Mesoporous Molecular Sieve MCM-41 as a Novel and Efficient Catalyst to Synthesis of 2-Substituted Benzimidazoles

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o-Phenylenediamine derivatives readily react with benzoyl chloride derivatives in the presence of MCM-41 as catalyst to yield 2-substituted benzimidazoles in very good yields.

Keywords: 2-Substituted benzimidazoles; MCM-41; Synthesis.

INTRODUCTION

The development of simple, efficient and environmentally benign chemical processes or methodologies for widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis.

The importance of benzimidazole units arises, because they are found in many biologically active compounds.¹ Several publications report benzimidazole-containing compounds showing biological activities such as selective neuropeptide YYI receptor antagonism,² and as 5-lipoxygenase inhibitors for use as novel antiallergic agents,³ factor Xa (FXa) inhibitors,⁴ poly (ADP-ribose) polymerase (PARP) inhibitors⁵ and as human cytomegalovirus (HCMV) inhibitors.⁶ In addition, benzimidazoles are very important intermediates in organic reactions.⁷ Therefore, the preparation of benzimidazoles has gained considerable attention in recent years.⁸⁻¹⁰ 2-Substituted benzimidazoles are widely used in medicinal chemistry because of their diverse biological activity and clinical applications.¹¹ The traditional synthesis of benzimidazoles involves the reaction between a o-phenylenediamine and a carboxylic acid under harsh dehydrating reaction conditions.¹² A number of synthetic methods have been developed in recent years to uncover a variety of new reagents for the synthesis of 2-substituted benzimidazoles under milder conditions by the addition of Lewis acids,¹³ inorganic clays,¹⁴ and mineral acids.¹⁵ Long reaction times for this reaction have been mitigated by the use of microwave heating,^{16,17,18} both with and without polyphosphoric acid.¹⁹

In recent years, great interest of many researchers has been focused on the heterogenizing of homogeneous catalysts.²⁰⁻²³ This is important because while some advantages of homogeneous catalysts such as catalytic activities and selectivities are retained, other properties like easier workup, recyclability and stability of heterogeneous systems will be obtained. Different approaches like encapsulation or immobilization of homogeneous catalysts in solid supports such as faujasite zeolites^{24,25} and covalent grafting of homogeneous catalysts on reactive polymer surfaces²⁶ or inorganic solids^{27,28} have been used. The latter is of great importance especially after the discovery of a new class of mesoporous molecular sieves such as MCM-41 containing reactive silanol groups which offer large pores and great surface area to accommodate the guest molecules. MCM-41 have attracted the attention of many researchers. These materials possess well-defined mesopores the diameters of which can be tailored to the desired value (18-100 Å) by the proper choice of surfactants, auxiliary organics and synthesis parameter.²⁹ Mesoporous silica of the MCM-41 type is an important class of a hexagonal arrangement of cylindrical pores between which an amorphous SiO2 network is interposed.^{30,31} The most interesting feature of MCM-41 is its regular pore system, which consists of a hexagonal array of one-dimensional, hexagonally shaped pores. Other interesting physical properties of MCM-41 include a highly specific surface area up to 1500 m²/g, a specific pore volume up to 1.3 mL/g and a high thermal stability. All the above properties make it suitable for many catalytic applications. Molecular sieves are widely used in acid catalyzed reactions for the production of petrochemicals and fine chemicals. In our attempts to develop new catalyst systems,³² we selected MCM-41 as a new catalyst for the synthesis of 2-substituted benzimidazoles (Scheme I).

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RESULTS AND DISCUSSION

Since the discovery of mesoporous molecular sieves MCM-41 by Mobile^{29,31} in 1992, it has attracted considerable attention for its potential use in catalytic reactions. MCM-41 has a hexagonal array of cylindrical pores, cubic ordered pores and lamellar structure, respectively. The main characteristics of this material are large surface areas and very narrow pore size distributions.³³⁻³⁷ In fact, it has space enough to accommodate the guest molecules and are used in catalytic reactions.^{28,38}

During the course of our studies directed at the development of practical and environmentally friendly procedures for some important transformations, ³² we developed for the first time the applicability of a novel recyclable heterogeneous MCM-41 for efficient, convenient and facile synthesis of 2-substituted benzimidazoles. 2-Substituted benzimidazoles were obtained by the condensation of ophenylenediamine derivatives with various benzoyl chlorides in the presence of MCM-41 as solid acid catalyst in CH₂Cl₂ (Scheme I) in good yields (Table 1). The effect of temperature was studied by carrying out the reactions at different temperatures. The yields of reactions increased as the reaction temperature was raised. From these results, it was decided that refluxing temperature would be the best temperature for all reactions. In each reaction, the yield is a function of the reaction time and the best time for all reactions was completed after 2 h. The reaction proceeds very cleanly under reflux conditions and is free of side products. In the absence of the catalyst, the reaction did not complete even after 24 h.

We used acetyl chloride as a alkyl acid chloride; it is noteworthy to mention that a slight amount of benzo [3,1,5] oxadiazepine derivatives were obtained as by-products in reactions including acetyl chloride. These by-products were detected using ¹H NMR, IR spectroscopy and GC-Mass analysis. Data were in accord with those reported for authentic samples. In the case of benzoyl chloride, these by-products were not observed. It may be due to the steric effect of phenyl groups which prevent the formation of cor-

Table 1. Synthesis of benzimidazole derivatives catalyzed by MCM-41

Entry	R'	R	Time (h)	Product	Yield (%) ^a
1	C4He-	Н	2	3a	95
2	4-Me-C ₆ H ₄ -	Н	2	3b	92
3	CH ₃	Н	2.5	3c	89
4	C_6H_5 -	CH_3	2	3d	93
5	4-Me-C ₆ H ₄ -	CH_3	2	3e	91
6	CH_3	CH_3	2.5	3f	90
7	C ₆ H ₅ -	NO_2	2	3g	90
8	4-Me-C ₆ H ₄ -	NO_2	2	3h	91
9	CH_3	NO_2	2.5	3i	90
10	C ₆ H ₅ -	Cl	2	3j	90
11	4-Me-C ₆ H ₄ -	Cl	2	3k	91
12	CH_3	Cl	2.5	31	89

^a Isolated yields

responding by-products.

We examined the reaction of o-phenylenediamines and benzoyl chloride or acetyl chloride in the presence of MCM-41 in different organic solvents (THF, acetonitrile, ethanol, chloroform, ethyl acetate). The expected products were obtained whose ratios depended on the nature of the solvent and the best yields were obtained in CH₂Cl₂.

In summary, we have developed the use of MCM-41 as an inexpensive, easy to handle, non-corrosive and environmentally benign catalyst for the synthesis of benzimidazole derivatives from *o*-phenylenediamine and benzoyl chlorides. The advantages of the present procedure are using inexpensive and environmentally benign catalyst, relatively short reaction time, simplicity of operation and work-up, and high yields of products which makes it a useful alternative to existing methods.

EXPERIMENTAL

All products are known compounds and were characterized by mp, IR, ¹H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ¹H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard (CDCl₃ solution). IR spectra were recorded from KBr disks on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Preparation of MCM-41

MCM-41 was prepared according to a procedure described previously.³⁹ A typical procedure was as follows: 1.8 g of fumed silica was added to a solution prepared from dissolving 0.6 g of NaOH in 25 mL of water. The resultant mixture was stirred for 2 h, and then 1.9 g of cetyltrimethyl ammonium bromide (CTABr) in 20 mL of water was added to this solution and stirred for one more hour. The resulting reaction mixture which has the molar composition of 1 SiO₂, 7.5 Na₂O, 5.2 CTABr, 2500 H₂O was kept over night and poured into a teflon lined stainless steel autoclave to make crystallization under static conditions at 100 °C. The product was filtered, washed with distilled water, dried at 70 °C and calcined in air at 540 °C for 4 h.

Typical procedure for the synthesis of 2-phenyl benzimidazole

In this condensation reaction, to a stirred solution of o-phenylendiamine (2 mmol) in CH₂Cl₂ (10 mL), benzoyl chloride (2 mmol) in CH₂Cl₂ (5 mL) was added dropwise at 0 °C for 20 min. After about 5 min of stirring at room temperature, MCM-41 (0.1 g) was added. The mixture was refluxed for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. After filtration (removed the catalyst and catalyst was washed with methanol for reuse), the filtrate was washed twice with 5% NaHCO₃ (5 mL) and dried over MgSO₄. The solvent was evaporated under reduced pressure and the crude product was obtained. The resultant solid product was recrystallized from ethanol to give the pure product. Mp 294 °C (290-293 lit⁴⁰); IR (KBr): 1600 (C=N), 3190 (NH) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): 6.9-8.2 (m, 9H, Ar-H), 9.9 (br. s, 1H, N-H), MS: m/z 194 $[M^+].$

All products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples.⁴¹

Reusability of MCM-41

Next, we investigated the reusability and recycling of MCM-41. At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst could be washed with methanol and subjected to a second run of the reaction process. To assure that catalysts were not dissolved in methanol, the catalysts were weighed after filteration and before using and reusing for the next reaction. The results show that these catalysts are not soluble in methanol. In Table 2, the comparison of efficiency of

Entry	Time (h)	Yield (%) ^a
1	2	95
2	2	93
3	2	90
4	2.5	90
5	3	88

Table 2. Reuse of the MCM-41 for synthesis of 3a

^a Isolated yields

MCM-41 in synthesis of 3a after five times is reported. As is shown in Table 1 the first reaction using recovered MCM-41 afforded a similar yield to those obtained in the first run. In the second, third, fourth and fifth runs, the yields were gradually decreased.

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