

Short communication

# H- $\beta$ Zeolite: an Efficient, Reusable Catalyst for One-Pot Synthesis of Isatins from Anilines

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## Abstract

We describe a simple and highly efficient procedure for the single-step preparation of isatins from the commercially available anilines using H- $\beta$  zeolite as a truly heterogeneous catalyst. H- $\beta$  zeolite is readily separated from reaction mixture by simple filtration and reused several times without considerable loss of activity.

**Keywords:** Anilines, isatins, heterogeneous catalyst, H- $\beta$  zeolite

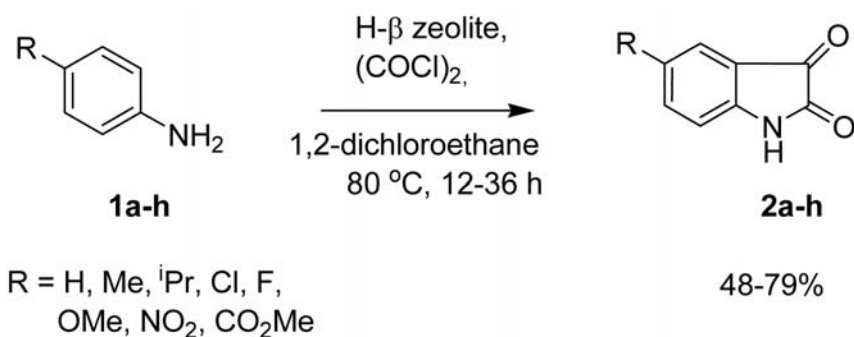
## 1. Introduction

Isatins (1*H*-indole-2,3-diones) **2** have been found in nature not only in plants of the genus *Isatis* but also in mammalian tissues where they act as a modulator of biochemical processes.<sup>1</sup> In particular, the derivatives of isatins are known to possess a wide range of interesting pharmacological properties,<sup>2–6</sup> such as antiprotozoal and inhibition of parasitic cysteine proteases.<sup>7</sup> Several methods exist in the literature for the synthesis of isatins, however, most of them are multistep, often employing moisture-sensitive reagents.<sup>8</sup> Recently, a single-step method for the synthesis of isatins **2a-h**, based on the oxidation of indoles with hypervalent iodine as oxidant and InCl<sub>3</sub> as catalyst,<sup>9</sup> was reported. In this note, we describe a new, one-pot procedure

for the synthesis of isatins **2a-h** starting from anilines **1a-h** by using oxalyl chloride as the acylating agent and H- $\beta$  zeolite<sup>10</sup> as a reusable catalyst under heterogeneous conditions (**Scheme 1**).

## 2. Results and Discussion

The results of H- $\beta$  zeolite catalyzed synthesis of isatins are presented in **Table 1**. When anilines **1a-h** were reacted with oxalyl chloride in the presence of H- $\beta$  zeolite (10% wt) in 1,2-dichloroethane as solvent at 80 °C, the corresponding isatins **2a-h** were obtained in good yields (48–79%). Control experiments showed that no reaction took place in the absence of H- $\beta$  zeolite, and lowering the amount of H- $\beta$  zeolite (5% wt) also resulted in the redu-



Scheme 1

ced yield of isatins. 1,2-Dichloroethane was found to be the solvent of choice for this transformation while other solvents like CH<sub>3</sub>CN and nitrobenzene were not effective. In order to understand the scope and generality of the reaction, a wide range of anilines **1a-h** were treated with oxalyl chloride in the presence of H-β zeolite (10% wt) under optimized reaction conditions (1 equiv. of oxalyl chloride, 1,2-dichloroethane, 80 °C). It may be noted from **Table 1** that for aromatic substrates with electron-withdrawing substituents the reaction time was longer and yields were only moderate. The catalyst was recovered and reused after activation (calcinations at 400 °C). In the case of aniline (**1a**), the reusability study showed that the catalyst was active for at least five reaction cycles without considerable loss of activity.

**Table 1.** The H-β zeolite catalyzed synthesis of isatins.<sup>a</sup>

Entry	Substrate <b>1</b>	Product <b>2</b>	Time (h)	Yield (%) <sup>b</sup>
a			24	71
b			24	76
c			24	61
d			30	59
e			36	51
f			12	79
g			30	48
h			30	69

<sup>a</sup>Reaction conditions: aniline (2 mmol), (COCl)<sub>2</sub> (2 mmol), H-β zeolite (10% wt), 1,2-dichloroethane (30 mL), 80 °C.

<sup>b</sup>Isolated yields after chromatographic purification.

### 3. Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer FTIR-1600 spectrophotometer; <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AMX (200 MHz) spectrometer using TMS as an internal standard. TLC analyses were performed on silicagel G plates and

compounds were located by iodine vapors. CHN analyses were obtained on Carlo ERBA EA 110B instrument.

### 3. 1. H-β Zeolite

The acidic form of the zeolite β (H-BEA) (Si/Al = 18, average crystal size 0.1–0.2 μm) was synthesized using tetraethylammonium hydroxide as template with subsequent calcinations at 823 K in an air flow for 6 h.<sup>10</sup>

### 3. 2. General Procedure for the Synthesis of Isatins

To a stirred mixture of aniline (2.0 mmol) and H-β zeolite (50 mg, 10 wt%) in 1,2-dichloroethane (30 mL) was added oxalyl chloride (2.0 mmol), and the mixture refluxed under nitrogen atmosphere. After completion of the reaction (as monitored by TLC), the catalyst was recovered by simple filtration. Distillation of solvent under reduced pressure furnished the crude isatins. The crude product was further purified by column chromatography on silica gel using CHCl<sub>3</sub> and MeOH (1:1) as eluent to afford pure isatins **2 a-h**.

#### 1*H*-indoline-2,3-dione (**2a**)

Yield: 71%; colorless solid; mp 207 °C (recrystallized from benzene) (lit.<sup>9</sup> mp 200–202 °C); IR (KBr): ν 3210 (aromatic CH), 1710 (CONH), 1610 (aryl), 1450 (NH), 1310 (NO), 1120 (C-C-C), 950 (=CH), 780–620 (CH=CH); <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>): δ 6.91 (d, *J* 7.8 Hz, 1H, ArH), 7.06 (t, *J* 7.8 Hz, 1H, ArH), 7.50 (dd, *J* 7.8, 1.3 Hz, 1H, ArH), 7.58 (t, *J* 7.8 Hz, 1H, ArH), 11.02 (s, 1H, NH); <sup>13</sup>C-NMR (50 MHz, DMSO-d<sub>6</sub>): δ 112.2 (C-8), 117.8, 122.8, 124.7, 138.4, 150.7 (C-9), 159.4 (C-2, C=O), 184.4 (C-3, C=O); Anal. Calcd for C<sub>8</sub>H<sub>5</sub>NO<sub>2</sub>: C 65.31, H 3.43, N 9.52. Found: C 65.36, H 3.48, N 9.55.

#### 5-methylindoline-2,3-dione (**2b**)

Yield: 76%; red needles; mp 187 °C (recrystallized from ethanol) (lit.<sup>9</sup> mp 185–187 °C); IR (KBr): ν 3322 (CH), 1750 (CONH), 1622 (aryl), 1527–1433 (NH), 1226–1151 (C-C-C), 1150–1044 (OC), 839–752 (CH=CH); <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>): δ 2.24 (s, 3H, CH<sub>3</sub>), 6.76 (d, *J* 8.0 Hz, 1H, ArH), 7.29 (s, 1H, ArH), 7.37 (d, *J* 8.0 Hz, 1H, ArH), 10.93 (s, 1H, NH); <sup>13</sup>C-NMR (50 MHz, DMSO-d<sub>6</sub>): δ 20.1 (CH<sub>3</sub>), 112.0 (C-8), 117.8, 124.8, 132.0, 138.8, 148.5 (C-9), 159.5 (C-2, C=O), 184.6 (C-3, C=O); Anal. Calcd for C<sub>9</sub>H<sub>7</sub>NO<sub>2</sub>: C 67.07, H 4.38, N 8.69. Found: C 67.09, H 4.33, N 8.61.

#### 5-isopropylindoline-2,3-dione (**2c**)

Yield: 61%; yellow solid; mp 166 °C; IR (KBr): ν 3351 (CH), 1752 (CONH), 1620 (aromatic), 1522–1431 (NH), 1149–1046 (OC), 848–706 (CH=CH) cm<sup>-1</sup>; <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>): δ 1.16 (d, *J* 6.9 Hz, 1H, CHMe<sub>2</sub>), 2.86 (m, 1H, CHMe<sub>2</sub>), 6.83 (d, *J* 8.0 Hz, 1H, Ar-

H), 7.37 (d,  $J$  2.8 Hz, 1H, ArH), 7.47 (dd,  $J$  8.0, 2.8 Hz, 1H, ArH), 10.95 (s, 1H, NH);  $^{13}\text{C}$ -NMR (50 MHz, DMSO- $d_6$ ):  $\delta$  23.7 (2xCH<sub>3</sub> isopropyl), 32.7 (CH isopropyl), 112.1 (C-8), 117.8, 122.3, 136.6, 143.2 (C-5), 148.9 (C-9), 159.6 (C-2, C=O), 184.6 (C-3, C=O); Anal. Calcd for: C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>: C 69.83, H 5.86, N 7.40. Found: C 69.89, H 5.81, N 7.49.

#### 5-chloroindoline-2,3-dione (2d)

Yield: 59%; red solid; mp 249 °C (recrystallized from ethanol) (lit.<sup>8a</sup> mp 248–251 °C); IR (KBr):  $\nu$  3190 (aromatic CH), 1780–1710 (CONH), 1610 (aryl), 1430 (NH), 1240–1205 (C-C-C), 1132 (OC), 1041 (OC), 842 (CH=CH), 770 (aromatic C-Cl) cm<sup>-1</sup>;  $^1\text{H}$ -NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  6.91 (d,  $J$  8.3 Hz, 1H, ArH), 7.54 (d,  $J$  2.3 Hz, 1H, ArH), 7.60 (dd,  $J$  8.3, 2.3 Hz, 1H, ArH), 11.15 (s, 1H, NH);  $^{13}\text{C}$ -NMR (50 MHz, DMSO- $d_6$ ):  $\delta$  113.9 (C-8), 119.2, 124.2, 126.8, 137.3 (C-Cl), 149.2, 159.2 (C-2, C=O), 183.4 (C-3, C=O); Anal. Calcd for: C<sub>8</sub>H<sub>4</sub>ClNO<sub>2</sub>: C 52.92, H 2.22, N 7.71. Found: C 52.97, H 2.21, N 7.79.

#### 5-fluoroindoline-2,3-dione (2e)

Yield: 51%; yellow solid; mp 223 °C (recrystallized from ethanol); IR (KBr):  $\nu$  3341 (aromatic CH), 1750 (CONH), 1625 (aromatic), 1521–1434 (NH), 1156 (OC), 1041 (C-F), 845 (CH=CH), 771 (C-F) cm<sup>-1</sup>;  $^1\text{H}$ -NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  6.91 (dd,  $J$  8.5, 4.0 Hz, 1H, ArH), 7.38 (dd,  $J$  7.2, 2.7 Hz, 1H, ArH), 7.44 (m, 1H, ArH), 11.02 (s, 1H, NH);  $^{13}\text{C}$ -NMR (50 MHz, DMSO- $d_6$ ):  $\delta$  111.3 (C-8), 113.4, 118.4, 124.4, 146.9, 147.0, 159.3 (C-2, C=O), 183.9 (C-3, C=O); Anal. Calcd for: C<sub>8</sub>H<sub>4</sub>FNO<sub>2</sub>: C 58.19, H 2.24, N 8.48. Found: C 58.16, H 2.21, N 8.44.

#### 5-methoxyindoline-2,3-dione (2f)

Yield: 79%; yellow solid; mp 201 °C (recrystallized from ethanol) (lit.<sup>9</sup> mp: 202–203 °C); IR (KBr):  $\nu$  3045 (aromatic CH), 2922 (CH), 1735 (CONH), 1602 (aryl), 1468 (NH), 1318 (C-O-H), 1253 (O-CH<sub>3</sub>), 1171 (OC), 1104 (OC), 904 (aromatic OCH<sub>3</sub>), 820–709 (CH=CH) cm<sup>-1</sup>;  $^1\text{H}$ -NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  3.75 (s, 3H, OCH<sub>3</sub>), 6.87 (d,  $J$  9.6 Hz, 1H, ArH), 7.1 (d,  $J$  9.6 Hz, 1H, ArH), 7.17 (m, 1H, ArH), 10.86 (s, 1H, ArH);  $^{13}\text{C}$ -NMR (50 MHz, DMSO- $d_6$ ):  $\delta$  55.8 (OCH<sub>3</sub>), 108.8, 113.3 (C-8), 118.1, 124.9, 144.7, 155.4 (C<sub>5</sub> methoxy), 159.6 (C-2, C=O), 184.1 (C-3, C=O); Anal. Calcd for: C<sub>9</sub>H<sub>7</sub>NO<sub>3</sub>: C 61.02, H 3.98, N 7.91. Found: C 61.04, H 3.93, N 7.97.

#### 5-nitroindoline-2,3-dione (2g)

Yield: 48%; yellow solid; mp 256 °C (recrystallized from ethanol) (lit.<sup>9</sup> mp: 252–254 °C); IR (KBr):  $\nu$  3101 (aromatic CH), 2925 (CH), 1749 (CONH), 1611 (aryl), 1518 (NO<sub>2</sub>), 1467, 1331 (N-O), 1168–1123 (OC), 1074 (OC), 1020 (OC), 885 (aromatic CH=CH) cm<sup>-1</sup>;  $^1\text{H}$ -NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  6.98 (d,  $J$  8.6 Hz, 1H, ArH), 8.30 (s, 1H, ArH), 8.36 (d,  $J$  8.6 Hz, 1H, ArH), 10.52 (s, 1H, NH);  $^{13}\text{C}$ -NMR (50 MHz, DMSO- $d_6$ ):  $\delta$  112.6 (C-8),

118.2, 119.6, 133.2, 142.7 (C-5 NO<sub>2</sub>), 155.3 (C-9), 159.9 (C-2, C=O), 182.4 (C-3, C=O); Anal. Calcd for: C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O<sub>4</sub>: C 50.01, H 2.10, N 14.58. Found: C 50.06, H 2.13, N 14.55.

#### Methyl 2,3-dioxo-2,3-dihydro-1H-indole-5-carboxylate (2h)

Yield: 69%; yellow solid; mp 258 °C (recrystallized from ethanol) (lit.<sup>9</sup> mp: 258–259 °C); IR (KBr):  $\nu$  2923 (C-Hester), 2852 (C-Hester), 1739 (C=Oester), 1609 (aryl), 1537 (C-O), 1440 (C-O-H), 1378 (C-O), 1323 (C-O), 1285 (O-C), 1193 (C-C-C), 1070 (O-C), 698 (C-Hester) cm<sup>-1</sup>;  $^1\text{H}$ -NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  3.89 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 6.99 (d,  $J$  8.1 Hz, 1H, ArH), 8.09 (s, 1H, ArH), 8.17 (d,  $J$  8.1 Hz, 1H, ArH), 11.37 (s, 1H, NH);  $^{13}\text{C}$ -NMR (50 MHz, DMSO- $d_6$ ):  $\delta$  52.3 (OMe ester), 112.3 (C-8), 117.8, 124.6, 125.0, 139.0, 154.1 (C-5 ester), 159.4 (C-2, C=O), 164.3 (CO<sub>2</sub>Me), 183.4 (C-3, C=O); Anal. Calcd for: C<sub>10</sub>H<sub>7</sub>NO<sub>4</sub>: C 58.54, H 3.44, N 6.83. Found: C 58.58, H 3.49, N 6.81.

## 4. Conclusions

This methodology provides simple and efficient procedure for the single-step preparation of isatins from the corresponding commercially available anilines using H- $\beta$  zeolite as the reusable catalyst. The catalyst is separated from reaction mixture by simple filtration, and recycled at least five times (in the case of aniline) without considerable loss in its activity. The methodology thus demonstrates that H- $\beta$  zeolite is superior catalyst as compared to homogeneous Lewis acid catalysts like SnCl<sub>4</sub> and BF<sub>3</sub>·Et<sub>2</sub>O. The procedure requires simple filtration of the catalyst and evaporation of the solvent to obtain good yields of isatins.

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## Povzetek

V prispevku je opisana enostavna in zelo učinkovita enostopenjska metoda priprave isatinov iz komercialno dosegljivih anilinov in uporabo H- $\beta$  zeolita kot pravega heterogenega katalizatorja. Tega lahko hitro in enostavno odstranimo iz reakcijske zmesi s filtracijo in ga večkrat ponovno uporabimo v reakciji, brez znatnega zmanjšanja njegove aktivnosti.