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# Regioselective N-allylation and N-cinnamylation of indoles using Cu<sup>1</sup>exchanged hierarchical nanoporous material

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**Abstract:** Regioselective N-allylation and N-cinnamylation of indoles are achieved using a novel catalyst of  $Cu^{I}$ -exchanged hierarchically architectured nanoporous material ( $MMZ_{Cu}^{I}_{Y}$ ). The catalyst was characterized by electron microscopy and X-ray methods. Other advantages like functional tolerance, easy separation and reusability of the catalyst are also highlighted.

Keywords: hierarchical nanoporous zeolite; regioselectivity; N-allylation; N-cinnamylation.

### 1. INTRODUCTION

Indole containing compounds are best known for their medicinal properties in the pharmaceutical industry [1]. Notably indolic aminoacid tryptophan is the precursor of the neurotransmitter serotonin. In last few years, it was reported that indole and its derivatives have antimicrobial activity against gram(+) and gram(-) bacteria and shows other biological activities those including anti-cancer drugs, anti-hypertensive drugs, antipsychotic agents, antiasthmatic drug, inhibitor of RNA polymerase-11 and for treating sexual dysfunction [2]. Lewis and Bronsted acid promoted Friedel-Crafts reaction [3] and metal complex/salts catalyzed alkylation of indole processes proved to be remarkably effective under homogeneous and heterogeneous

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conditions [4-6]. Although the alkylation of indoles with allyl halides, allyl acetates or allyl carbonates provides a valuable method for the direct allylation of indoles. However, most of the described procedures generally suffer from problems associated with the regiochemistry of alkylation at the N1, C2 or C3 positions of the indole nucleus. Thus the functionalization of indole ring system is an area of great interest and challenging task, because of the discrimination between the N- alkylated product and the C3-alkylated product with unsubstituted indoles. Regioselective C-2 allylation of indoles has also been achieved by the use of catalysts such as Potassium organotrifluoroborate salts [7], Pd [8] and Rh [9] catalysts. Similarly selective synthesis of C-3 allylated indoles includes the use of catalysts such as H<sub>2</sub>SO<sub>4</sub> [10], Ru [11], amberlyst-15 [12], Et<sub>3</sub>B [13], Pd [14-15]. Recently, N-allylation of amines and O-allylation of phenols have been reported with allyl acetate using Pd Catalyst [16-17]. However, a clean regioselective N-allylation of indoles has rarely been explored due to its weak acidity of the N-H group [18-20]. But many of the reports generally suffer from the disadvantages such as use of expensive catalysts, low yield, longer reaction time and functional intolerance. As its consequence, the challenging task of selective N-allylation welcomes newer methods and catalysts particularly those involve the efficient, inexpensive and environmentally benign catalyst for the allylation of indoles with higher yield.

In recent years, hierarchical nanoporous materials [21-24] have been emerging with significant scientific interest because of its potential application in its multidisciplinary field of study, hydrocarboncracking [25], adsorption/separation [26], drug delivery [27], microelectronics, biomolecular separation and dye sensitized solar cells [28]. However, the catalytic applications of nanoporous materials in fine chemical synthesis are very few in number. In catalysis, the active sites of hierarchical nanoporous materials are often located in the

micropores and mesopores, whereas the macropores favor mass transfer and reduce transport limitations and the micropores enhances the selectivity [29] due to their high surface area and unique pore size [30] and also they having high thermal stability [31].

We have been involved in showing the hierarchically ordered nanoporous material as a versatile catalyst for the organic transformations due to its nature of ease of preparation, handling and separation, environmental benign nature, high selectivity. Herein, we report the selective NH-allylic alkylation of indoles and its derivatives at room temperature in a shorter time.

### 2. Experimental Section

### Synthesis and Characterization of Hierarchical Nanoporous Zeolite (MMZ<sub>Cu</sub><sup>I</sup><sub>Y</sub>):

MMZ<sub>Y</sub> zeolite was synthesized from the commercially available NH<sub>4</sub>-Y zeolite according to the procedure reported by Ryoo *et. al* [21]. A mixture of CuCl and MMZ<sub>Y</sub> was ground by pestle and mortar, it was heated in flowing nitrogen atmosphere at a heating rate of 10°C/min. The ion-exchange of Cu(I) in solid CuCl with H<sup>+</sup> in MMZ<sub>Y</sub> zeolite occured at over 300°C and the maximum ion-exchange rate was reached at 340°C with the consequent release of HCl gas [32-34]. After the preparation was over, the MMZ<sub>Cu</sub><sup>I</sup><sub>Y</sub> was kept under vaccum. The as prepared catalyst was characterized by SEM, TEM, EDAX and powder XRD analysis. Scanning Electron Microscopy (SEM) and EDAX images were taken by using FEI Quanta FEG 200-High Resolution Scanning Electron Microscope, and X–ray diffraction (XRD) patterns were taken with a Bruker D8 advance, Cu K $\alpha$  radiation (40 kV, 30 mA). Transmission Electron Microscopy (TEM) image of MMZ<sub>Cu</sub><sup>I</sup><sub>Y</sub> was obtained using a JEOL JEM-2100 LaB6 instrument equipped with the high-resolution (HRP), style objective-lens pole piece at an acceleration voltage of 200 kV.

# General procedure for the synthesis of N-allyl and N-cinnamyl indole derivatives (3a-l) using $MMZ_{CuY}^{I}$ zeolite:

A 100mg of hierarchical  $MMZ_{CuY}^{I}$  zeolite was taken in a reaction tube contains DMF (3mL) as a solvent and K<sub>2</sub>CO<sub>3</sub> (1mmol) as base. A mixture of indole **1a** (1mmol) and allylbromide **2a** (1.2mmol) were added simultaneously to the reaction tube. The reaction mixture was placed onto a magnetic stirrer for 10 hours at room temperature and the proceedings of the reaction was constantly monitored by TLC carried out on silica plates with iodine and UV light for visualization. After dilution with dichloromethane (15 mL), the mixture was washed with brine solution. The organic layer was separated, dried and concentrated *in vacuo*, and the residue was subjected to column chromatography over silica gel (silica gel 60-120 mesh, hexane 99% and ethyl acetate 1%) to give **3a** as a colourless oil.

### 3. Results and discussion

Our earlier studies [35] particularly the use of Cu<sup>I</sup>Y in Click Chemistry and MMZ<sub>Y</sub> in chemoselective synthesis of benzimidazoles [36], have prompted us to prepare  $MMZ_{Cu}^{I}_{Y}$  and employ as a novel catalyst in the present study. The morphology of the as prepared hierarchical nanoporous  $MMZ_{Cu}^{I}_{Y}$  zeolite was characterized by XRD, SEM and TEM methods. It clearly shows the uniform formation of Cu(I) species in the MMZ<sub>Y</sub> framework of the catalyst with the particle size range of 0.5–1µm. The XRD pattern of the  $MMZ_{Cu}^{I}_{Y}$  are found to be in good agreement with the parent zeolite framework structure. It clearly reveals that there is no change in crystallinity.

The optimization and screening study of reaction was performed by having indole and allylbromide using different materials and the results are summarized in table1.



Fig. 1. (a) SEM, (b) TEM, (c) p-XRD and (d) EDAX spectrum of  $MMZ_{Cu}^{I}_{Y}$  Zeolite.

 $\Pi$ 

### Table 1

Optimization of reaction conditions for the selective N-allylation of indoles<sup>a</sup>

| $ \begin{array}{c}  \\  \\  \\  \\  \\  \\  \\  \\  \\  \\  \\  \\  \\ $ |                      |      |       |                        |  |  |  |
|--|----------------------|------|-------|------------------------|--|--|--|
|  | 1 2                  | 3    | 4     |                        |  |  |  |
| Entry  | Catalyst             | Time | Yield | Yield <sup>b</sup> (%) |  |  |  |
|  |                      |      | (3)   | (4)                    |  |  |  |
| 1.   | CuCl <sub>2</sub>    | 24   |       |                        |  |  |  |
| 2.   | CuCl                 | 24   | 16    | 15 <sup>c</sup>        |  |  |  |
| 3.   | NaY                  | 10   | 18    | 21                     |  |  |  |
| 4.   | Cu(I)Y               | 10   | 69    | 28                     |  |  |  |
| 5  | $MMZ_{Cu}^{I}{}_{Y}$ | 10   | 91    |                        |  |  |  |

<sup>a</sup>Reaction conditions: **1**(1mmol), **2**(1.2 mmol), catalyst(100 mg), DMF(3 mL), base(1mmol), rt, 10h. <sup>b</sup>Isolated Yields.

<sup>c</sup>Trace amount of diallylated product also noted (confirmed by GC-MS).

In the absence of zeolite, there was no significance in selectivity and also in the yield of allylated indole as in the case of  $CuCl_2$  in this reaction (entry 1). In the presence of CuCl alone as a catalyst, only 31% of allylated products were obtained but with no selectivity. In sharp contrast to entries 2 and 3, the use of  $Cu^IY$  affords 68% of N-allylated product however along with the notable amount of C-3 allylated product. The use of Cu(I)-exchanged hierarchically architectured

 $MMZ_Y$  afforded regioselectively an excellent amount of N-allylated product (Table 1, entry 5). To check the functional tolerance of  $MMZ_{Cu}^{I}{}_{Y}$  towards the selective N-allylation, we have also employed the substituted indoles for allylation and the obtained results are summarized in table 2. We have extended our present investigation into the cinnamylation of indoles also, which was actually failure to achieve by the Pd/PPh<sub>3</sub> system [15] and the interesting results are presented in table 2.

### Table 2

Synthesis of N-allyl and N-Cinnamyl indoles using MMZ<sub>Cu</sub><sup>I</sup> Zeolite<sup>a</sup>



| S. No | Substrate      | Allylating agent | Product              | Yield <sup>b</sup> (%) |
|-------|----------------|------------------|----------------------|------------------------|
| 1.    |                | —Br              | (3a)                 | 91                     |
| 2.    | N<br>H         | =Br              | (3b)                 | 89                     |
| 3.    |                | Br               |                      | 93                     |
| 4.    | COOH<br>N<br>H | Br               | (3C)<br>(3C)<br>(3d) | 90                     |
| 5.    | Br             | =\Br             | Br<br>(3e)           | 97                     |
| 6.    | NC             | =\Br             | NC<br>N<br>(3f)      | 94                     |

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<sup>&</sup>lt;sup>a</sup> Reaction conditions: 1(1 mmol), 2(1.2 mmol),  $MMZ_{CuY}^{1}(100 \text{ mg})$ , DMF(3 mL),  $K_2CO_3(1 \text{ mmol})$ , rt, 10h. <sup>b</sup> Isolated Yields.

The present catalytic system shows an excellent tolerance toward the sterically crowded cinnamylation also and gives the N-cinnamylated indole in high yields. In the presence of both indoles bearing electron releasing and electron withdrawing groups, the reaction with allyl bromide/cinnamyl bromide proceeded effectively and yielding regioselectively N-allylated/N-cinnamylated products (82-97%) in higher yields. We have also examined the recycling of the catalyst which afforded the same result even after two time usage.

It is believed that this reported reaction supports and proceeds through the proposed mechanism [18] which involves the addition of a base favours proton abstraction from the heteroatom followed by the catalyst coordination through its Cu(I) sites. The high polar solvent favours the N-allylation, because of dissociation of the N-Cu bond by the stronger solvation of the counter ion, is subsequently attacked by the allylbromide and gives regioselectively N- allylated product in higher yield.

### 4. Conclusions

In summary, we have developed a simple procedure for the clean regioselective N-allylation and N-cinnamylation of indoles by a one pot strategy promoted by an inexpensive, reusable, non-toxic and environmentally benign novel catalytic system  $MMZ_{CuY}^{I}$  zeolite. These reactions encompass a broad range of indole substituents as well as simple and bulkier allylating agents. The other advantages of this procedure are no need of external stabilizing ligand for  $Cu^{I}$  metal ion, use of a simple base, shorter reaction time and excellent regioselectivity with higher yield. Further works are now in progress to explore the catalytic system of  $MMZ_{CuY}^{I}$  for other organic synthesis.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at ...... These data include NMR files of all reported compounds described in this article.

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### **GRAPHICAL ABSTRACT**



Where R = H,  $C_6H_5$ ; R' = H, 2-Me, 3-Me, 5-CN, 5-Br, 3-CH<sub>2</sub>COOH

**Abstract:** Regioselective N-allylation and N-cinnamylation of indoles are achieved using a novel catalyst of  $Cu^{I}$ -exchanged hierarchically architectured nanoporous material (MMZ<sub>Cu</sub><sup>I</sup><sub>Y</sub>). The catalyst was characterized by electron microscopy and X-ray methods. Other advantages like functional tolerance, easy separation and reusability of the catalyst are also highlighted.

Keywords: hierarchical nanoporous zeolite; regioselectivity; N-allylation; N-cinnamylation.

### **Highlights of the Work:**

- > Prepared a new and novel catalyst  $MMZ_{CuY}^{I}$  and achieved a regioselective N-allylation and N-cinnamylation.
- > The catalyst would find extensive applications in organic synthesis filed.
- ➤ No external stabilizing ligand was required for Cu(I).
- ➤ Catalyst was reused for two times and which afforded the same yield.
- ➤ Simple experimental conditions were followed.
- Catalyst was characterized by the instrumental methods like SEM, TEM, XRD, EDAX.
- > Products are well characterized by NMR and MS.

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