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$InCl_3$-catalyzed efficient one-pot synthesis of 2-pyrrolo-3′-yloxindoles

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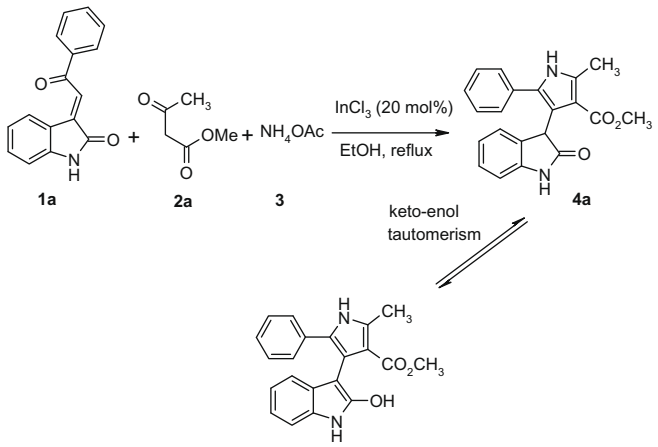
ABSTRACT

An $InCl_3$-catalyzed one-pot synthesis of 2-pyrrolo-3′-yloxindoles was achieved via three-component reaction of 3-phenacylideneoxindole, β-keto ester, and ammonium acetate at reflux by a sequential Michael addition followed by Paal–Knorr condensation.

Multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to give a final product in a one-pot procedure. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high-throughput generation of organic compounds.[1] In the past decades, there have been tremendous developments in three- and four-component reactions and great efforts have been and still are being made to find and develop new MCRs.[2]

Pyrroles are one of the most prevalent heterocyclic compounds, which are present as the basic cores in many natural products,[3] potent pharmaceutical compounds,[4] and various kinds of functional materials.[5] Despite numerous diverse approaches toward the synthesis of pyrroles developed so far,[6] it is still challenging to prepare polysubstituted pyrroles with various substituents from readily available building blocks. In addition, oxindoles are attractive targets in organic synthesis because of their significant biological activities as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals.[7] To the best of our knowledge, there have been only two reports on the synthesis of pyrrolo oxindoles. Previously, Bergmann et al.[8] reported the synthesis of pyrrolo oxindoles from 3-acetonylideneoxindole and 3-amino crotonates in toluene under reflux for several hours. Muthusamy et al.[9] synthesized less substituted 2-pyrrol-3′-yloxindoles from 3-diazooxindoles and pyrroles in the presence of rhodium(II) acetate catalyst. In view of their importance, the development of a new and simple method for the synthesis of highly substituted pyrrole moiety is of importance.

Lately, the utility of indium(III) Lewis acids[10] in organic synthesis has received a great deal of interest due to their relatively low toxicity, stability in air and water and recyclability. As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds and in the application of $InCl_3$[11] in organic synthesis, we herein disclose a simple and improved method for the synthesis of 2-pyrrolo-3′-yloxindoles using a catalytic amount of $InCl_3$ (20 mol %) in ethanol at reflux in a shorter reaction time (10–15 min). To the best of our knowledge, this is the first report for the synthesis of 2-pyrrolo-3′-yloxindoles from 3-phenacylideneoxindole, β-keto ester, and ammonium acetate (Scheme 1).



Scheme 1.

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Table 1
Catalytic activity of various Lewis acids on the three-component reaction[a]

Entry	Catalyst	Time (h)	Yield (%)
1	None	2.5	20
2	$SnCl_2.H_2O$	1.5	48
3	NH_2SO_3H	1.5	45
4	CAN	1.0	40
5	$Bi(OTf)_3$	1.0	56
6	$BiCl_3$	1.0	60
7	$In(OTf)_3$	0.50	85
8	$InCl_3$	0.25	92

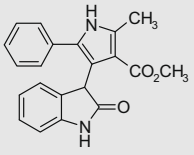
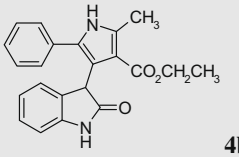
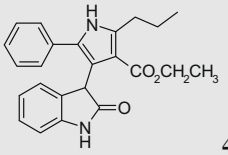
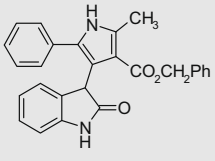
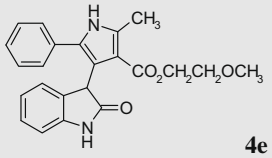
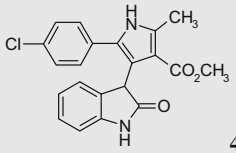
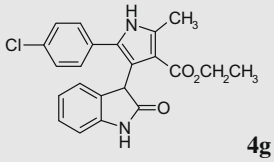
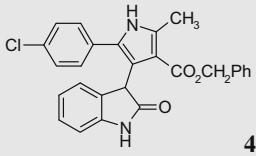
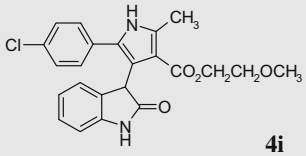
[a] Reaction of phenacylideneoxindole, methyl acetoacetate, and ammonium acetate in ethanol at reflux.

In order to study the scope and limitations of the three-component reaction, various Lewis acid catalysts, including $SnCl_2{\cdot}H_2O$, NH_2SO_3H, CAN, $Bi(OTf)_3$, $BiCl_3$, $In(OTf)_3$, and $InCl_3$ were investigated (Table 1). The best overall yield (92%) was obtained with $InCl_3$ in ethanol. Optimum results were obtained using 20 mol % of $InCl_3$.

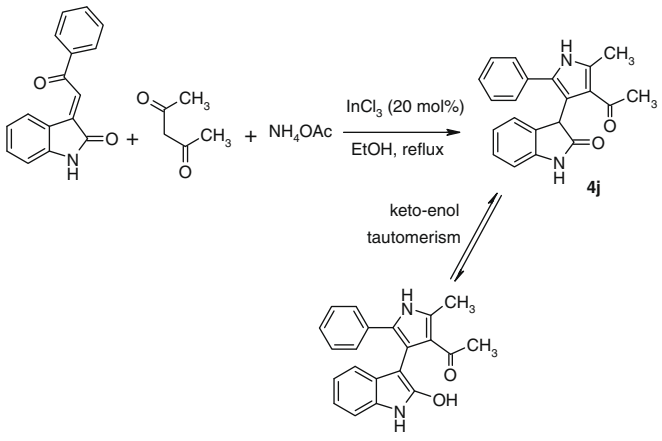
The reaction was carried out with 3-phenacylideneoxindole[12] **1** (1 equiv), β-keto ester **2** (1 equiv), and ammonium acetate **3** (2.5 equiv) catalyzed by $InCl_3$ (20 mol %) in ethanol and was refluxed for 10–15 min. The product precipitated from the reaction mixture.[13] This protocol is remarkably simple and requires no purification technique like column chromatography.

Table 2 summarizes our results on the one-pot reaction of various 3-phenacylideneoxindole and β-keto ester with ammonium acetate. All the reactions went smoothly and afforded the

Table 2
Synthesis of 2-pyrrolo-3′-yloxindoles **4a–i**

S.no	Product (**4**) (keto:enol)[a]	Time (min)	Yield[b] (%)
1	 **4a** (10:1)	10	92
2	 **4b** (10:1)	10	93
3	 **4c** (8:1)	15	90
4	 **4d** (9:1)	10	94
5	 **4e** (7:1)	15	91
6	 **4f** (9:1)	10	93
7	 **4g** (8:1)	15	92
8	 **4h** (10:1)	15	88
9	 **4i** (8:1)	15	90

[a] Ratio obtained from ^1H NMR analysis of the NH protons.
[b] Isolated yield.



Scheme 2.