



## Michael addition of indoles to $\beta$ -nitrostyrenes catalyzed by HY zeolite under solvent-free conditions



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### ARTICLE INFO

#### Article history:

Received 4 January 2014

Revised 22 January 2014

Accepted 24 January 2014

Available online 1 February 2014

#### Keywords:

Michael addition

HY zeolite

Indole

$\beta$ -Nitrostyrenes

C–C bond formation

### ABSTRACT

Michael addition of indoles to  $\beta$ -nitrostyrenes is reported using HY zeolite as catalyst under mild reaction conditions. This methodology allows the synthesis of various indole derivatives in good to high yields at 50 °C under solvent-free conditions. The short reaction time and achieving high yield of the desired products are the main advantages of the present work. The catalyst can be easily recovered and reused for six successive runs without considerable changes in yields. This Michael addition catalyzed by HY zeolite is operationally simple and can be considered as a greener protocol as it avoids the use of corrosive acids and toxic reagents.

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Michael addition is one of the most important reactions for the construction of carbon–carbon bonds in organic reactions.<sup>1</sup> Among the Michael acceptors, nitroolefins are very attractive, since the nitro moiety is a strong electron-withdrawing group that can be readily transformed into a range of different functionalities.<sup>2,3</sup> Indole and many of its derivatives are relevant units in many naturally occurring compounds, because of their pharmacological and biological properties.<sup>4</sup> Due to the increased nucleophilic reactivity of C<sub>3</sub> position of indole ring, it is often used for the subsequent transformations leading to different indole alkaloids. In general, indole 3-derivatives were prepared by the Michael addition of indoles in the presence of samarium(III) iodide,<sup>5</sup> CeCl<sub>3</sub>·7H<sub>2</sub>O–NaI/SiO<sub>2</sub>,<sup>6</sup> Yb(OTf)<sub>3</sub>,<sup>7</sup> InCl<sub>3</sub>,<sup>8</sup> InBr<sub>3</sub>,<sup>9</sup> iodine,<sup>10</sup> sulfamic acid,<sup>11</sup> boric acid,<sup>12</sup> Bi(OTf)<sub>3</sub>,<sup>13</sup> H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>,<sup>14</sup> basic alumina,<sup>15</sup> carbohydrate-based tolylsulfonyl hydrazines,<sup>16</sup> K10 montmorillonite,<sup>17</sup>  $\beta$ -cyclodextrin,<sup>18</sup> silica sulfuric acid,<sup>19</sup> and Sc(OTf)<sub>3</sub><sup>20</sup> as catalysts. Recently catalyst-free conjugate addition of indole to  $\beta$ -nitrostyrene was reported in aqueous medium<sup>21</sup> at 100 °C with 5–15 h of extended reaction time. Many of these reported procedures involve strongly acidic conditions, expensive reagents, and longer reaction times, and involve tedious procedures for the isolation of product. Also in some cases lower yield of products were observed due to dimerization of indole or polymerization of the nitroalkene. To overcome these problems, developing a simple

and efficient method is always desirable for the conjugate addition of indoles to electron-deficient olefins.

Zeolites are microporous, crystalline aluminosilicates built from infinitely extending three-dimensional network of SiO<sub>4</sub> and AlO<sub>4</sub> tetrahedra that are linked together through oxygen bridges. By virtue of their structure, crystallinity, and variable stoichiometry, zeolite catalysts have well defined pore size distributions, adjustable acidity, very high surface area and good thermal stability.<sup>22</sup> Zeolites are also efficient inorganic solid acids, which are cheap and show high activities in organic reactions under heterogeneous reaction conditions.<sup>23</sup> They have been extensively used as solid heterogeneous catalysts in organic synthesis<sup>24</sup> due to their non-corrosive and non-toxic nature. In particular, HY zeolite has been reported as catalyst for the synthesis of heterocyclic compounds like imidazoles,<sup>25a</sup> tetrahydrocarbazoles,<sup>25b</sup> bis(indolyl)methanes,<sup>25c</sup> benzimidazoles,<sup>25d</sup> polyhydroquinolines,<sup>25e</sup> 1,4-dihydropyridines,<sup>25f</sup> and quinzolin-4(3H)ones.<sup>25g</sup> In continuation of our interest on the development of heterogeneous catalysts for organic transformations,<sup>26</sup> herein we report a new and efficient method for the Michael addition of indoles to  $\beta$ -nitrostyrenes in the presence of HY zeolite as a catalyst under mild and solvent-free conditions. Although zeolites have been used as catalysts for the synthesis of many heterocycles as mentioned above, this is the first report where the synthesis of indole derivatives being carried out in the presence of HY zeolite.

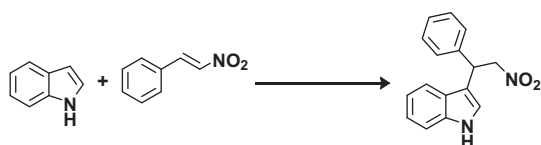
The reaction conditions were optimized for the Michael addition between indole and  $\beta$ -nitrostyrene under various parameters

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**Table 1**

Optimization of reaction conditions for the Michael addition of indole to  $\beta$ -nitrostyrene under different conditions<sup>a</sup>



Entry	Catalyst	Solvent	Time (h)	T (°C)	Yield <sup>b</sup> (%)
1	—	Neat	3	RT	—
2	—	Neat	3	50	9
3	NaY	Neat	1	RT	11
4	NaY	Neat	1	50	40
5	HY	Acetonitrile <sup>c</sup>	3	50	45
6	HY	Acetone <sup>c</sup>	3	50	41
7	HY	Ethanol <sup>c</sup>	3	50	38
8	HY	Tetrahydrofuran <sup>c</sup>	3	50	48
9	HY	Neat	2	RT	25
10	HY	Neat	0.5	50	51
11	HY	Neat	1	50	55 <sup>d</sup>
12	HY	Neat	1	50	78 <sup>e</sup>
13	HY	Neat	1	50	93 <sup>f</sup>
14	HY	Neat	1	50	93 <sup>g</sup>
15	HY	Neat	1	75	91

<sup>a</sup> Reaction conditions: indole (1 mmol),  $\beta$ -nitrostyrene (1 mmol), catalyst (100 mg).

<sup>b</sup> Isolated yield.

<sup>c</sup> Solvent (5 mL).

<sup>d–g</sup> 20, 50, 100, and 200 mg of catalyst, respectively.

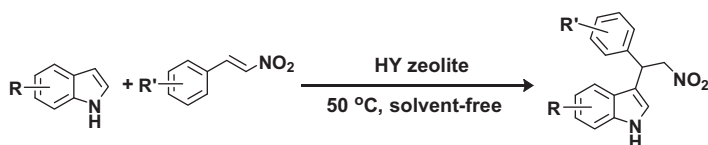
like temperature, solvent, and catalyst loading. The observed results are given in Table 1. Control experiments in the absence of catalyst showed 0% and 9% yields in 3 h at room temperature and at 50 °C, respectively under neat conditions. On the other hand, NaY zeolite<sup>27</sup> resulted in 11% and 40% yields of the desired product at room temperature and at 50 °C in 1 h, respectively under neat conditions. HY zeolite gave moderate yields in the presence of organic solvents like acetonitrile, acetone, ethanol, and THF at 50 °C. In contrast, HY zeolite<sup>27</sup> showed a promising yield of 93% at 50 °C under neat conditions. Table 1 shows the influence of catalyst loading on the product yield. The high yield was achieved with 100 mg of HY zeolite and increasing its loading further to 200 mg failed to increase the yield. Also, it was found that high yield was achieved at 50 °C under the present experimental conditions.

The present methodology will be highly useful to synthesize a series of indole derivatives as it employs milder conditions and no solvent is required for this transformation. These encouraging results obtained in the preliminary experiments prompted us to expand the generality of this catalytic system to various other substituted indoles and  $\beta$ -nitrostyrenes and the observed results are given in Table 2.<sup>28</sup> In general, mono/di-substituted indole derivatives were readily reacted with mono/di-substituted  $\beta$ -nitrostyrenes in very high yields at short reaction times. This catalytic system allowed us to synthesize a series of indole derivatives containing fluoro, chloro, methyl, and ester groups and interestingly they are not affected during the course of reaction. This is yet another example to demonstrate nicely the catalytic activity of HY zeolite through its Bronsted acidity to promote this transformation.

In order to check the stability of catalyst under the present experimental conditions, reusability experiments were performed in the reaction between indole and  $\beta$ -nitrostyrene. Thus, after completion of the Michael addition, product was extracted with ethyl acetate. The catalyst was filtered, washed with ethyl acetate, and dried under vacuum. The recovered catalyst was reused in the next cycle. As it is shown in Table 3, the catalyst maintains its activity

**Table 2**

Michael addition of substituted indoles to substituted  $\beta$ -nitrostyrenes catalyzed by HY zeolite under solvent-free conditions<sup>a</sup>



R = H, 6-Cl, 6-F, 4-Cl, 5-Cl, 4-F, 5-F, 5-COOCH<sub>3</sub>

R' = H, 3,4-di-Cl, 2-CH<sub>3</sub>, 4-Cl

Entry	Substituted Indole	Substituted $\beta$ -Nitrostyrene	Time (h)	Yield <sup>b</sup> (%)
1			1	95
2			1	93
3			1.5	89
4			1	92
5			1.5	87
6			1	93
7			2	85
8			1.5	88
9			1.5	90
10			2	83
11			1.5	87
12			1.5	89
13			2	84
14			1.5	90
15			1.5	85

<sup>a</sup> Reaction conditions: substituted indole (1 mmol), substituted  $\beta$ -nitrostyrene (1 mmol), HY zeolite (100 mg), 50 °C under solvent-free conditions.

<sup>b</sup> Isolated yield.

up to 6 reuses without much loss in its activity. This test clearly demonstrates the stability of catalyst over multiple runs and supporting its stability over extended duration.

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