



## Indium trichloride catalyzed regioselective synthesis of substituted pyrroles in water

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### ABSTRACT

A facile and regioselective synthesis of polysubstituted pyrroles from  $\alpha$ -azido chalcones and 1,3-dicarbonyl compounds is described. Indium trichloride in water is found to be efficient in catalyzing this transformation.

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Pyrrole is an important heterocyclic nucleus found in a number of natural<sup>1</sup> and unnatural compounds. Its derivatives find many applications in material science<sup>2</sup> and display several biological activities.<sup>3–6</sup> Although many synthetic protocols have been developed to access these valuable motifs,<sup>7–9</sup> efficient and new synthetic strategies are in high demand, particularly in the preparation of polysubstituted pyrroles. It is found that 1,3-dicarbonyl compounds are versatile starting materials employed in the synthesis of many important heterocycles including pyrroles.<sup>10,11</sup> Performing organic transformations in aqueous media or with the assistance of water<sup>12</sup> has gained much attention due to their greener glamour. A transition metal catalyst employed in a reaction should have low toxicity, reasonable stability toward air and water, and recyclability.<sup>13</sup> Considering the above factors and in continuation of our efforts to carry out organic reactions in water,<sup>14</sup> this Letter describes the indium trichloride catalyzed synthesis of polysubstituted pyrroles in aqueous medium. A related work with azido chalcones has been reported in which  $\text{In}(\text{OTf})_3$  has been employed as the catalyst.<sup>15</sup> This work is aimed at increasing the scope of this reaction<sup>11b,15</sup> with expanded substrate modification in a more greener route accompanied by a possible product selectivity.

$\alpha$ -Azido chalcones **1** were obtained from the corresponding benzylidene acetophenones in two steps following the literature procedure.<sup>16</sup> Treatment of azido chalcone **1a** with acetylacetone

**2a** in toluene at reflux afforded highly substituted pyrrole derivative **3a** in low yield. The reaction has then been screened for an optimized yield in different solvents and solid acid catalysts (Table 1). The effect of adding one or more equivalents of water along with the organic solvent has also been studied. When indium chloride was used as the Lewis acid catalyst and water was employed as the solvent, excellent yield (90%) of **3a** has been obtained. Thus  $\text{InCl}_3$  in water, the combination of which has already been known to display good catalytic activity,<sup>17</sup> has been found to complete the reaction in 30 min under conventional heating. The catalyst load has also been optimized and it is found that the yield of the reaction is appreciable only when 20 mol % was employed. Microwave irradiation reduced the reaction time to 10 min. It is appropriate to mention that vinyl azides have been shown to react with ethyl acetoacetate in the presence of  $\text{In}(\text{OTf})_3$  to provide pyrroles with no regioselectivity.<sup>15</sup> The catalyst may enhance the electrophilicity of the carbonyl group during the nucleophilic attack.

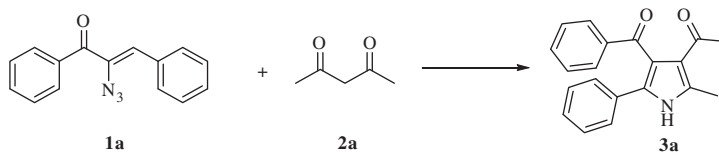
In order to explore the synthetic utility of this method, various  $\alpha$ -azido chalcones (**1a–1k**) were subjected to the reaction with different 1,3-dicarbonyl compounds (**2a–2e**) under optimized condition to generate a library of pyrroles (**3a–3t**) in good yields (Table 2). Products have been adequately characterized by NMR and mass spectral data. The structure of **3e** has been unambiguously assigned by single crystal X-ray analysis (Fig. 1).<sup>18</sup>

Unlike ketones **2d** and **2f**, when the reaction is carried out with ketones **2b** and **2c** or ester **2e**, there is a possibility of getting regioisomers of **3**. But in all these cases, only one regioisomer

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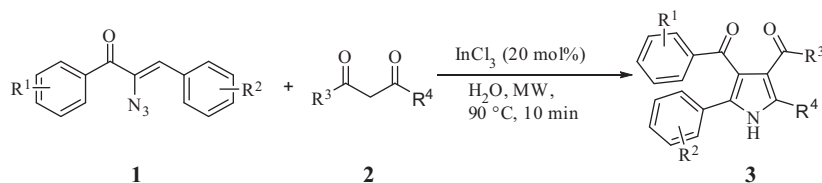
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**Table 1**  
Screening impact of solvents and Lewis acids



Entry	Lewis acid (mol%)	Solvent	Water	Reaction time (h)	Isolated yield <b>3a</b> (%)
1	—	Toluene, 120 °C	—	12	32
2	—	Toluene, 120 °C	1 equiv	12	25
3	<i>p</i> -TsOH (100)	Toluene, 120 °C	—	12	26
4	<i>p</i> -TsOH (100)	Toluene, 120 °C	1 equiv	12	19
5	<i>p</i> -TsOH (100)	EtOH, 90 °C	—	12	23
6	BF <sub>3</sub> ·OEt <sub>2</sub> (100)	Toluene, 120 °C	—	5	52
7	Sc(OTf) <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	—	8	47
8	Sc(OTf) <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	2 equiv	8	18
9	La(OTf) <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	—	8	43
10	La(OTf) <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	2 equiv	8	16
11	AgOTf (20)	CH <sub>3</sub> CN, 90 °C	—	8	45
12	AgOTf (20)	CH <sub>3</sub> CN, 90 °C	2 equiv	8	—
13	FeCl <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	—	24	38
14	FeCl <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	2 equiv	24	36
15	ZnCl <sub>2</sub> (20)	CH <sub>3</sub> CN, 90 °C	—	12	44
16	ZnCl <sub>2</sub> (20)	CH <sub>3</sub> CN, 90 °C	2 equiv	12	21
17	InCl <sub>3</sub> (100)	Toluene, 120 °C	—	12	56
18	InCl <sub>3</sub> (100)	CH <sub>3</sub> CN, 90 °C	—	12	64
19	InCl <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	—	12	64
20	InCl <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	2 equiv	2	78
21	InCl <sub>3</sub> (20)	CH <sub>3</sub> CN, 90 °C	5 equiv	30 min	90
22	InCl <sub>3</sub> (20)	Water, 90 °C	—	30 min	<b>92</b>
23	InCl <sub>3</sub> (20)	Water, MW, 90 °C	—	10 min	<b>92</b>

**Table 2**  
Synthesis of polysubstituted pyrroles



Entry	Azide, <b>1</b>	1,3-Dicarbonyl, <b>2</b>	Product, <b>3</b>	Yield (%)
<b>3a</b>				94
<b>3b</b>		<b>2a</b>		91
<b>3c</b>		<b>2a</b>		89

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