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A Straightforward Synthetic Approach for Roxindole

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Abstract: A concise synthetic approach to the dopamine autoreceptor agonist roxindole **1** has been devised. The key step in the novel route is the addition of succinic anhydride to 5-methoxyindolylmagnesium bromide, which circumvents the cumbersome construction of the indole moiety - via the Japp Klingemann- Fischer indole methodology - in the original route. This novel route will enable a quick, multi-gram synthesis of roxindole from cheap starting materials.

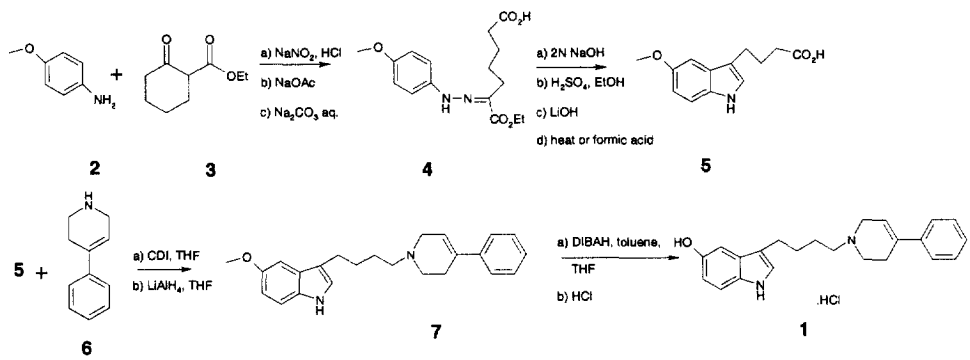
Keywords: Agonist; Neurologically active compounds; Neurotransmitters; Receptors; Roxindole

Introduction

Dopamine is an important neurotransmitter both in the brain and in the periphery. Antipsychotic activity has been associated with dopaminergic (D_2) receptor blocking activity[1]. Roxindole[2] **1** is a dopamine autoreceptor agonist found by Merck[3]. Roxindole **1** may be very useful for the treatment of CNS disorders such as schizophrenia, depression and Parkinson's disease.

Results and discussion

Roxindole **1** can be prepared via Merck's route[2,4] which is depicted in Scheme 1. We started our synthesis via this route. The conversion of the acid **4** into **5**[5] in which the indole nucleus is formed (Japp Klingemann-type Fischer indole synthesis[6]) proved to be a very troublesome reaction sequence in our hands. This disappointing result prompted to investigate alternative synthetic routes, in which the cumbersome indole ring construction is avoided.



2 **3** **4** **5** **6** **7** **1**

Scheme 1

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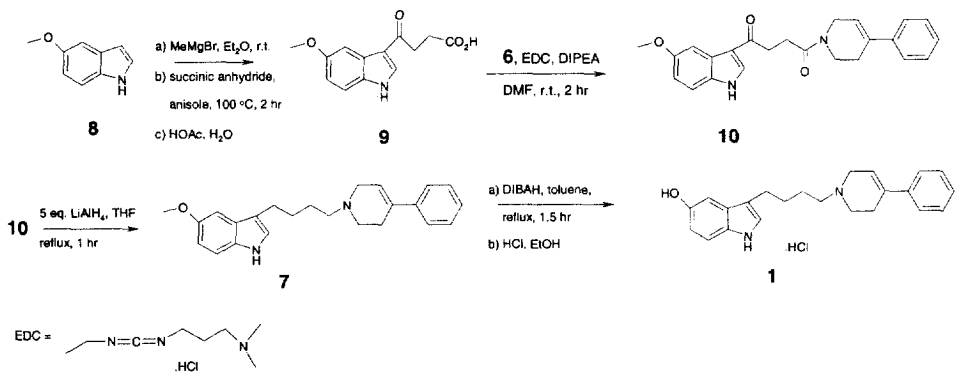
This resulted in a novel straightforward synthetic approach to **1**, which is depicted in Scheme 2. This route starts from the commercially available 5-methoxyindole **8**. The key step is the conversion of its Grignard intermediate[7,8] with succinic anhydride to the acid[9] **9**. Subsequent addition of **9** to the tetrahydropyridine derivative[4] **6**, in the presence of the coupling reagent EDC, affords the amide[10] **10** in 66 % yield. Subsequent $LiAlH_4$ treatment at reflux temperature in THF causes the reduction of both the amide and keto group in a single step, to give **7**[4] in high yield (85 %), which can be efficiently demethylated to **1**, according to Merck's procedure[4,11].



Scheme 2

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References and notes

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9. The moderate, not optimised yield (26 %) of pure **9** is due to the concurrent attack of the succinic anhydride at the N_1-position of the Grignard derivative of **8**. Analytical data for **9**: m.p. 237-9 °C (dec.); ^{1}H NMR (200 MHz; DMSO-d_6) δ 11.75 (br s, 2H), 8.20 (t, J= 3 Hz, 1H), 7.70 (d, J=3 Hz, 1H), 7.33 (d, J=8 Hz, 1H), 6.81 (dd, J= 8 Hz, J = 3 Hz, 1H), 3.80, (s, 3H), 3.13 (t, J=6 Hz, 2H), 2.57 (t, J=6 Hz, 2H); EIMS exact mass calcd for $C_{13}H_{13}N_1O_4$ m/z, 247.0845 ([M]$^+$), found: 247.0861.
10. Analytical data for **10**: m.p. 177-9 °C; ^{1}H NMR (200 MHz; $CDCl_3$) δ 9.78 (br s, 1H), 7.85 (br d, J ~ 3 Hz, 1H), 7.73 (d, J=3 Hz, 1H), 7.40-7.20 (m, 6H), 6.85 (dd, J= 8 Hz, J = 3 Hz, 1H), 6.12-6.02, (m, 1H), 4.30 (m, 2H), 3.95-3.75 (m, 5H), 3.22 (t, J=7 Hz, 2H), 3.00-2.85 (m, 2H), 2.71-2.52 (m, 2H); EIMS exact mass calcd for $C_{24}H_{24}N_2O_3$ m/z, 388.1787 ([M]$^+$), found: 388.1813.
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