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A Practical and Efficient Route for Synthesis of 6-Aminomethyl-4-oxo-4,5,6,7-tetrahydroindoles as New CNS Agent Precursors

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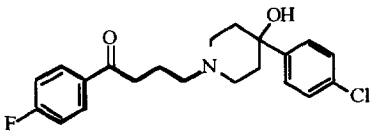
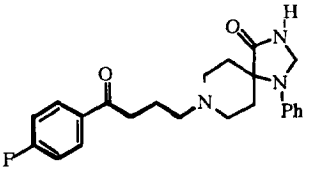
Abstract: Starting from 2,5-dimethoxybenzoic acid we described a practical and efficient route for synthesis of 6-aminomethyl-4-oxotetrahydroindoles with good to acceptable overall yields of 50-30%.

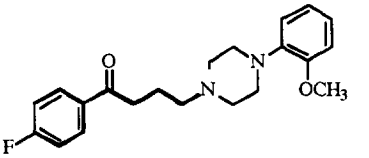
It is known that haloperidol is the prototype of a group of butyrophenone derivatives with a very potent antipsychotic activity among them the most potent neuroleptics spiperone and fluanisone, which are 4-amino-*p*-fluorobutyrophenone derivatives.[1] Also several aminoketones possess potent antipsychotic (neuroleptic) activity: molindone, first marketed in the USA in 1974, has been used in the treatment of schizophrenia and psychosis but its associated incidence of extrapyramidal side effects (EPS) is significant[2].



Haloperidol

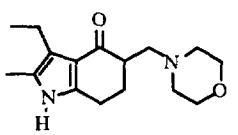


Spiperone

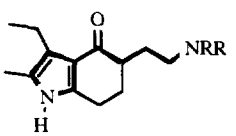


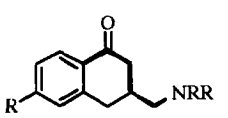
Fluanisone

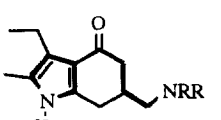
Recently, we have prepared and studied several 5-aminoethyl-1,2,3,4-tetrahydroindol-4-ones as butyrophenone homologues of molindone.[3] Also, in previous papers[4,5] we have reported the synthesis and neuroleptic activity of 3-aminomethyl tetralones and 2-aminoethyl benzocycloalkanones which are conformationally restricted butyrophenone analogues of haloperidol with the aminobutyl side chain partially incorporated in a semi rigid framework.[6,7] Now we wish to report an effective synthetic strategy for preparing 6-aminomethyl-4,5,6,7-tetrahydroindol-4-ones as cyclic butyrophenone derivatives.



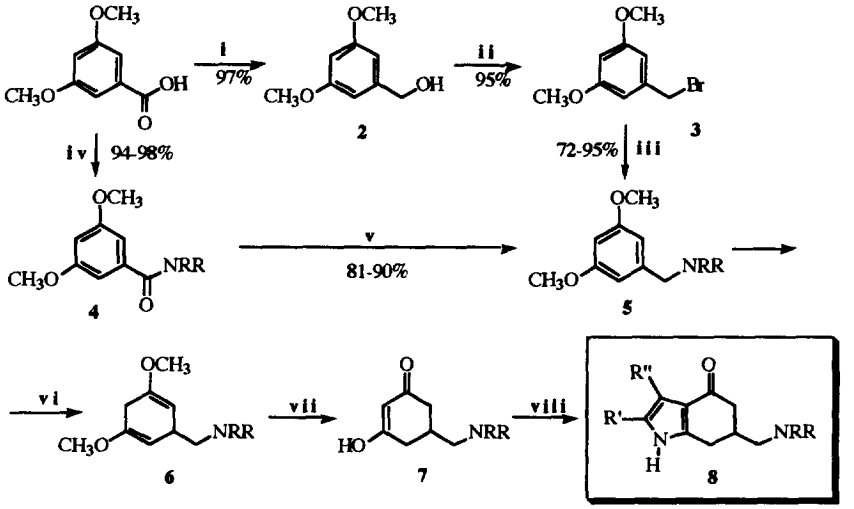
Molindone







As outlined in Scheme, lithium aluminum hydride reduction of 3,5-dimethoxybenzoic acid in THF for twelve hours gave the hydroxymethyl alcohol **2**[8] which was treated with carbon tetrabromide-triphenylphosphine in dichloromethane to afford the desired bromoderivative **3** in quantitative yield.



Reagents: i: $LiAlH_4$, THF, r.t., 12 h; ii: CBr_4, Ph_3P, CH_2Cl_2, r.t., 24 h; iii: HNRR, Na_2CO_3, IK, MIK, reflux, 20 h; iv: HNRR, DCC, HOBt,CH_2Cl_2, r.t., 6 h; v: $LiAlH_4$, THF, r.t., 12 h; vi: Li, NH_3, MeOH, t-BuOH, -40°C, 2 h; vii: HCl, THF, r.t., 3 h; viii: R'CNOHCOR", Zn, AcOH 70%, reflux, 4 h.

Scheme

Subsequent nucleophilic displacement of the bromine atom in methyl isobutyl ketone in the presence of potassium carbonate and catalytic amounts of potassium iodide at reflux for twenty hours afforded 1-aminomethyl-3,5-dimethoxybenzenes **5** in good to excellent yields (Method A). Alternatively, 1,3-dicyclohexylcarbodiimide mediated coupling in the presence of 1-hydroxybenzotriazole in DMF at room temperature gave amides **4** in quantitative yields,[9,10] which were reduced by lithium aluminum in THF at room temperature for twelve hours yielded aminomethyl derivatives **5** with yields ranging 85-95% (Method B), (Table 1).

Birch reduction of **5** with lithium-ammonia in methanol containing *tert*-butyl alcohol afforded the bis(enol)ethers 1-aminomethyl-3,5-dimethoxy-2,5-cyclohexadienes **6** in quantitative yields.[11] Acid hydrolysis of **6** with hydrochloric acid in THF at room temperature for three hours gave 1-aminomethyl-3,5-cyclohexanediones **7** as white crystalline hydrochlorides also in quantitative yields.

Finally, the pyrrole ring was formed by Knorr reaction with isonitrosoketones in 70% acetic acid in the presence of Zn powder at reflux to give tetrahydroindolones **8** in variable yields (Table 2).[12] The preparation of 6-morpholinomethyl-4,5,6,7-tetrahydroindol-4-one **8a2** by the Knorr procedure was unsuccesfully. This compound was prepared in reasonable yields by sequential treatment of the bis(enol)ether **7a** with aminoacetaldehyde dimethyl acetal in benzene in the presence of *p*-TsOH at reflux for 24 hours with removal of water followed by ring closure of the resulting oxo enamine with dilute HCl in chloroforme at room temperature.[13]

Table 1: Synthesis of 1-Aminomethyl-3,5-dimethoxybenzenes **5** from 3,5-Dimethoxybenzoic acid

Product	NRR	Method	mp (°C)	Yield (%)
5a	morpholine	A	188-189[a]	88
		B		88
5b	diethylamine	A	oil[b]	79
		B		80
5c	piperazine	A	151-152[a]	66
		B		82
5d	N-methylpiperazine	A	207-209[a]	81
		B		78

[a] Hydrochloride salt. [b] B.p. 95-100°C/0.1 mm.

Table 2: 6-Aminomethyl-4,5,6,7-tetrahydroindol-4-ones **8**

Product	NRR	R'	R''	mp (°C)	Yield (%)
8a1	morpholine	Me	Et	128-130	60
8a2	morpholine	H	H	151-153	37
8b	diethylamine	Me	Et	134-136	38
8c1	piperazine	Me	Et	176-178	40
8c2	piperazine	Me	Ph	175-176	45
8d	N-methylpiperazine	Me	Et	222-224	46

In summary, an aproach has been developed as a pathway to obtain new derivatives in the indol series.[14] Likewise further nucleophilic displacement with alkyl or acyl pharmacophores on the free piperazine nitrogen will provided new entries for developing new CNS agents. In this way, works are in progress in our Laboratory.

Acknowledgement

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(9) **4a**: white solid; mp = 67-69°C. IR: 2971, 1633, 1587, 1457, 1420, 1319, 1106, 1021 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.46-3.71 (m, 8H); 3.80 (s, 6H); 6.50 (t, J= 2.2 Hz, 1H); 6.51 (d, J= 2.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 43.2; 48.5; 55.9; 67.3; 102.1; 105.3; 137.6; 161.3; 170.4.

(10) Quantitative yields in amides were also obtained by using bis(2-oxo-3-oxazolidinyl)phosphinic chloride as coupling reagent.

(11) **6a**: white crystals; mp = 158-160°C. IR: 2939, 2853, 2802, 1693, 1660, 1442, 1399, 1232, 1206, 1148, 1117 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ: 2.25 (d, J= 7.3 Hz, 2H); 2.46 (t, J= 4.6 Hz, 4H); 2.78 (dd, J= 6.4, 0.9 Hz, 2H); 3.11-3.18 (m, 1H); 3.57 (s, 6H); 3.72 (t, J= 4.6 Hz, 4H); 4.69 (dd, J= 2.0, 1.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz) δ: 31.9; 33.7; 54.6; 67.4; 67.5; 94.8; 152.5.

(12) **8a1**: IR: 3238, 2924, 1624, 1474, 1117 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.11 (t, J= 7.4 Hz, 3H); 2.14 (s, 3H); 2.18-2.23 (m, 1H); 2.30-2.57 (m, 9H); 2.64 (c, J= 7.4 Hz, 2H); 2.85-2.95 (m, 1H); 3.69 (t, J= 4.4 Hz, 4H); 7.94 (s, 1H). ^{13}C-NMR ($CDCl_3$, 300 MHz) δ: 10.7; 15.9; 18.4; 28.1; 34.3; 43.9; 54.4; 64.1; 67.4; 118.9; 121.2; 124.1; 141.4; 194.1. MS (m/z)= 276 ($M^{+\cdot}$); 189, 176, 175, 132, 100 (100%), 56.

(13) An intramolecular enamine-aldehyde condensation leading to 4,5,6,7-tetrahidro-4-oxo-indoles has been reported previously. See, Bobbitt, J. M.; Kulkarni, C. L.; Dutta, C. P.; Kofod, H.; Chiong, K. N. *J. Org. Chem.* **1978**, *43*, 3541.

(14) All new compounds gave satisfactory spectral data (IR and NMR) and elemental analyses within 0.4%.

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