



## Nano indium oxide catalyzed tandem cyclization of amidine with nitroolefin



Shubhanjan Mitra, Avik Kumar Bagdi, Adinath Majee\*, Alakananda Hajra\*

Department of Chemistry, Visva-Bharati (A Central University), Santiniketan 731235, India

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### ABSTRACT

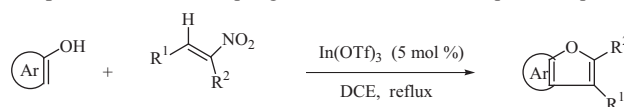
A tandem cyclization of amidine with nitroolefin has been described using nano  $\text{In}_2\text{O}_3$  as an efficient catalyst. The reaction is effective for the preparation of 4,5-unsymmetrically substituted 1-*H* imidazole in moderate to good yields. The catalyst was successfully reused for four consecutive cycles with similar catalytic activities.

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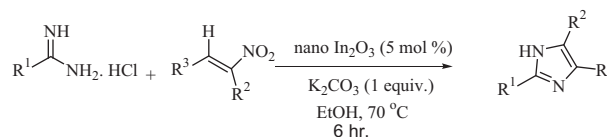
Recently metal nano catalysts have received considerable importance in organic synthesis due to their better catalytic properties and selectivity compared to their bulk counterparts.<sup>1</sup> In the context of green chemistry they have earned more significance due to their effective reusability as well as greater efficiency because of their higher surface area.<sup>2</sup> Indium metal and its salts have attracted attention of the synthetic community due to their wide applications in the field of organic synthesis.<sup>3</sup> Our group has been actively engaged in utilizing indium metal and its salts for useful reactions for more than a decade.<sup>4</sup> It is significant to note that the application of nano  $\text{In}_2\text{O}_3$  as catalyst has not been well studied.<sup>5a,b</sup> Our recently reported work<sup>5c,d</sup> with nano  $\text{In}_2\text{O}_3$  inspired us to explore its catalytic activity for useful transformations and preparation of important organic compounds.

Nitroolefins are easily prepared<sup>6a</sup> and considered as a useful substrate in many synthetic strategies like Michael addition,<sup>6b</sup> cycloaddition,<sup>6c-e</sup> Morita–Baylis–Hillman reaction,<sup>6f</sup> and two component coupling reaction.<sup>7</sup> Previous work by our group<sup>7</sup> on the synthesis of arenofurans has demonstrated an important use to nitroolefins (Scheme 1). It has been established that *N*-arylamidines serve as precursors to the synthesis of biologically important heterocycles.<sup>8</sup> We have used nitroolefins as starting material for the synthesis of 4,5-unsymmetrically substituted 1-*H* imidazoles (Scheme 1). Attempts made for the synthesis of imidazoles stem from the broad range of their applications in biological<sup>9</sup> as well as synthetic fields.<sup>10</sup> The traditional methods for the preparation of both 2,4,5-substituted and 1,2,4,5-substituted imidazoles are

**Our previous work :** Coupling between nitroolefin and phenol/naphthols<sup>7</sup>



**Present work :** Tandem cyclization between amidine and nitroolefin



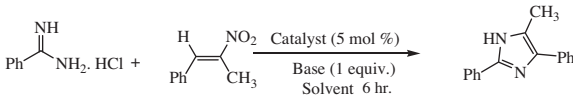
Scheme 1.

based on the multicomponent reaction using 1,2-dicarbonyl compounds, different aldehydes, and a nitrogen source.<sup>11</sup> There are a number of methods in the literature following this strategy<sup>11</sup> with variation of parameters and catalysts.<sup>12</sup> Most of these traditional methods involved the synthesis of symmetrically substituted imidazole at 4,5-position. This is due to the lesser availability of unsymmetric 1,2-diketones. Accordingly, a methodology for the synthesis of 4,5-unsymmetrically substituted imidazoles using a simple two-component one-pot reaction is highly desirable. Herein, we report a method for the synthesis of 4,5-unsymmetrically substituted 1-*H* imidazoles using nano  $\text{In}_2\text{O}_3$  as catalyst,  $\text{K}_2\text{CO}_3$  as base, and ethanol as solvent (Scheme 1).

Being encouraged by our previous results,<sup>7</sup> we initiated our study taking amidine hydrochloride, nitroolefin, and  $\text{In}(\text{OTf})_3$  as

\* Corresponding authors.

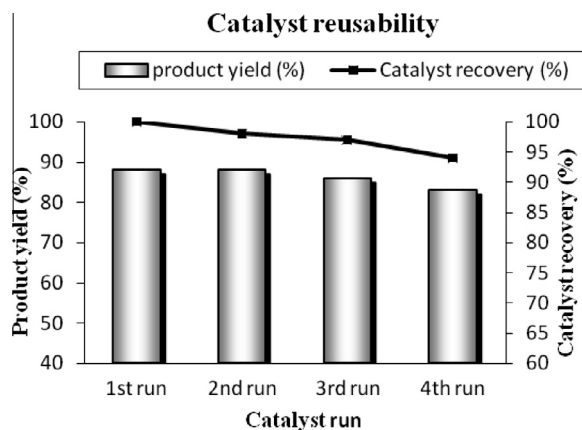
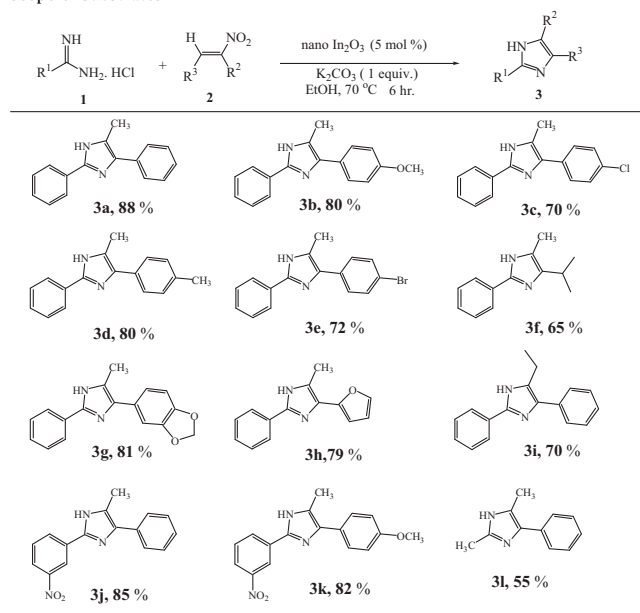
E-mail address: [adinath.majee@visva-bharati.ac.in](mailto:adinath.majee@visva-bharati.ac.in) (A. Majee).

**Table 1**  
Optimization of the reaction conditions


Entry	Catalyst	Base	Solvent	Temp (°C)	Yield <sup>a</sup> (%)
1	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	EtOH	70	86
2	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DCB	70	40
3	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	1,2-DCE	70	80
4	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	70	62
5	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DMSO	70	43
6	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DMF	70	40
7	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	PEG400	70	51
8	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	Toluene	70	72
9	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	70	56
10	In(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	EtOH	70	59
11	In(OTf) <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	EtOH	70	71
12	In(OTf) <sub>3</sub>	KOH	EtOH	70	72
13	In(OTf) <sub>3</sub>	KOAc	EtOH	70	52
14	In(OTf) <sub>3</sub>	DABCO	EtOH	70	58
15	In(OTf) <sub>3</sub>	Et <sub>3</sub> N	EtOH	70	78
16	In(OTf) <sub>3</sub>	—	EtOH	70	—
17	InCl <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	EtOH	70	81
18	Powder In <sub>2</sub> O <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	EtOH	70	70
19	<b>Nano In<sub>2</sub>O<sub>3</sub></b>	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>EtOH</b>	<b>70</b>	<b>88</b>
20	Nano ZnO	K <sub>2</sub> CO <sub>3</sub>	EtOH	70	74
21	Nano CuO	K <sub>2</sub> CO <sub>3</sub>	EtOH	70	70
22	Nano In <sub>2</sub> O <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	1,2-DCE	70	<5
23	Nano In <sub>2</sub> O <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	70	58
24	Nano In <sub>2</sub> O <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	PEG 400	70	53
25 <sup>b</sup>	Nano In <sub>2</sub> O <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	EtOH	70	90
26	Nano In <sub>2</sub> O <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	EtOH	Reflux	89
27 <sup>c</sup>	Nano In <sub>2</sub> O <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	EtOH	70	78

<sup>a</sup> Isolated yield.<sup>b</sup> 10 mol % catalyst used.<sup>c</sup> 3 mol % catalyst used.

catalysts using 1,2-DCE as solvent and K<sub>2</sub>CO<sub>3</sub> as base (Table 1, entry 3) and were able to synthesize the desired imidazole in 80% yield. Other solvents like DCB, CH<sub>3</sub>CN, DMSO, DMF, dioxane, PEG-400, toluene, and H<sub>2</sub>O (entries 2–10) gave lower yields. However, EtOH (Table 1, entry 1) was found as the best solvent increasing the product yield to a good extent (86%). We varied the bases like Cs<sub>2</sub>CO<sub>3</sub>, KOH, and KOAc (Table 1, entries 11–13) instead of K<sub>2</sub>CO<sub>3</sub> but no enhancement of yield was observed. Application of organic bases like DABCO and Et<sub>3</sub>N (Table 1, entries 14 and 15) furnished 58% and 78% yields, respectively. The reaction did not proceed at all, in the absence of base (Table 1, entry 16). Therefore, the choice of base has important role in the reaction path and is probably required to free the amidine hydrochloride. Indium chloride was also able to perform the reaction with good yields (81%, Table 1, entry 17). Motivated by this result, we then used powder In<sub>2</sub>O<sub>3</sub> (Table 1, entry 18) and nano In<sub>2</sub>O<sub>3</sub> (Table 1, entry 19) and obtained very good yields, 70% and 88%, respectively. To investigate the effect on the choice of catalyst, we have used different nano metal oxides like ZnO and CuO, (Table 1, entries 20 and 21), but no enhancement of yield has been observed. Thus we have found that nano In<sub>2</sub>O<sub>3</sub> is an effective catalyst under the reaction conditions. Further, the efficiency of different solvents for nano In<sub>2</sub>O<sub>3</sub>-catalyzed reaction (Table 1, entries 22–24) has been examined and no promising result was found. Next, with EtOH as the solvent we tested the catalyst loading and observed that no considerable improvement was made on increasing the amount of catalyst or increasing the temperature from 70 °C to reflux (Table 1, entries 25 and 26). On lowering the amount of catalyst (3 mol %) yield of the reaction was reduced (Table 1, entry 27). The detailed optimization is summarized in Table 1.

**Table 2**  
Scope of substrates**Figure 1.** Reusability of the catalyst.

The substrate scope and limitations of our method were investigated and are summarized in Table 2. The reaction of (2-nitropropenyl)-benzene with benzamidine was very clean giving 88% yield (3a). We have performed the reactions varying the amidines with a wide range of structurally diverse nitroolefins and isolated the desired products in good yields. As it is evident from Table 2, this procedure is uniformly effective for nitroolefins with different substituents on the benzene ring as well as for aliphatic nitroolefin (3f). Nitroolefins with a methylenedioxy group on the aromatic moiety underwent smooth reaction with 81% yield (3g). The heterocyclic moiety (3h) remains unaffected under the present reaction conditions and furnished good yield (79%). However, using acetamidine (3i) over benzamidine resulted in a lower yield (55%). The reaction did not proceed for (2-nitro-vinyl)-benzene with acetamidine or benzamidine under the present reaction conditions.

To check the reusability of the catalyst, the catalyst after each run, the latter was centrifuged and washed with ethanol and water followed by drying at 110 °C. The recovered catalyst was reused for four subsequent runs without any significant deactivation of the catalytic activity (Fig. 1).

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