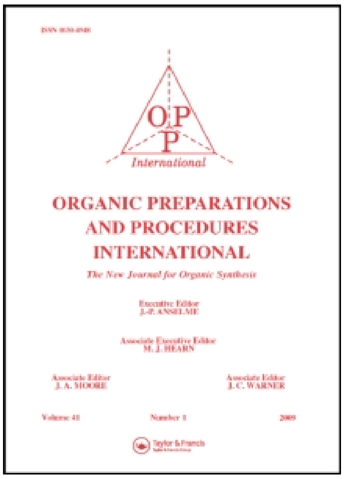

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AN EFFICIENT SYNTHESIS OF 2-(3,4-DIMETHOXYPHENYL) SUCCINIMIDE

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AN EFFICIENT SYNTHESIS OF 2-(3,4-DIMETHOXYPHENYL)SUCCINIMIDE

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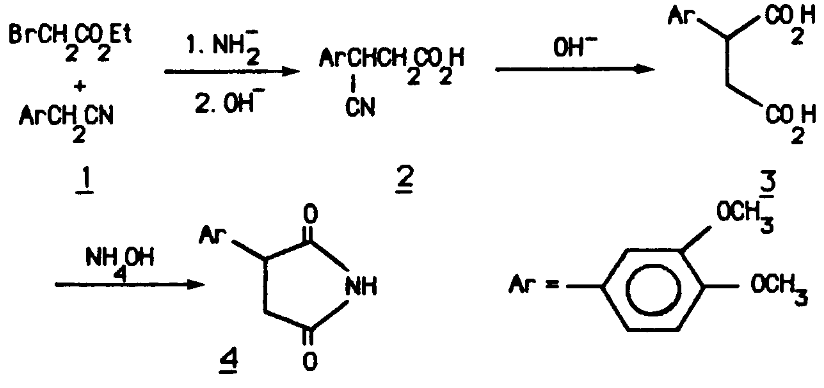
In connection with the synthesis of 3-(3,4-dimethoxyphenyl) pyrrolidine, an intermediate for compounds with central dopaminergic activity,[1] large quantities of 2-(3,4-dimethoxyphenyl)succinimide (4) were required. Compound 4 had been prepared previously by multistep routes starting from 3,4-dimethoxyphenylsuccinic acid (obtained by condensation of 3,4-dimethoxybenzaldehyde with sodium cyanoacetate,[2] ethyl cyanoacetate,[3] or diethylmalonate[4]) and from 3,4-dimethoxyphenylsuccinonitrile, obtained by reaction of 3,4-dimethoxyphenylbenzaldehyde and ethyl cyanoacetate.[1]

We now report a three-step synthesis of 4 from commercially available 3,4-dimethoxyphenylacetonitrile (1) through intermediates 3-cyano-3-(3,4-dimethoxyphenyl)propanoic acid (2) and 3,4-dimethoxyphenylsuccinic acid (3). The synthesis of 2 has appeared in the patent literature;[5] however, these patents make no mention of the synthetic procedure, yields or physical properties. Furthermore, the compounds 3 and 4 were obtained in lower yields[1,3,4] than those achieved by the present method.



The nitrile 1 was condensed with ethyl bromoacetate and sodium amide in toluene. Treatment of the crude residue with sodium hydroxide gave a 71% yield of the nitrile 2 which was hydrolyzed by treatment with conc. potassium hydroxide to afford the acid 3; the best yield (86%) was obtained using three equivalents of potassium hydroxide. Finally, treatment of acid 3 with ammonium hydroxide yielded 4 which can be reduced by lithium aluminum hydride to the desired 2-(3,4-dimethoxyphenyl)pyrrolidine.

In summary, this work describes efficient syntheses of 2, 3, and 4. 3-Cyano-(3,4-dimethoxyphenyl)propanoic acid (2) also serves as a precursor of 4-(3,4-dimethoxyphenyl)-2-pyrrolidinones, which show central nervous system depressant activity.[5]

EXPERIMENTAL SECTION

The mps were measured on a Büchi apparatus and the NMR spectrum was run on a Varian EM-390 90 MHz spectrometer.

3-Cyano-3-(3,4-dimethoxyphenyl)propanoic Acid (2).- A solution of 3,4-dimethoxyphenylacetonitrile (1) (35.44 g., 0.2 mol) in dry toluene (250 ml) was added to a stirred suspension of 7.8 g. (0.20 mol) $NaNH_2$ in dry toluene (100 ml) under N_2. The mixture was heated at 130° for 3 hrs and then cooled to 5°. A solution of ethyl bromoacetate (0.21 mol) in dry toluene (50 ml) was added dropwise and the mixture heated to reflux for 3 hrs. After cooling, the toluene solution was washed with water, dried over $CaCl_2$ and evaporated. The crude residue was dissolved in ethanol (200 ml) and 6N NaOH (36 ml) was added. The solution was stirred at 20° for 2 hrs, diluted with water and extracted with CH_2Cl_2. The aqueous solution was acidified with 6N HCl and extracted with chloroform. Evaporation of the solvent gave 33.4 g (71%) of a solid which was crystallized from isopropyl alcohol, mp. 126-127°.

IR (nujol): 2240 (C≡N), 1715 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 10.50 (s, 1H, COOH), 7.12-6.82 (m, 3H, ArH), 4.24 (t, J = 7.5 Hz, CHCN), 3.88 (s, 6H, OCH_3), 2.98 (dd, 2H, J = 7.5 Hz, J = 7.5 Hz, J = 6 Hz, CH_2CO).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95

Found: C, 61.32; H, 5.41; N, 6.09

3,4-Dimethoxyphenylsuccinic Acid (3).- A mixture of 2 (19.28 g., 0.082 mol) in ethanol (20 ml) and KOH (13.8 g., 0.246 mol) in water (40 ml) was heated at reflux until ammonia evolution ceased. The ethanol was evaporated under reduced pressure and water was added. The aqueous solution, washed with ether and acidified with 2N HCl gave 17.9 g. (86%) of solid which was collected and crystallized from ethyl acetate, mp. 178-180°, lit.[3] 174°.

2(3,4-Dimethoxyphenyl)succinimide (4).- An excess of conc. NH_4OH (30 ml) was added to 3 (10.16 g., 0.04 mol). The solution was then evaporated and the crude salt was heated at 220° for 0.5 hr. After cooling, the amorphous solid (6.1 g., 65%) was crystallized from ethanol, mp. 181-182°, lit.[1] 181-183°.

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