



AN EFFICIENT SYNTHESIS OF 3-AMINO ALKYLATED INDOLES  
Via A MANNICH-TYPE REACTION CATALYZED BY SiO<sub>2</sub>-I

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**Abstract**

An efficient methodology for the synthesis of 3-aminoalkylated indoles was developed using SiO<sub>2</sub>-I as an efficient heterogeneous catalyst via a Mannich-type reaction. The mild reaction conditions, shorter reaction times, excellent yields at room temperature, simple work-up procedure, cost effectiveness and re-usability of the catalyst and no by-product formation are the key advantages of our protocol over reported ones.

**Keywords** : Mannich-type reaction, 3-aminoalkylated indoles, one-pot synthesis, silica iodide.

**Introduction**

3-substituted indole scaffolds are privileged and prominent structures which are found in a number of pharmaceutical drugs and natural products. They are also established as an acclaimed pharmacophore and have numerous biological activities such as HIV-1 integrase inhibitor **A**<sup>i</sup>, aromatase inhibitor for breast cancer **B**<sup>ii</sup>, Gramine **C**, and Sumatriptan **D**, Ergine **E** (Figure: 1).

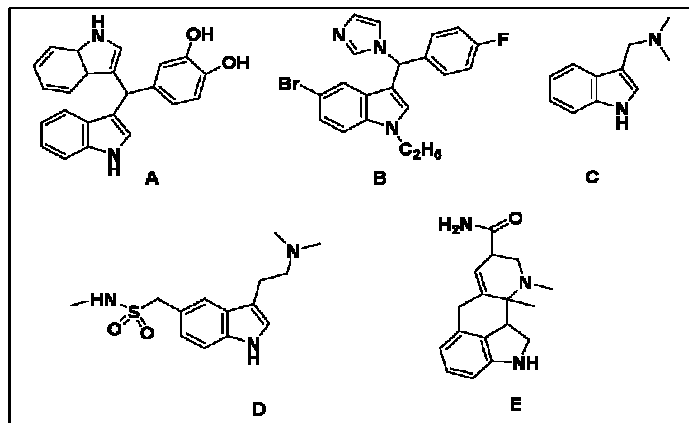


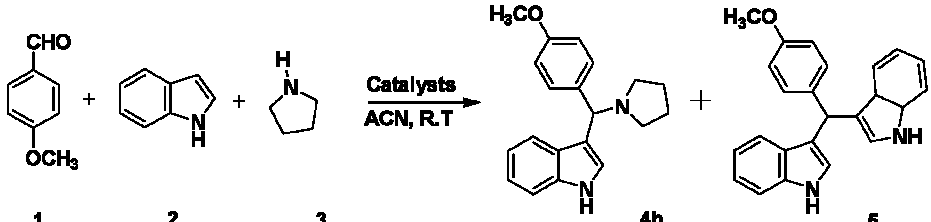
Figure: 1

Multicomponent reactions have steadily gained much significance in synthetic organic chemistry due to their remarkable advantages of operational simplicity, structural diversity, convergence, intrinsic atom economy and reduction in waste generation.<sup>iii-ix</sup> Mannich reaction is one such multicomponent reaction that executes a highly efficient method for the formation of C-N and C-C bonds to synthesize many natural products and pharmaceuticals.<sup>x,xi</sup> Various pathways are developed for the synthesis of amino substituted indoles by using various reagents, catalysts and conditions.<sup>xii-xviii</sup> Most of the reported procedures have shortcomings such as use of expensive reagents, strong acidic conditions, lower yields of products, long reaction times and high temperature conditions that are not acceptable in the perspective of green chemistry. Therefore, the development of convenient and eco-friendly approaches for the synthesis of 3-amino alkylated indoles is highly desirable. Here, in continuation of our work towards development of convenient and eco-friendly protocols for various heterocycles<sup>xix-xxv</sup>, we report here for the first time synthesis of 3-amino alkylated indoles via a mannich-type multicomponent reaction catalyzed by silica iodide (SiO<sub>2</sub>-I) as a heterogeneous catalyst. Heterogeneous catalysts have achieved great importance in organic synthesis. SiO<sub>2</sub>-I is non-corrosive, economical, provide ease of preparation and handling, cleaner reaction profile; can be separated easily with high recovery and reusability. These features lead to decreasing environment pollution and equipment cauterization, as the hallmarks of green chemistry are atom efficiency, elimination of toxic reagents, safe and cleaner reaction profile, reduction in the generation of waste and re-usability of the reagents. To our knowledge, this is a first simple and efficient synthetic strategy to the 3-amino alkylated indoles via multicomponent reaction catalyzed by silica iodide (SiO<sub>2</sub>-I) at ambient condition.

## Results and discussion

Initially, 4-OCH<sub>3</sub> benzaldehyde, indole and pyrrolidine in acetonitrile were chosen as the starting reactants in the model reaction. Different catalysts were screened such as FeCl<sub>3</sub>, NiCl<sub>2</sub>, aspartic acid, glycine, perchloric-SiO<sub>2</sub> etc (Table 1).

**Table1:** Screens of catalysts



Entry	Catalyst (mol %)	Yield of 4b (%) <sup>a</sup>	Yield of 5 (%) <sup>a</sup>
1	FeCl <sub>3</sub> (10 mol %)	30	30
2	ZnCl <sub>2</sub> (10 mol %)	40	20
3	Acetic acid (10 mol %)	25	60
4	NiCl <sub>2</sub> .6H <sub>2</sub> O (10 mol %)	10	50
5	Perchloric-SiO <sub>2</sub> (0.10g)	10	75
6	Glycine (10 mol %)	30	40
7	Aspartic acid (10 mol %)	40	35
8	SiO <sub>2</sub> -Cl (0.10g)	40	30
9	I <sub>2</sub>	25	70
10	----	Trace	20
11	SiO <sub>2</sub> -I (0.10g)	90	--

12	SiO <sub>2</sub> -I (0.08g)	80	--
13	SiO <sub>2</sub> -I (0.12g)	90	--

<sup>a</sup> isolated yields

However, almost all these acids gave the desired product in poor yields along with the undesired by-product bisindolymethane (5) (Table 1, entries 1-9). When iodine alone was used as a catalyst, it was also found to be inefficient to yield the desired single product and affords the corresponding bisindolymethane (5) as a by-product (Table 1, entry 9). Interestingly, when the silica iodide (SiO<sub>2</sub>-I) was used as the catalyst (Table 1, entry 11), the highest yield (90%) of the product 4b was obtained as a single desired product. Here, the yield could not be enhanced by increasing the amount of catalyst (Table 1, entries 13). However, the product yield fell to 80 % by decreasing the catalyst amount to 0.08g (Table 1, entry 12). In the absence of catalyst, the reaction failed to afford the desired product (Table 1, entry 10). Therefore, 0.10g of SiO<sub>2</sub>-I was selected as a catalyst for further investigating other reaction conditions.

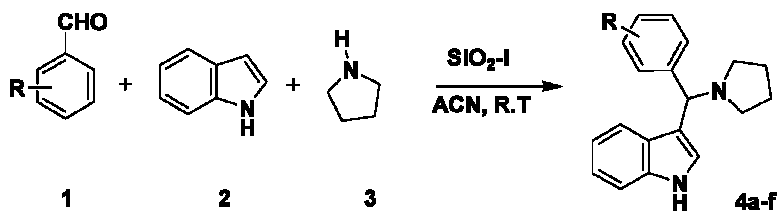
To study the optimum reaction conditions, the influence of other reaction parameters such as the temperature, solvent and reaction time were observed. We performed the reaction in different other solvents including ethanol, tetrahydrofuran (THF), toluene, acetonitrile, dimethylsulfoxide and water, but in all these solvents lower to moderate yields were obtained (Table 2). So the best result was obtained in acetonitrile in which both the yield and reaction time were considerably improved (Table 1, entry 4).

**Table 2:** Optimization of reaction condition

Entry	Solvent	Temperature	Time(h)	Yield (%) <sup>a</sup>
1	EtoH	R.T	4	60
2	THF	R.T	5	30
3	Toulene	R.T	5	35
4	ACN	R.T	3	90
5	DMSO	R.T	4	40
6	Water	R.T	5	50

<sup>a</sup> isolated yields

Subsequently, various substituted aldehydes were subjected to examine the generality and scope of this developed protocol (**Scheme: 1**) and the results are summarized in Table 3. A variety of functional groups of substituted aldehydes were well tolerated to afford good to excellent yields of amino alkylated indoles, inconsiderate of their steric hindrance or electronic nature (Table 3, entries 1-6). After completion of the reaction, SiO<sub>2</sub>-I catalyst can be easily separated from the reaction mixture and after drying, it was reused at least four additional times with no significant loss of activity (90-82% of 4b).

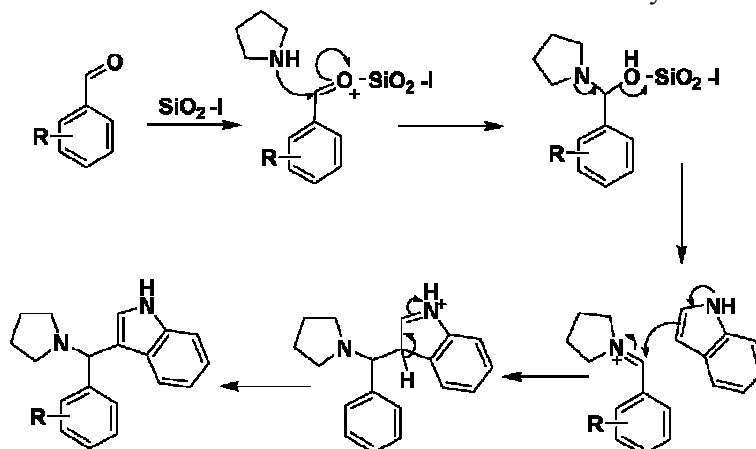


**Table 3:** Synthesis of 3-amino alkylated indoles

Entry	R	Product (P)	Time (h)	Yield (%) <sup>a</sup>	M. p (°C)	
					Observed	Literature
1	H	4a	3	90	142-145	145-147 [22]
2	4-OCH <sub>3</sub>	4b	3	90	168-170	170-172 [18]
3	4-Cl	4c	3.5	92	150-152	152-155 [22]
4	2-Cl	4d	4	89	158-160	154-156 [22]
5	4-Br	4e	3.5	88	142-144	145-147 [18]
6	3-OCH <sub>3</sub>	4f	3	91	156-158	159-160 [22]

<sup>a</sup> Isolated yields.

A plausible mechanism for the SiO<sub>2</sub>-I catalyzed reaction is proposed in **Scheme: 2**. The initial iminium ion generation is proposed to be facilitated by the electrophilic activation of the aldehyde carbonyl through SiO<sub>2</sub>-I catalyst. In the next step, the nucleophilic attack of electron rich indole on iminium ion intermediate to form 3-aminoalkylated indole.



**Scheme: 2.** Plausible mechanism of SiO<sub>2</sub>-I catalyzed synthesis of 3-amino-alkylated indole

## Experimental Section

### Preparation of Silica Iodide

Silica gel (10 g) was dispersed in dichloromethane (25 ml), and thionyl chloride (10 ml) was added dropwise (addition funnel) with stirring (stir bar) at 20-30°C. After 1 hr, the solvent was removed by rotary evaporation in vacuo to give 13.0 g of silica chloride (SiO<sub>2</sub>-Cl) as a dry solid. It was washed with water and dried at 80°C under vacuo (2 mm Hg, 1hr). Then a solution of sodium iodide (1.5 g) in a mixture of EtOH-H<sub>2</sub>O (4:1, 5 mL) was added to 3.0 g of the solid SiO<sub>2</sub>-Cl and the suspension was stirred for 30 min. The solid obtained was collected, washed with water and dried at 80°C under vacuo (2 mm Hg, 1hr) to afford 3.5 g of SiO<sub>2</sub>-I as a colorless solid. In order to confirm the presence of iodide in SiO<sub>2</sub>-I, chemical tests of sodium fusion extract (SFE) were performed. Silver nitrate test gave a very positive result, formed a yellow precipitate, which confirmed the presence of iodine in the catalyst.

### General procedure for the synthesis of 3-amino alkylated indoles (4a-4f)

In a 25mL RBF, aldehyde (1 mmol), pyrrolidine (1.5mmol) in acetonitrile (5 mL) was added SiO<sub>2</sub>-I (0.10g) and the reaction mixture was stirred at room temperature for 30 min. To this indole (1 mmol) was added and the reaction was stirred till the completion of the reaction as monitored by TLC. After completion of the reaction, solvent was removed under reduced pressure. To the residue, diethyl ether was added and filtered to separate the catalyst. The obtained catalyst was washed with acetone and dried and stored for reuse. The filtrate was

dried over anhydrous sodium sulfate and the residue was subjected to column chromatography (silica gel, hexane-EtOAc) to obtain pure product.

### Spectral Data

**3-((4-Methoxyphenyl) (pyrrolidin-1-yl)methyl)-1H-indole (4b):** M. p. 168-170 °C; <sup>1</sup>HNMR (CDCl<sub>3</sub>, 400MHz) /δ (ppm): 8.01 (brs, 1H), 7.78 (d, 1H), 7.44 (d, 2H), 7.30 (d, 1H), 7.21 (t, 2H), 7.06 (t, 1H), 6.79 (d, 2H), 4.55 (s, 1H), 3.74 (s, 3H), 2.56-2.46 (m, 4H), 1.75 (s, 4H); <sup>13</sup>C NMR(CDCl<sub>3</sub>, 100MHz)/ δ(ppm): 158.22, 137.74, 136.19, 128.74, 126.53, 121.86, 121.70, 119.88, 119.34, 113.50, 110.99, 67.28, 55.19, 53.67, 23.55; Mass(m/z) = 305.3 (M-1).

### Conclusion

In conclusion, to the best of our knowledge, this is the first report of the use of silica iodide (SiO<sub>2</sub>-I) as a catalyst in the three-component mannich-type synthesis of 3-amino alkylated indoles. The mild reaction conditions, shorter reaction times, excellent yields obtained at room temperature, simple work-up procedure, cost effectiveness and re-usability of the catalyst and no by-product formation are the key advantages of our protocol over reported ones.

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