Nano-Ordered MCM-41-SO3H as a Heterogeneous and Efficient Catalyst for Synthesis of Bis(indolyl)methanes Under Solvent-Free Conditions

Mohammad G. Dekamin*, Maryam Khayati, Ali Maleki

Pharmaceutical and Biologically-Active Compounds Research Laboratory, Department of Chemistry, Iran University of Science and Technology, Tehran 16846-13114, Iran

E-mail: mdekamin@iust.ac.ir

Abstract

MCM-41-SO_3H was found to be an efficient catalyst for the condensation of Indoles with various carbonyl compounds to afford the corresponding bis(indolyl)methanes in good yields under solvent-free conditions using ball milling at room temperature.

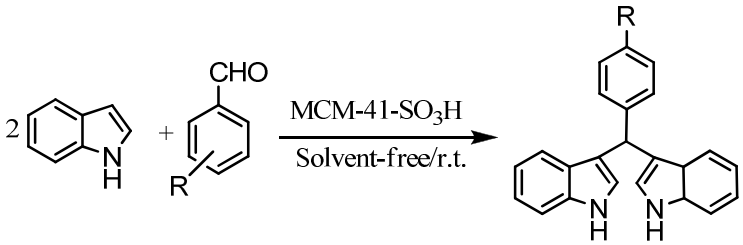
***Keywords*:** MCM-41-SO_3H, Indole, Bis(indolyl)methane, Solvent-free, Ball milling

1. Introduction

Indoles and their derivatives are known to possess various pharmacological and biological properties, including antibacterial, cytotoxic, antioxidative, and insecticidal activities [1]. Bis(indolyl)methanes (BIMs) are important biologically-active compounds that the indole unit forms the basis of them. Many of the most important BIMs were widely isolated from various terrestrial and marine natural sources. These natural products have novel structures and many BIMs are known to demonstrate growth inhibitory activity on many cancers [2]. As BIMs are important compounds, a number of synthetic methods for the preparation of them have been broadly explored with conventional Bronsted and Lewis acids; but these catalytic systems involve harmful wastes and pose environmental problems. On the other hand, there are drawbacks in these catalytic systems, such as the requirement for a large quantity of catalyst, long reaction times, and poor yield of products, drastic conditions for catalyst preparation, or tedious workup procedure that leads to the generation of large amounts of toxic waste [3]. With the rapid development in the field of catalytic and synthetic chemistry, researchers have started to pay more attention to develop eco-friendly and reusable catalysts to avoid or minimize these harmful environmental pollution problems [4].

The use of solid acid catalysts has received considerable attention in organic synthesis due to their environmental compatibility, ease of handling, non-toxic nature and their reusability [5]. Recently, development of mesoporous materials (MCMs) has attracted extensive interest as potential heterogeneous catalysts to replace the homogeneous catalytic systems [6]. A possibility to develop modified mesoporous materials is the modification of their surfaces by covalent anchoring of different acidic functionalities. For example, several types of mesoporous sulfonic acids have been reported in the recent years. However, their applications as catalyst in chemical

transformations has not been thoroughly explored [7]. Along this line, mesoporous MCM-41 ordered silica material with covalently bonded sulfonic acid groups (MCM-41-SO_3H) has been found to be an effective solid acid catalyst for different organic reactions under environmentally friendly conditions [6]. In this work, an efficient and simple method is presented for the synthesis of BIMs *via* the condensation reaction of indole with aldehydes in the presence of a catalytic amount of MCM-41-SO_3H nanocatalyst in good yields at room temperature using ball milling under solvent-free conditions (Scheme 1).



Scheme 1. The synthesis of BIMs *via* condensation of indoles with aldehydes.

2. Experimental

2.1. General

All chemicals and reagents were purchased from Merck and Aldrich and used without further purification. Tetraethylorthosilicate (TEOS) and cetyltrimethylammonium bromide (CTAB) were used as source of silicon and structure directing agent, respectively. MCM-41-SO_3H was synthesized according to the reported procedure and was characterized by FT-IR spectroscopy and scanning electron microscopy (SEM) [7]. Infrared spectra were recorded using a Shimadzu FT-IR 8400S instrument. SEM micrographs were obtained, using a JEOL microscope model JEM 6300 (Japan).

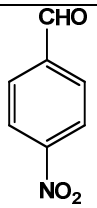
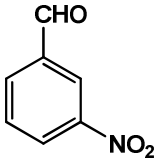
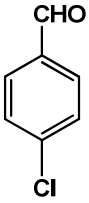
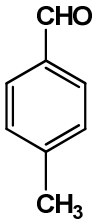
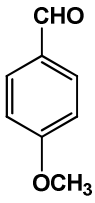
2.2. Typical experimental procedure for the preparation of bis(indolyl)methanes

To a mixture of 4-nitrobenzaldehyde (0.5 mmol) and MCM-41-SO_3H (0.01 g) in ball mill container was added indole (1.0 mmol) and the mixture was ground over a period of 10 min at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was suspended in EtOAc (25 mL), filtered and the catalyst was washed with hot ethyl acetate. Then filtrate was washed with a saturated solution of $NaHCO_3$ (2×20 mL), saturated solution of $NaHSO_3$ (2×20 mL), and water (2×20 mL). The organic layer was separated and dried with Na_2SO_4. Then, the filtrate was then evaporated under reduced pressure to give the crude product. The pure product was crystallized from ethanol/water.

3. Results and Discussion

In a pilot reaction, the reaction of indole with 4-nitrobenzaldehyde in the presence of MCM-41-SO_3H nanocatalyst was studied. Thus, to a mixture of 4-nitrobenzaldehyde and MCM-41-SO_3H was added indole and the resulting mixture was mixed with ball milling at room temperature for 10 min. The completion of the reaction was monitored with TLC. Then, ethyl acetate was added and the reaction mixture filtered. The catalyst was washed with hot ethyl acetate. Then filtrate was washed with a saturated solution of $NaHCO_3$, saturated solution of $NaHSO_3$, and water. The organic layer was separated and dried with Na_2SO_4.The filtrate was then evaporated under reduced pressure to give the product. A similar procedure was then used for different aromatic aldehydes carrying electron withdrawing and or electron releasing substituent (Table 1).

Table 1: Preparation of bis(indolyl)methanes catalyzed by MCM-SO_3H.

Entry	Aldehyde	Time (min)	Yield (%)	Mp (^oC) [Lit.]
1		10	92	225 (217-219) [10]
2		10	90	220 (218-220) [10]
3		10	91	82 (78-80) [8]
4		15	85	97 (97-99) [11]
5		20	80	190 (191-193) [12]

4. Conclusion

In summary, MCM-41-SO_3H is a strong and effective nanocatalyst for the synthesis of bis(indolyl)methanes using ball milling at room temperature. The procedure offers several

advantages, including mild reaction conditions and simple experimental and isolation procedures, which makes it is a useful process for the synthesis of bis(indolyl)methanes.

5. Acknowledgments

We are grateful for the financial support from The Research Council of Iran University of Science and Technology (IUST), Iran. We would also like to acknowledge the support of Iran Nanotechnology Initiative Council (INIC).

6. References

[1] Qu, H.E.; Xiao, C.; Wang, N.; Yu, K.H.; Hu, Q.S.; Liu, L.X. *Molecules* **2011**, *16*, 3855.

[2] Shiri, M.; Zolfigol, M.A.; Kruger, H.G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250.

[3] Rafiee, E.; Zolfagharifar, Z.; Joshaghani, M.; Eavani, S. *Catal. Commun*. **2011**, *41*, 459.

[4] Srinivasa, A.; Varma, P.P.; Hulikal, V.; Mahadevan, K.M. *Monatsh. Chem.* **2008**, *139*, 111.

[5] Shaabani, A.; Soleimani, K.; Bazgir, A. *Synth. Commun.* **2004**, *34,* 3303.

[6] Karmakar, B.; Sinhamahapatra, A.; Panda, A.B.; Banerji, J.; Chowdhury, B. *App. Catal. A: Gen*. **2011,** *392,* 111.

[7] Rostamizadeh, Sh.; Mohammad Amani, A.; Mahdavinia, Gh.H.; Amiri, G.; Sepehrian, H. *Ultrasonics Sonochem.* **2010**, *17*, 306.

[8] Hasaninejad, A.; Zare, A.; Sharghi, H.; Niknam, Kh.; Shekouhy, M. *ARKIVOC, xiv* **2007**, *39*.

[9] Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem*. **2002**, 1184.

[10] Hasaninejad, A.; Parhami, A.; Zare, A.; Khalafi-Nezhad, A.; Nasrolahi Shirazi A.; Moosavi Zare, A. R. *Polish J. Chem.,* **2008,** *82*, 565.

[11] Pore, D.M.; Desai, U.V.; Thopate, T.S.; Wadgaonkar, P.P. *ARKIVOC, xii* **2006**, *75.*

[12] Zhang, Z. H.;.Yin, L.; Wang, Y.M. *Synthesis* **2005,** *12*, 1949.