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One-pot synthesis of homotryptamines from indoles

Derek J. Denhart,* Ronald J. Mattson, Jonathan L. Ditta and John E. Macor

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492-7660, USA

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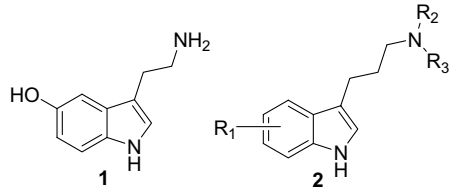
Abstract—A method is presented for the one-pot synthesis of homotryptamines by the MacMillan reaction of indoles with acrolein followed by reductive amination.

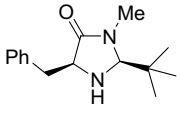
The indole heterocycle is ubiquitous to both natural and unnatural products. Consequently, indole containing compounds have been the target of many synthetic investigations over many years. Of special interest is the indole neurotransmitter serotonin **1** (5-hydroxytryptamine or 5-HT), which is an important component of the central nervous system. Molecules that mimic serotonin have been used effectively as treatments for a variety of psychiatric illnesses including depression, anxiety, and migraine.[1] While extensive synthetic and medicinal chemistry studies have been done on tryptamines, significantly less work has been done examining the synthesis and biological activity of homotryptamines. Homotryptamines **2** can be constructed from indoles[2] or indole precursors[1b] in a number of ways by multistep routes. Driven by our interest to further study the neuropharmacology of this series of indole derivatives, we believed a shorter route to homotryptamines could be realized by the conversion of indoles directly to indole propionaldehydes, followed by reductive amination to the desired target.



1 **2**

There is a dearth of reports of indole propionaldehydes, specifically those lacking additional substituents on the propionaldehyde chain. When they do appear in literature reports, they are generally made and used immediately for subsequent transformations.[3,4] This is likely due to the observed instability of the indole propionaldehyde moiety. Accordingly, our goal was to find a direct and simple method to generate the desired aldehydes in situ, followed immediately by reductive amination to afford the desired homotryptamines.

One reaction, which has been used to form 3-substituted indole propionaldehydes is the amine-catalyzed Michael addition of α–β unsaturated aldehydes developed by Austin and MacMillan.[5] To our knowledge, this has not yet been applied to the unsubstituted acrolein. Herein, we describe the reaction of indoles with acrolein in the presence of the MacMillan amine catalysts, and the subsequent transformation of the resulting indole propionaldehydes to homotryptamines.



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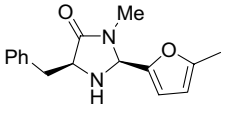

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We have found two catalysts to be efficacious in this sequence: *t*-butyl catalyst **3** and methylfuryl catalyst **4**.[6] It should be noted that simpler secondary amines such as pyrrolidine and diisopropylamine were ineffective in catalyzing the desired Michael reaction. In a typical reaction, acrolein[7] and the desired indole were stirred at low temperature in the presence of the amine catalyst

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* Corresponding author. Tel.: +1-203-677-7117; fax: +1-203-677-7702; e-mail: derek.denhart@bms.com

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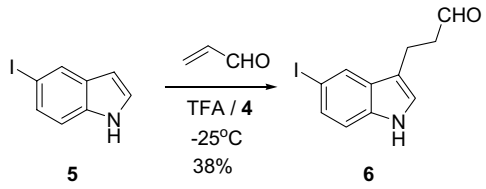
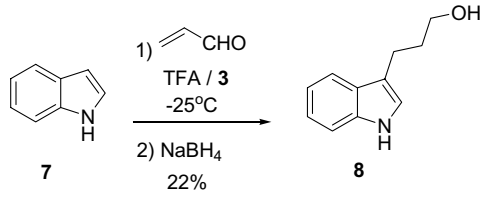


Scheme 1.

and TFA for an appropriate length of time. This reaction produced a solution containing the indolepropionaldehyde. In most cases involving indoles without electron withdrawing substituents, attempts to work up and purify the product were unsuccessful. It appears, however that some indolepropionaldehydes stabilized by electron withdrawing groups can be isolated in reasonable yield and purity. For example, reaction of 5-iodoindole **5** gave the indole propionaldehyde **6**[8] (Scheme 1).

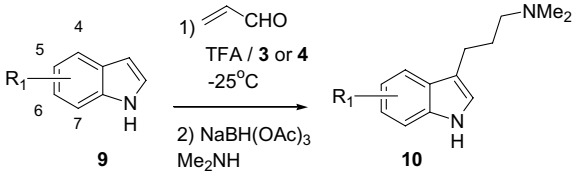


Scheme 2.

Direct reduction of the indole propionaldehyde using sodium borohydride in methanol afforded the corresponding alcohol. For example, treatment of indole **7** under MacMillan conditions followed by borohydride reduction gave alcohol **8** (Scheme 2).

Alternatively, directly applied reductive amination converted the indole propionaldehydes to homotryptamines (Table 1). Accordingly, reaction of indole **9** with acrolein in the usual way, followed by reductive amination in the same pot afforded homotryptamines **10**.[9] For our initial study, we chose dimethylamine as a standard amine for all reductive aminations. This sequence represents a general and direct synthesis of homotryptamines.

Table 1. Conditions and yields for homotryptamine synthesis



Entry	R_1	Catalyst	Time for acrolein addition	Yield of product **10**
1	H	4	3 h	**10a** 29%
2	5-MeO	4	3 h	**10b** 25%
3	5-BnO	4	3 h	**10c** 35%
4	5-F	4	3 h	**10d** 16%
5	5-CN	3	2 days	**10e** 34%
6	4-Cl	3	5 h	**10f** 34%
7	5-Cl	3	5 h	**10g** 28%
8	6-Cl	3	5 h	**10h** 30%
9	7-Cl	3	5 h	**10i** 15%
10	5-Br	3	5 h	**10j** 37%
11	5-I	3	5 h	**10k** 14%

As shown in Table 1, a variety of substituted indoles can be used. The speed of the addition to acrolein is dependent on the nucleophilicity of the indole, such that 5-methoxyindole (entry 2) is faster than indole (entry 1), while 5-cyanoindole (entry 5) is very slow under the same conditions. Both catalysts **3** and **4** appear to be efficacious for these reactions. The reaction produces a number of undesired products, which results in low (but reproducible) yields and often challenging purifications. Nevertheless, the directness of the procedure, only one step from indoles, has made it more convenient than alternative routes.

In conclusion, we have developed a convenient method for the concise synthesis of homotryptamines directly from indoles. This sequence has produced a series of homotryptamines, whose neuropharmacology is presently under investigation. The results from this study will be presented in due course.

References and notes

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4. Indole-3-propionaldehydes with an additional substituent at the 3 position of the propionaldehyde appear to be more stable than the similar molecules lacking this substitution, based on unpublished results.
5. Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.
6. Catalyst **3** is available from commercial sources; catalyst **4** according to: Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.
7. Reactions performed using 90% acrolein from the Aldrich Chemical Company, Inc, but the reagent should be checked by ^{1}H NMR before use. The use of freshly distilled acrolein did not produce significant improvement in yield or purity.
8. **Compound 6**: Acrolein (0.082 mL) and catalyst **4** (22 mg) were stirred in CH_2Cl_2/*i*PrOH (85:15; 10 mL) at −40 °C and TFA (0.006 mL) was added. After 15 min indole **5** (200 mg) was added as a solution in CH_2Cl_2/*i*PrOH (3 mL). The reaction was stirred at −30 °C for 2 h. Added aqueous $NaHCO_3$, extracted with CH_2Cl_2, and dried with $MgSO_4$. Purified by chromatography on SiO_2 eluting with 4:1

hexanes/ethyl acetate. Obtained 94 mg (38%) of aldehyde **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, $J = 1.4$ Hz, 1H), 8.01 (br s, 1H), 7.91 (t, $J = 1.0$ Hz, 1H), 7.43 (dd, $J = 8.4$, 1.5 Hz, 1H), 7.13 (d, $J = 8.6$ Hz, 1H), 6.95 (t, $J = 1.0$ Hz, 1H), 3.05 (t, $J = 7.2$ Hz, 2H), 2.82 (td, $J = 7.2$, 1.2 Hz, 2H); MS (EI) 256.21.

9. *Representative procedure for preparation of homotryptamines*: Acrolein (0.050 mL, 5 mmol) and catalyst **3** (135 mg, 0.5 mmol) were stirred in CH_2Cl_2/*i*PrOH (85:15; 10 mL) at −40 °C and TFA (0.039 mL, 0.5 mmol) was added. After 15 min 5-chloroindole (758 mg, 151.6 mmol) was added as a solution in CH_2Cl_2/*i*PrOH (5 mL). The reaction was stirred at −25 °C for 5 h. Dimethylamine (10 mL of a 2 M solution in THF, 20 mmol) was added followed by methanol (10 mL) and sodium triacetoxyborohydride (2.1 g, 10 mmol). The reaction was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue was taken up in aqueous $NaHCO_3$, extracted with ethyl acetate, and dried with $MgSO_4$. Purified by careful chromatography on SiO_2 eluting with 95:5 CH_2Cl_2/2 M NH_3 in MeOH. Obtained 329 mg (28%) of compound **10g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.55 (d, $J = 1.9$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 1H), 7.11 (dd, $J = 8.4$, 2.0 Hz, 1H), 6.99 (t, $J = 1.2$ Hz, 1H), 2.72 (t, $J = 7.5$ Hz, 2H), 2.35 (t, $J = 7.4$ Hz, 2H), 2.24 (s, 6H), 1.86 (pentet, $J = 7.5$ Hz, 2H); MS (EI) 236.99.