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New Approach to Synthesis of 6,7-Dimethoxyisatin

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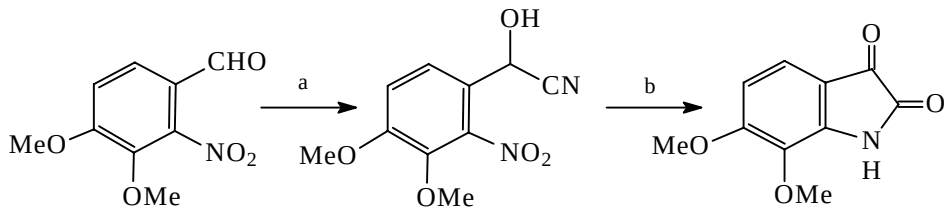
Abstract: A new approach to synthesis of 6,7-dimethoxyisatin is reported. 2-nitro-3, 4-dimethoxy mandelonitrile in glacial acetic acid was treated with the solution of stannous chloride in hydrochloric acid to give 6, 7-dimethoxyisatin in a high yield.

Keywords: Isatin, stannous chloride, mandelonitrile, synthesis.

Isatins are synthetically versatile substrates. They can be used for the synthesis of a large variety of heterocyclic compounds such as indoles and quinolines. They also display diverse pharmacological activities[1]. In nature, isatin and its derivatives were found in various plants[2~5]. Therefore the synthesis of isatins are of great importance and interest.

Scheme 1



1 **2**

a: i) $NaHSO_3$, KCN, 0°C,3hrs; ii) H_2SO_4, 0°C,85.8%; b: $SnCl_2$, HOAc, HCl, 50°C, 3hrs, 83.6%.

In the literatures[1, 6] there were some reports about synthesizing of isatins. Three methods of synthesizing 6,7-dimethoxyisatin **2** from 2, 3-dimethoxyaniline are as follows: I) Martinet procedure[7]: condensation of aniline and diethylketomalonate gave mainly oxindole (69%), which was treated with sodium hydroxide solution and oxygen to give isatin **2**. The first step of this method also gave other two by-products. II) Stolle produre[5]: Aniline reacted with oxalyl chloride only gave the product **2** with a very poor

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yield (5%). III) Sandmeyer methodology[8]: it is the oldest and the most frequently used method for the synthesis of isatins. Also, aniline was treated with chloral hydrate to give isatin **2** in poor yield. There are two other methods of synthesizing **2** from the same substance 2-nitroveratraldehyde[9]. But these methods were both more complex and with poor yields.

In connection with our research project, 2-amino-3, 4-dimethoxy- phenylacetic acid was needed. It was outlined by reduction of 2-nitro-3, 4-dimethoxy mandelonitrile **1**, which was prepared from 2-nitroveratraldehyde with stannous chloride in acid medium[10]. However, only a yellow solid was obtained with a good yield (83.6%). ^{1}H NMR, ^{13}C NMR, IR, UV and FAB-MS (**Scheme 1**) confirmed the product to be 6, 7-dimethoxy-isatin (**Scheme 1**) [11].

Experimental

Synthesis of 2-nitro-3,4-dimethoxy mandelonitrile: 2-nitroveratraldehyde (1.688 g, 8 mmol) was added to the solution of $NaHSO_3$ (0.998 g, 9.6 mmol) in water (7 mL), then the mixture was heated to 50°C. After 2-nitroveratraldehyde was dissolved, cooled to 0°C, the solution of KCN (1.042 g, 16 mmol) in water (2.7 mL) was added dropwise. After stirred for 3 hrs at 0°C, 2mol/L H_2SO_4 (3.2 mL) was added, then the mixture was stirred for 2 hrs at same temperature, extracted with ether. The extract was washed with water and then dried (Na_2SO_4). The solvent was evaporated and the residue was recrystallized from CH_2Cl_2 to give white prisms **1**, mp 88-90°C (1.634 g, 85.8%).

Synthesis of 6,7-dimethoxyisatin: 2-nitro-3,4-dimethoxy mandelonitrile (0.238 g, 1.0 mmol) was dissolved in glacial acetic acid (4.0 mL), and the solution of stannous chloride (0.677 g, 3.0 mmol) in hydrochloric acid (0.4 mL) gradually introduced with stirring. The mixture was heated to 50°C and then stirred for 3 hrs. After being cooled to room temperature, the mixture was diluted with water (6.0 mL). The orange solution was extracted with chloroform and the extract was washed with water and then dried (Na_2SO_4). The solvent was evaporated leaving 0.173 g (83.6% yield) yellow solid of isatin. Recrystallization from toluene gave yellow needles. mp 209-211°C (lit[5]. mp 209-210°C).

In summary, this methodology shows an obvious improvement over the literature methods in terms of its convenient operation and higher yield[1]. Furthermore, the present procedure may be considered as a more practical procedure for the preparation of isatins.

References and Notes

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11. Spectral data:
1: ^{1}H NMR (300MHz, $CDCl_3$) δ3.2 (br, 1H, OH), 3.958 (s, 3H, OCH_3), 3.961 (s, 3H, OCH_3), 5.667 (s, 1H, CHCN), 7.09 (d, 1H, J = 8.1Hz, Ar-H), 7.41 (d, 1H, J = 8.1Hz, Ar-H). υ (cm^{-1}, KBr) 3417 (OH), 2252 (CN).
2: ^{1}H NMR (300MHz, $CDCl_3$) δ3.91 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.60 (d, 1H, J = 8.4Hz, Ar-H), 7.42 (d, 1H, J = 8.1Hz, Ar-H), 7.74 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ56.67, 61.43, 106.88, 112.83, 123.60, 133.47, 142.55, 160.21, 161.46, 181.07. υ (cm^{-1}, KBr) 3228, 1751, 1709, 1628. λ_{max} (MeOH) 206, 217, 255, 338 nm. FAB-MS: 208.0 (base), 93.0, 75.0.

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