

## MICROWAVE-INDUCED INDIUM-CATALYZED SYNTHESIS OF PYRROLE FUSED WITH INDOLINE IN WATER

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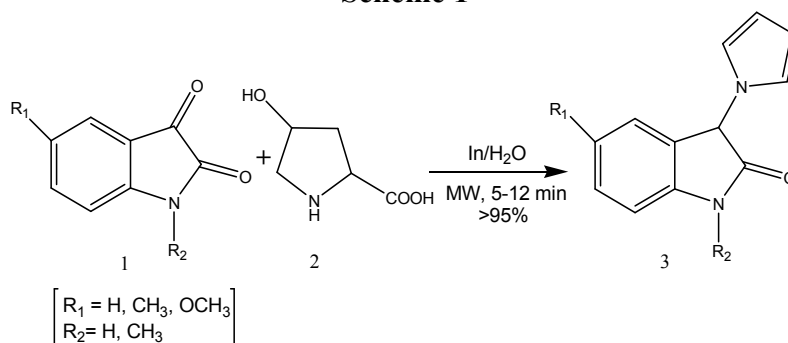
**Abstract:** An expeditious microwave-induced indium metal-catalyzed synthesis of pyrrole fused with indoline in water is developed by reacting isatin and 4-hydroxyproline.

**Keywords:** Pyrrole, indoline, microwave, catalysis, water

**Introduction:** Pyrroles important classes of compounds with many medicinal activities.<sup>1</sup> For these reasons, many methods for the synthesis of substituted pyrroles are known in the literature.<sup>2a</sup> However, synthesis of pyrroles fused to indoline has not been explored systematically. Conjugate addition reactions have been useful for the synthesis of substituted pyrroles.<sup>2b</sup> These compounds have also be synthesized using various other methods. For example, transition metal intermediates,<sup>2c</sup> reductive couplings,<sup>2d</sup> aza-Wittig reactions,<sup>2e</sup> Paal-Knorr reaction<sup>2f</sup> and multistep operations have been used for the preparation of pyrroles.<sup>3</sup> We describe herein a novel method for the synthesis of substituted pyrroles fused to indole skeleton by microwave-induced indium-catalyzed reaction in water.

**Results and Discussion:** We<sup>4</sup> have demonstrated bismuth nitrate-catalyzed synthesis of pyrroles. The reaction medium of our reaction was slightly acidic. During the course of our investigation on the preparation of diverse organic compounds, we have identified that our work on indium-catalyzed organic transformations can be used to prepare pyrroles fused with an indole, although an aqueous suspension of indium is slightly basic (Scheme 1, 1 to 3). This method is therefore, unique because there are no other methods that describe the preparation of these types of heterocycles by indium metal. Most of methods including our own have used acidic reagents.

### Scheme 1



The keto group of Isatin derivatives (1) is activated. Reaction of 1 with 4-hydroxy proline (2) in the presence of catalytic amount of indium metal in water under microwave irradiation for 5-12 minutes produced 3-pyrrole substituted indole system in 95% yield (3). The use of organic solvents slowed down the reaction. The reaction did not proceed without indium. After many experimentations, it was found that approximately 10 mol% indium metal with 1 mmol substrate in 2 mL water produced the best results. The amino and the carboxy group may undergo a condensation reaction to the highly reactive keto group of the indolinone in the presence of indium in water. This supports that slightly basic indium/water may serve as an activator in catalyzing a number of spontaneous processes and finally can produce pyrrole-substituted indole systems.

**Experimental:** To isatin (1 mmol), hydroxyproline (1 mmol), indium (20 mg) was added water (2 mL) and the reaction mixture was irradiated using a CEM microwave. The reaction was extracted with dichloromethane, washed with saturated sodium chloride solution (10 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Pure product (approximately, 90%) was isolated through column chromatography (ethyl acetate/hexane=30/70).

**Conclusion:** In conclusion, we have demonstrated pyrrole-substituted indoles can be prepared using indium metal-catalyzed reaction. Notably this method does not require any acidic reagents. The reaction is rapid, isolation of products is easy and the yields of the products are excellent. In this paper, we have uncovered an interesting role of indium/water for the preparation of important heterocycles. This method has the potential to prepare optically active compounds as described in structure 3.

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