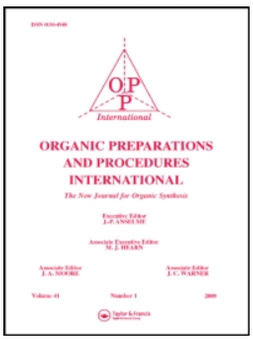

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OPPI BRIEF

A Practical Synthesis of Indole-2-carboxylic Acid

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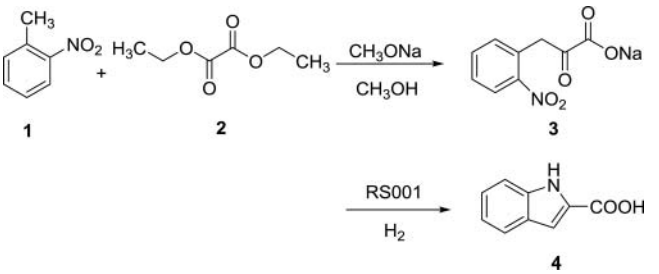
Indole-2-carboxylic acid (**4**) is a versatile intermediate in the preparation of many pharmaceutically active agents.[1] A review of the literature and patents indicates that several synthesis procedures[2–5] already exist for this useful molecule. Among these, the reduction of 3-(2-nitrophenyl)-2-oxopropanoic sodium salt (**3**) prepared from 1-methyl-2-nitrobenzene (**1**) and diethyl oxalate (**2**) is generally used. For example, Wang *et al.*[3] developed a method using ferrous sulfate and ammonium hydroxide as the reducing agents to obtain indole-2-carboxylic acid. But the crude product needed to be recrystallized because of the precipitation of a large amount of iron mud. In addition, Kong *et al.*[4] developed a ferrous hydroxide-catalyzed method with 80% (w/w) hydrazine hydrate as a reductant to obtain indole-2-carboxylic acid. And Kong *et al.*[5] also developed a Raney-Ni catalyzed hydrogen reduction process to obtain indole-2-carboxylic acid, albeit in only moderate isolated yield. However, environmental concerns have led to increased interest in alternate processes.

As a continuation of our interest in the study of medicinal compounds and the need for the title compound,[6–7] we have developed a practical hydrogen reduction process with Pd-loaded Al-MCM-41 mesoporous catalyst (RS001)[8] for the synthesis of indole-2-carboxylic acid (**4**) (*Scheme 1*).



Scheme 1

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It is noteworthy that in this procedure RS001 is immobilized and used as a catalyst which can be easily reused. The process is environmentally benign, easy to work up and leads to product of excellent purity in 56% yield.

Experimental Section

Mp of product was uncorrected. The HPLC purity of product was established on an Agilent 1260. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker 400 (400 MHz) instrument with TMS as internal standard. All chemicals were reagent grade and available commercially.

Pd-loaded Al-MCM-41 Mesoporous Catalyst (RS001)

One g of $PdCl_2$ was dissolved in a mixture of 2 mL hydrochloric acid (37%) and 15 mL of deionized water. Ten g of Al-MCM-41 mesoporous molecular sieve was poured into the solution with rigorous stirring at 75°C for 30 min. Then 8 mL of 0.7 M sodium formate was added. The mixture was kept under stirring at the same temperature for another 2 h and then filtered at the pump. The filter cake was washed with 15 mL water, collected, dried *in vacuo* at 100°C for 4 h, then calcined at 500°C for 3 h with a heat rate 1.5°C/min in air to afford the Pd-loaded Al-MCM-41 mesoporous catalyst, RS001.

Indole-2-carboxylic acid (4)

In a 150 mL round-bottomed flask was placed of a solution of 5.94 g (0.11 mol) sodium methylate in 20 mL methyl alcohol, and a mixture of 13.7 g (0.10 mol) nitrotoluene (**1**) and 14.6 g (0.10 mol) of diethyl oxalate (**2**) was added. The mixture was kept stirring at 65°C for 2 h and then poured into 500 mL ice water. The aqueous solution was purified through steam distillation until no emulsion dropped out. Then the mother liquor was decolorized with 10 g actived carbon and concentrated to a solution (70 g) of 3-(2-nitrophenyl)-2-oxopropanoic sodium salt (**3**), directly used in the next step. In a 250 mL pressure reactor was placed the above sodium salt (**3**) and 70 g methyl alcohol. Then 1.5 g RS001 was added while the pH of the mixture was adjusted to 7.5 with ammonium hydroxide. Under a hydrogen pressure of 1.5 Mpa, the mixture was stirred at 70°C for 4 h. Then the mixture was cooled and filtered at the pump. The filtrate was acidified with 4 M hydrochloric acid to pH 3 which led to precipitation. The precipitated solid was collected and dried *in vacuo* to afford 9.05 g (56%) product (**4**) (HPLC >97%), ^{1}H NMR (DMSO-d_6): δ 12.93 (1 H, s), 11.76 (1 H, s), 7.65 (1 H, d, J = 8.0 Hz,), 7.48–7.42 (1 H, m), 7.28–7.20 (1 H, m), 7.13–7.03 (2 H, m). An analytical sample was prepared by recrystallization from methanol, mp 204–205°C, lit mp 204°C.[9]

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