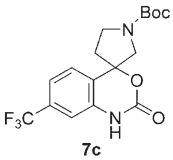
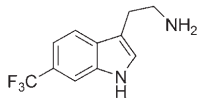
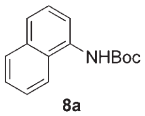
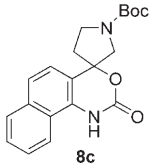
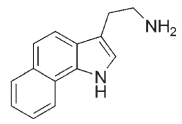
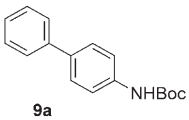
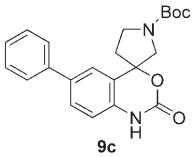
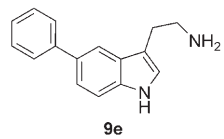
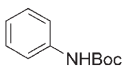
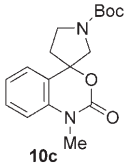
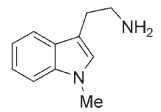
Figure 1. X-ray derived ORTEP drawings of compounds **1c** and **1d** drawn at the 50 % probability level.

The generality and scope of this new methodology are demonstrated by the examples shown in Table 1. Thus, in addition to aniline itself (Table 1, entry 1), a number of substituted anilines, including *meta*- (Table 1, entries 2 and 7) and *para*-substituted anilines (Table 1, entries 3–6) were successfully employed as starting materials leading to an array of heterocyclic systems, including tryptamine **2e**, whose structure is related to the antipsychotic agents psilocin and psilocybin.[10,11] Furthermore, the sequence is tolerant of chlorine and fluorine atoms (Table 1, entries 3 and 4) as well as trifluoromethyl groups (Table 1, entries 6 and 7), noteworthy features for medicinal chemistry applications. Naphthyl (Table 1, entry 8) and biphenyl (Table 1, entry 9) derivatives also enter the cascade sequence, permitting further expansion of the scope and generality of the method. Whereas in situ N-silylation[8] was necessary for the procurement of free indole tryptamines, N-methylated spirocarbamate **10c**



Scheme 3. Construction of Corey and co-workers' tryptamine **11f**. Reagents and conditions: a) Boc_2O (1.2 equiv), DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 2 h; then reflux in *t*BuOH, 6 h; b) NaH (1.5 equiv), MeI (2.0 equiv), THF, 25 °C, 2 h, **11b** (62 %); c) *i*PrMgCl·LiCl (1.0 M in THF, 1.1 equiv), THF, −70 °C, 2 h; then $LaCl_3$·2 LiCl (0.33 M in THF, 1.1 equiv), −70 °C, 1 h; then **A** (1 M in THF, 1.0 equiv), −70→25 °C, 1 h, **11c** (78 %); d) TFA (0.1 equiv), CH_2Cl_2, 0 °C, 1 h, **11d** (96 %); e) LDA (1.0 M in THF, 1.1 equiv), −50→−30 °C, 3 h, **11e** (92 %); f) TFA (0.1 equiv), CH_2Cl_2, 0→25 °C, 2 h, **11f** (96 %). DMAP = 4-dimethylaminopyridine; LDA = lithium diisopropylamide.

Table 1: Synthesis of spiro-heterocycles and tryptamines.

Entry	*N*-Boc aniline	Spiro-heterocycle[a]	Yield[b] [%]	Tryptamine[c]	Yield[b] [%]
1	 **1a**	 **1c**	72	 **1e**	76
2	 **2a**	 **2c**	76	 **2e**	84
3	 **3a**	 **3c**	81	 **3e**	80
4	 **4a**	 **4c**	70	 **4e**	71
5	 **5a**	 **5c**	74	 **5e**	66
6	 **6a**	 **6c**	72	 **6e**	68
7	 **7a**	 **7c**	74	 **7e**	77
8	 **8a**	 **8c**	79	 **8e**	41
9	 **9a**	 **9c**	80	 **9e**	87
10	 **1a**	 **10c**	71[d]	 **10e**	65

[a] Reactions were carried out on 3.0-mmol scale in anhydrous ether. [b] Yield of isolated product. [c] Reactions were carried out on 0.1-mmol scale in anhydrous THF. [d] Obtained by in situ N-methylation of the anion of spirocycle **1c** with MeI prior to quenching.

(obtained from **1a** by in situ N-methylation of the corresponding anion with MeI) afforded 1-methyltryptamine **10e** directly upon treatment with LDA (Table 1, entry 10).

As a first application of the described methodology, we report a short and efficient synthesis of 6,7-dimethoxy-1-methyltryptamine (**11f**), a compound used by Corey and coworkers in the synthesis of aspidophytine[12] (Scheme 3). Thus, N-Boc protection (Boc_2O, DMAP; then *t*BuOH, reflux)[13] and subsequent methylation (NaH, MeI) of known iodoaniline **11a**[14] afforded iodide **11b** (62% yield), which was reacted sequentially, and in one pot, with *i*PrMgCl·LiCl,[15] $LaCl_3$·2 LiCl,[6] and *N*-Boc pyrrolidin-3-one (**A**) to give aniline derivative **11c**, in 78% yield. Exposure of the latter compound to TFA in CH_2Cl_2 then furnished spirocycle **11d** in quantitative yield. Since the nitrogen atom of the cyclic carbamate has no acidic protons, in this case, the rupture of spirocycle **11d** was performed directly by treatment with LDA and led to bicycle **11e**, whose rearrangement/deprotection to tryptamine **11f** was accomplished through the action of TFA in 96% yield.

The chemistry described herein provides facile and direct entries into a variety of novel N-heterocycles and substituted tryptamines. This general method is expected to find applications in chemical synthesis in general, and in the construction of tryptamine-based complex molecules in particular.

Received: January 25, 2008
Published online: April 11, 2008

Keywords: heterocycles · indoles · metalation · synthetic methods · tryptamines

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