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Reduction of 1-pyrrolyl and 1-indolyl carbamates to hemiaminals

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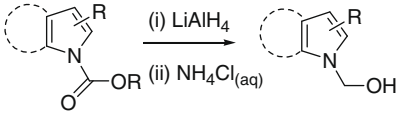
ABSTRACT

Hemiaminals of pyrroles and indoles have been prepared from the lithium aluminum hydride reduction of 1-pyrrolyl and 1-indolyl carbamates with good yields (67–82%). These carbamates are more reactive than aliphatic amides and carbamates under the LAH reduction, but less reactive than esters.

Hemiaminals of pyrrole, indole, and related N-heterocycles are labile materials, which fragment to formaldehyde and the corresponding amine under a basic condition.[1] Recently, some hemiaminals have been reported to possess anti-tumor activity,[2] serve as the precursor to formaldehyde,[3] and a self-cleavable linker for drug molecules to improve their bioavailability.[4]

However, the conventional methods to prepare hemiaminals are the addition of formaldehyde or paraformaldehyde to the amines with moderate yields (34–70%).[2,5] Alternatively, the deprotection of *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM-NR_2) or benzyloxymethylamine (BOM-NR_2) occasionally has given hemiaminals as the byproducts.[6,7] Recently, Bergman et al. reported that the reaction of the ethyl carbamate of a carbazole and lithium aluminum hydride (LAH) provided *N*-hydroxymethylcarbazole.[8] We observed a similar phenomenon while reducing the carbamates of pyrroles and indoles (Eq. 1). Since the application of aqueous solution of formaldehyde (37% in water) or polymerized formaldehyde could be troublesome to certain organic compounds and complicate the operations, this LAH reduction of carbamates provides an alternative method to prepare hemiaminals. Further studies on this methodology are reported here:

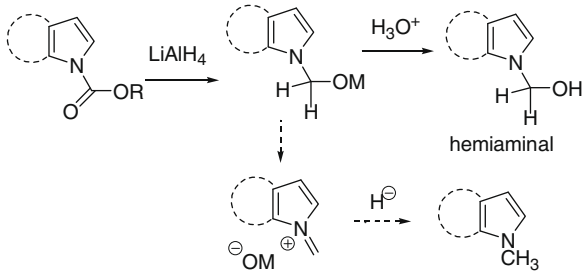


(1)

The generality of this reaction can be known from that the four 1-indolyl carbamates **1a–d** (Cbz, Fmoc, BOC, and ethyl carbamate protected indoles) have been successfully reduced to the hemiaminal by LAH with good yields (67–80%, entries 1–4, Table 1).[9] In most cases, the optimized reaction temperature was 50 °C, and the reactions completed in 30 min. 1-Pyrrolyl carbamate **5** is also a good substrate (entry 6). The methyl substituents on the indole or pyrrole moiety of compounds **3**, **7**, and **9** have little influence on this reaction. Selective reductions of the carbamates with multi-functional groups (**11**, **13**, **15**, and **17**) have been achieved, which clearly shows the relative reactivity of the 1-indolyl carbamates, esters, and amides toward the LAH reduction. For example, entries 9 and 10 show that the N-heterocyclic carbamates are more reactive than the aliphatic amide and the aliphatic carbamate. On the other hand, both ester groups of compounds **15** and **17** were first reduced when the lower reaction temperature (25 °C) and the shorter reaction time (20 min) were applied (entries 11 and 12). Hemiaminal **14** is a prodrug of melatonin.[10] However, the reaction of the imidazole-derived carbamate **19** regenerated the free imidazole.

The LAH reduction of 1-pyrrolyl and 1-indolyl carbamates to the corresponding hemiaminals is another example where the aromaticity has strong influence on the reaction. The incorporation of the lone pair electrons of the nitrogen into the aromatic system impedes the formation of the iminium ion and further reduction (Scheme 1).[11] Thus, the hemiaminals are produced after the protonation of the N-substituted methoxide anion.

In conclusion, we report a new, reliable method to prepare the hemiaminals of pyrrole and indole.



Scheme 1. Mechanistic rational for the formation of hemiaminals.

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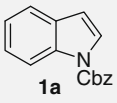
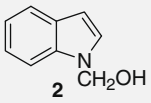
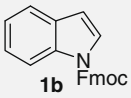
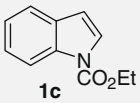
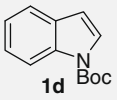
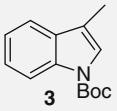
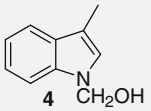
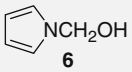
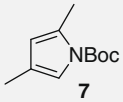
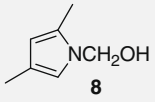
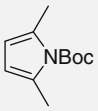
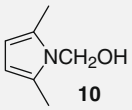
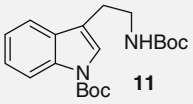
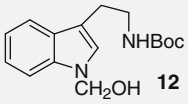
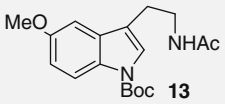
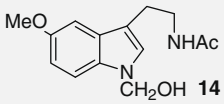
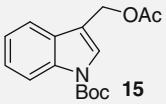
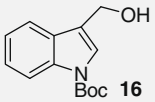
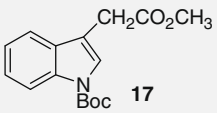
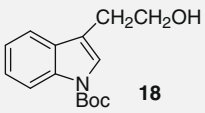
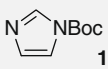
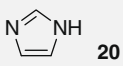
Table 1
Reduction of carbamates to hemiaminals

Entry	Reactant	Product	Temp (°C)	Yield (%)
1	 **1a**	 **2**	25	67
2	 **1b**	**2**	50	76
3	 **1c**	**2**	50	80
4	 **1d**	**2**	50	79
5	 **3**	 **4**	50	80
6	 **5**	 **6**	50	88
7	 **7**	 **8**	25	80
8	 **9**	 **10**	50	82
9	 **11**	 **12**	25	73
10	 **13**	 **14**	25	45
11	 **15**	 **16**	25[a]	91
12	 **17**	 **18**	25[a]	74
13	 **19**	 **20**	25[a]	90

[a] Reaction time: 20 min.

Acknowledgments

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Supplementary data

Experimental procedures, ^{1}H NMR and ^{13}C NMR spectra for all the new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.025.

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9. *Typical procedure*: Lithium aluminum hydride (94.0 mg, 2.5 mmol) was added to the solution of *tert*-butyl *1H*-indole-1-carboxylate (100.0 mg, 0.46 mmol) and THF (5 mL) portionwise at 0 °C. After the gas evolution ceased, the flask was transferred to a preheated oil bath (50 °C). After being stirred at 50 °C for 30 min, the reaction was quenched with satd $NH_4Cl_{(aq)}$ and the reaction mixture was extracted with ether. The organic layers were combined, dried over $Na_2SO_{4(s)}$, filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:3; R_f: 0.20) to give 1-hydroxymethyl-1*H*-indole (53.4 mg, 0.36 mmol, 79%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70 (br, 1H), 5.54 (s, 2H), 6.52 (dd, J = 3.3 Hz, J = 0.8 Hz, 1H), 7.11–7.26 (m, 3H), 7.42–7.45 (m, 1H), 7.61–7.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 69.4, 102.7, 109.4, 120.2, 121.0, 122.1, 127.3, 129.1, 135.5; HRMS-EI (m/z): $[M]^+$ calcd for (C_9H_9NO), 147.0684; found 147.0683. The spectroscopic data were consistent with the reported value.[6f]
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