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# An ultrasound-promoted green approach for the synthesis of 3-(indol-3-yl)-3-hydroxyindolin-2-ones catalyzed by Fe(III)

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*Abstract*: Ferric chloride hexahydrate was used as a recyclable homogeneous catalyst in aqueous media for the synthesis of 3-(indol-3-yl)-3-hydroxyindolin-2-ones under sonication. It was found that the employed conditions afford the products smoothly in good to excellent yields.

*Keywords*: ultrasonic irradiation; homogeneous; catalysis; ferric chloride hexahydrate.

## INTRODUCTION

Indole-containing structures have widespread occurrence in many pharmacologically and biologically active compounds and the investigation of the chemistry of indoles has been, and continues to be, one of the most active areas of heterocyclic chemistry.[1–4] Isatins are also familiar for their biological activities. Oxindoles are well known amongst different isatin derivatives and are useful as antibacterial, anti-inflammatory and laxatives.[5,6] Such heterocyclic compounds were recently isolated from plants and marine animals, for example, the marine alkaloid convolutamydine A from the marine bryozoan *Amathia convoluta*.[7] Recently, efficient routes to the synthesis of oxindole derivatives were reported.[8,9] The synthesis of 3-(indol-3-yl)-3-hydroxyindolin-2-ones, however, would be a synthetically useful transformation since Friedel–Crafts reaction of indoles and isatins usually results in 3,3-di-3-indolylindolin-2-ones.[10–13] A literature survey showed that the reported methods on the synthesis of 3-(indol-3-yl)-3-hydroxyindolin-2-ones have several drawbacks, such as long reaction times, low yields, use of toxic solvents and need for specific reagents.[14–17] Thus, a mild and environmentally benign practical methodology under neutral conditions with a recyclable catalyst is actively sought after. Organic reactions in aqueous media have attracted increasing interest due to environmental and economical issues.[18]

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Considerable organic solvent waste in the purification step, however, is still a major concern.

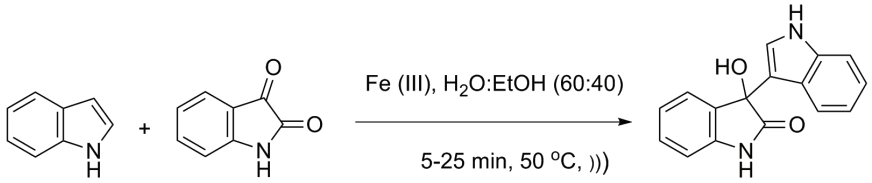
In recent years, iron(III) chloride has emerged as a powerful Lewis acid catalyst and has catalyzed many useful organic transformations under mild reaction conditions.[19,20] Moreover, iron salts are inexpensive, easy to handle and are environmentally friendly.

Ultrasound irradiation, on the other hand, has emerged as an efficient technique for reagent activation in organic synthesis. Using cavitation as an energy source to promote molecular interactions resulted in shorter reaction times. The rarefaction-compression cycle in the cavitation process, which involves the separation of molecules of the liquid and then the collapse of the bubbles, provides violent impulsions that generate short-lived regions with high temperature and pressure. Such localized hot spots can be thought of as micro reactors in which the sound energy is transformed into a useful chemical form.[21–23]

In this contribution, the synthesis of 3-indolyl-3-hydroxyoxindoles from isatins and indoles utilizing Fe(III) as a recyclable homogeneous catalyst under ultrasound irradiation is described.

## RESULTS AND DISCUSSION

The optimized details of the ultrasound-promoted reaction of indoles with isatins to give the corresponding products (**3**) are summarized in Scheme 1.




Scheme 1. Ultrasound-promoted, Fe(III) catalyzed 3-indolylation of isatins.

In order to optimize the reaction conditions, indole and isatin were selected as model substrates and the progress of the reaction was monitored by gas liquid chromatography (GLC). To examine the influence of the catalyst concentration, the reaction was performed with different catalyst concentrations. The decrease in the corresponding indole peak area was selected as a measure of the reaction coordinate. In addition, the ethanol peak was used as an internal standard. The results are summarized in Table I.

Based on these data, 2.5 mol % Fe(III) per mole of indole was selected as the optimized catalyst concentration. Solvent screening experiments showed that the yields were solvent dependent (Table II).

TABLE I. Fe(III)-catalyzed reaction of indole and isatin using different catalyst concentrations (the reaction was carried out according to the general experimental procedure)

| Entry | Reaction time, min | Indole consumption, % | Fe catalyst content, mol % |
|---|---|---|---|
| **1** | 1 | 20 | 1 |
| **2** | 3 | 45 | 1 |
| **3** | 5 | 65 | 1 |
| **4** | 10 | 80 | 1 |
| **5** | 1 | 30 | 2.5 |
| **6** | 3 | 65 | 2.5 |
| **7** | 5 | 95 | 2.5 |
| **8** | 1 | 33 | 5 |
| **9** | 3 | 78 | 5 |
| **10** | 5 | 95 | 5 |

Since ultrasound is known to generate extremely fine emulsions to enhance mass transfer,[24] a mixture of $H_2O$:ethanol (60:40) was used as the best solvent. The large excess of water may have a dual role. First, it helps in the precipitation of the products and results in an easy work-up procedure and catalyst recycling (see experimental), which minimizes organic solvent waste. Second, it may prevent dehydration of the product and subsequent attack of a second indole nucleophile to form 3,3-di-3-indolylindolin-2-one.

TABLE II. Effect of solvents on the yield of 3-(indol-3-yl)-3-hydroxyindolin-2-one (the reaction was carried out according to the general experimental procedure)

| Entry | Solvent | Reaction time, min | Isolated yield, % |
|---|---|---|---|
| **1** | 1,2-Dichloroethane | 60 | 50 |
| **2** | Acetonitrile | 45 | 55 |
| **3** | Methanol | 5 | 78 |
| **4** | Ethanol | 5 | 77 |
| **5** | $H_2O$: Ethanol (60:40) | 5 | 95 |

The effect of the intensity of the ultrasound irradiation on the reaction time is summarized in Table III. As it is shown, increase in the rated power of the ultrasonic horn from 20 to 100 % (92 to 460 W $cm^{-2}$, respectively) resulted in a decrease in the reaction time. This could be due to maximization of cavitation and effective distribution of the reactants throughout the reaction mixture. In the absence of ultrasound irradiation, however, the yields were unsatisfactory.

With the optimized conditions to hand (Scheme 1), various substrates were used, indicating the generality and scope of the reaction. Typical results are shown in Table IV. In all cases, the products were insoluble in the reaction media and simple filtration followed by rinsing with cold reaction solvent provided spectroscopically pure products.

One interesting example is the reaction of 3-methylindole with isatin (Table IV, entry **c**), which provided the product **3c**, while other reported methods failed

for this reaction. 3-Alkylation of 7-azaindole, which is susceptible to *N*-alkylation,[25] is also noteworthy (entry **e**). $FeCl_3 \cdot 6H_2O$ was found to be an efficient catalyst in terms of handling, temperature, yields and reaction times.

TABLE III. The effect of ultrasound irradiation intensity on the reaction time (the reaction was carried out according to the general experimental procedure)

| Max. power density, W $cm^{-2}$ | 92 | 184 | 276 | 368 | 460 |
|---|---|---|---|---|---|
| Reaction time, min | 25 | 20 | 15 | 10 | 5 |

TABLE IV. Ultrasound-promoted synthesis of 3-(indol-3-yl)-3-hydroxyindolin-2-ones catalyzed by Fe(III)

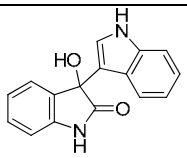
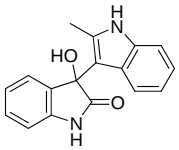
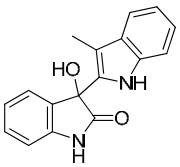
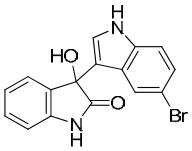
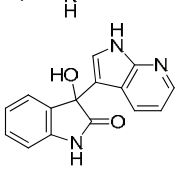
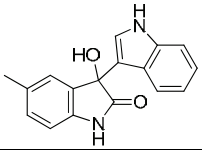
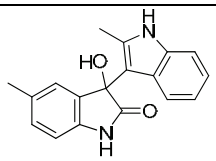
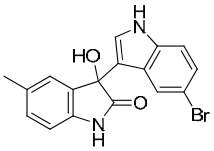
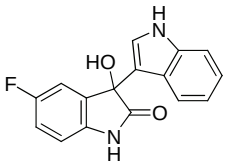
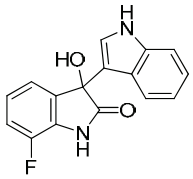
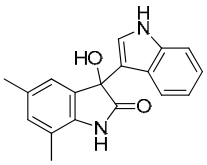
| Entry[a] | Indole | Isatin | Product | Reaction time min | Yield[b] % |
|---|---|---|---|---|---|
| **3a** | Indole | Isatin |  | 5 | 95[c] |
| **3b** | 2-Methylindole | |  | 5 | 97[c] |
| **3c** | 3-Methylindole | |  | 15 | 85 |
| **3d** | 5-Bromoindole | |  | 10 | 88[c] |
| **3e** | 7-Azaindole | |  | 10 | 90[c] |
| **3f** | Indole | 5-Methylisatin |  | 10 | 93[c] |

TABLE IV. Continued

| Entry[a] | Indole | Isatin | Product | Reaction time min | Yield[b] % |
|---|---|---|---|---|---|
| **3g** | 2-Methylindole | 5-Methylisatin |  | 5 | 95[c] |
| **3h** | 5-Bromoindole | |  | 10 | 88[c] |
| **3i** | Indole | 5-Fluoroisatin |  | 5 | 92[c] |
| **3j** | Indole | 7-Fluoroisatin |  | 10 | 87[c] |
| **3k** | Indole | 5,7-Dimethylisatin |  | 15 | 70[c] |

[a]All products were characterized by $^{1}$H-NMR, $^{13}$C-NMR and IR data; [b]isolated yields; [c]identified by comparison with authentic samples[14]

One of the main aims of the study was to investigate the reuse and recycling of $FeCl_3 \cdot 6H_2O$. After filtration of the cold reaction mixture to separate the product (**3a**), the filtrate was charged with the same substrates and was reused for four cycles, which afforded yields similar to those obtained in the first run, although increases in reaction time were observed (Table V).

TABLE V. The reuse of $FeCl_3 \cdot 6H_2O$ in successive runs (the reaction was carried out according to the general experimental procedure

| Run No. | Isolated yield, % | Reaction time, min |
|---|---|---|
| 1 | 95 | 5 |
| 2 | 89 | 20 |
| 3 | 85 | 60 |
| 4 | 77 | 120 |

## EXPERIMENTAL

*General*

The IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. The $^{1}$H-NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer and $^{13}$C-NMR spectra were obtained on a Bruker DRX-125 Avance spectrometer. Chemical shifts of the $^{1}$H- and $^{13}$C--NMR spectra were expressed in ppm downfield from tetramethylsilane. Melting points were measured on a Büchi Melting Point B-540 instrument and are uncorrected. Elemental analyses were made by a Carlo-Erba EA1110 CNNO-S analyzer and the results agreed with the calculated values. The ultrasonic device used was a UP 400 S instrument, emitting 24 kHz ultrasound at tunable intensity levels (up to a maximum of 460 W cm$^{-2}$). Analytical GLC evaluations of product mixtures were performed on a Varian CP-3800 chromatograph (using a split/splitless injector, CP Sil 8CB column, FID assembly).

*Materials*

All materials were purchased from Merck and used without further purification.

*General procedure for the ultrasound-promoted synthesis of 3-(indol-3-yl)-3-hydroxyindolin--2-ones catalyzed by Fe(III)*

Indole (1 mmol), isatin (1 mmol) and $FeCl_3 \cdot 6H_2O$ (2.5 mol %) were added to 20 mL of a 60:40 mixture of $H_2O$:ethanol and the reaction mixture was irradiated at 50 °C for the appropriate time (Table IV). After completion of the reaction (as indicated by GLC), the mixture was cooled in an ice bath and then filtered to separate the precipitated product, which was further purified by rinsing with cold reaction solvent. The filtrate was charged with the same substrates and was reused for successive cycles. The products were identified by comparison with authentic samples.

## CONCLUSIONS

In conclusion, an operationally simple and efficient synthesis of 3-indolyl-3--hydroxyoxindoles is reported. Highlights of the present work are:

*i*) Simultaneous application of sonic waves and Fe(III) resulted in greater efficiency in terms of reaction time and yield.

*ii*) All products were solely monoindolylated isatins and were not contaminated by 3,3-di-3-indolylindolin-2-ones.

*iii*) The reusability of the catalyst and environmentally friendly conditions are also noticeable.

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## ИЗВОД

## СИНТЕЗА 3-(ИНДОЛ-3-ИЛ)-3-ХИДРОКСИИНДОЛИН-2-ОНА КАТАЛИЗОВАНА Fe(III) И УНАПРЕЂЕНА ПОД ДЕЈСТВОМ УЛТРАЗВУКА

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Фери-хлоридхексахидрат је употребљен као хомогени катализатор у воденој средини за синтезу 3-(индол-3-ил)-3-хидроксииндолин-2-она под условима озрачивања ултразвуком.

Утврђено је да под примењеним условима, производи настају у добром до одличном приносу.

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