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Synthesis of Benzoxazoles Catalyzed by MCM-41, a Green and Reusable Catalyst

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Synthesis of Benzoxazoles Catalyzed by MCM-41, a Green and Reusable Catalyst

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Abstract: Benzoxazoles can be rapidly and efficiently synthesized from acyl chloride with 2-aminophenols in one simple step, which provided a practical and efficient method for high-throughput synthesis of this important class of heterocyclic compounds.

Keywords: Benzoxazoles, catalyst, MCM-41, reusable

The benzoxazole scaffold is a useful structural motif for the development of molecules of pharmaceutical or biological interest. Appropriately substituted benzoxazole derivatives have found diverse therapeutic activities including antibiotic,[1] antimicrobial,[2–5] antiviral,[6] topoisomerase I and II inhibitory,[7] and antitumor activities.[8] Hence, the synthesis of benzoxazole derivatives is currently of much importance. Common synthetic routes to benzoxazoles have typically involved coupling of carboxylic acids or their derivatives with 2-aminophenols in the presence of acids at high temperatures.[9] However, some of these methods suffer from one or more of the following drawbacks such as strong acidic conditions, long reaction times, low yields of the products, tedious workup, need for

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excess amounts of reagent, and the use of toxic reagents, catalysts, and/or solvents. Therefore, there is a strong demand for a highly efficient and environmentally benign method for the synthesis of these heterocycles.

Solvent-free reactions obviously reduce pollution and bring down handling costs because of the simplification of experimental procedure and workup technique. These would be especially important during industrial production, and also heterogeneous catalysts make synthetic processes clean, safe, high-yielding, and inexpensive.

Porous materials have been intensively studied with regard to technical applications as catalysts and catalyst supports. According to the International Union of Pure and Applied Chemistry (IUPAC) definition, porous materials are divided into three classes: microporous (pore size <2 nm), mesoporous (2–50 nm), and macroporous (>50 nm) materials.[10] Among the family of microporous materials, the best-known members are zeolites, which have a narrow and uniform micropore size distribution due to their crystallographically defined pore system. In recent years, environmental and economic considerations have raised strong interest in redesigning commercially important processes so that the use of harmful substances and the generation of toxic waste could be avoided. In this respect, there is no doubt that heterogeneous catalysis can play a key role in the development of environmentally benign processes in petroleum chemistry and in the production of chemicals, for instance, by substitution of liquid acid catalysts by solid materials. Zeolites especially have attracted strong attention as such acids but also as base and redox catalysts. However, zeolites present severe limitations when large reactant molecules are involved, especially in liquid-phase systems, as is frequently the case in the synthesis of fine chemicals, because mass transfer limitations are very severe for microporous solids. Attempts to improve the diffusion of reactants to the catalytic sites have so far focused on increasing the zeolite pore sizes,[11] decreasing zeolite crystal size,[12] and providing an additional mesopore system within the microporous crystals.[13,14] An important line of research has focused on the enlargement of the pore sizes into the mesopore range, allowing larger molecules to enter the pore system, be processed there, and leave the pore system again. The first synthesis of an ordered mesoporous material was described in the patent literature in 1969. However, because of a lack of analysis, the remarkable features of this product were not recognized.[15] In 1992, a similar material (M41S family) was obtained by scientists in Mobil Oil Corporation, who discovered the remarkable features of this novel type of silica and opened up a whole field of research.[16] The M41S family has been classified into four main groups, as depicted in Fig. 1. The first one refers to disordered rods, and the three others are well-defined mesostructures: (i) MCM-41, with a hexagonal array of unidirectional and noninterconnecting pores; (ii) MCM-48, with a three-dimensional cubic pore structure; and (iii)

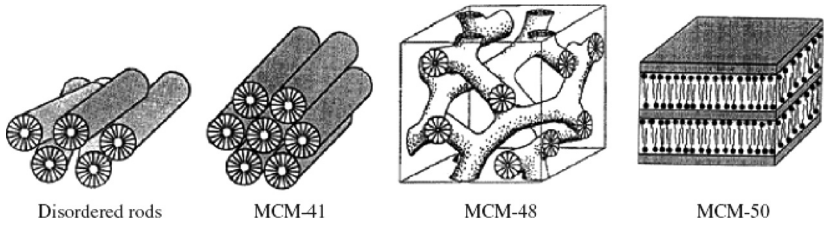


Figure 1. The M41S family structures.

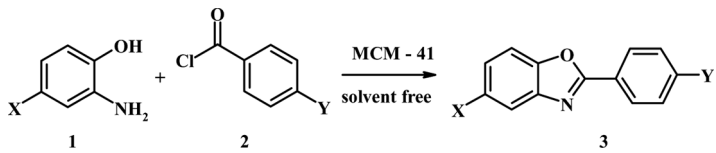
MCM-50, with an unstable lamellar structure. MCM-41 could be viewed as the ultimate model for mesoporous adsorbent material for investigating fundamental features of adsorption, such as the effects of pore size and hysteresis, because of its relatively uniform cylindrical/hexagonal pore channels.[17] MCM-41 was recently reported to be an efficient agent to some reactions such as hydrodesulfurization, hydrodenitrogenation, and mild hydrocracking (MHC)[18] and as an acid catalyst for Friedel–Crafts alkylation of 2,4-di-*tert*-butylphenol (bulky aromatic) with cinnamyl alcohol and for the tetrahydropyranylation of alcohol and phenol.[19,20]

Herein, we report an efficient, convenient, and facile method for the condensation of 2-aminophenols with benzoyl chlorides using MCM-41 as catalyst to obtain the corresponding benzoxazoles (Scheme 1).

RESULTS AND DISCUSSION

At first we studied the synthesis of benzoxazoles from the condensation of 2-aminophenol and benzoyl chloride to optimize the reaction conditions (Table 1).

The optimum yield of the product was obtained when 0.02 g of MCM-41 was used. Among the solvents tested for this reaction (i.e., EtOH, AcOH, CH_3CN, and water), it was found that the best result (short reaction time and maximum yield of the product) was obtained under solvent-free condition, which is also economically and environmentally favorable.



Scheme 1. The condensation reaction of 2-aminophenols with benzoyl chlorides using MCM-41 as catalyst.

Table 1. Optimization of the reaction conditions (30 min)

Entry	Catalyst (g)	Solvent	Yield (%)[a]
1	MCM-41 (0.01)	—	45
2	MCM-41 (0.02)	—	94
3	MCM-41 (0.03)	—	94
4	MCM-41 (0.02)	CH_3CN	45
5	MCM-41 (0.02)	EtOH	50
6	MCM-41 (0.02)	AcOH	55
7	MCM-41 (0.02)	Watet	—

[a]Yields refer to the isolated pure products.

In a typical general experimental procedure, a mixture of 2-aminophenol and benzoyl chloride were heated together in solvent-free condition in the presence of a catalytic amount of MCM-41. To study the generality of this procedure, a series of benzoxazoles were synthesized with similar operation. The results are listed in Table 2.

It is noteworthy that the catalyst is recyclable and could be reused without significant loss of activity. MCM-41 was recovered and reused in the model reaction four times (Table 3).

In conclusion, we developed the use of MCM-41, a mesopore-type catalyst, as an inexpensive, reusable, easy-to-handle, noncorrosive, and environmentally benign catalyst for the synthesis of benzoxazoles from 2-aminophenoles and benzoyl chlorides.

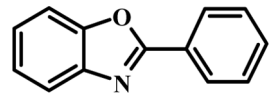
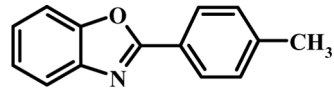
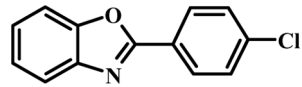
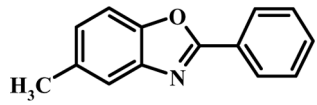
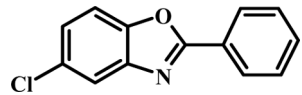
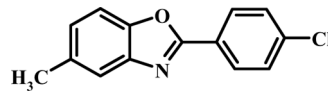
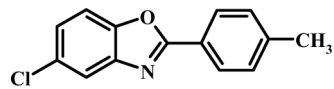
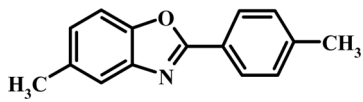
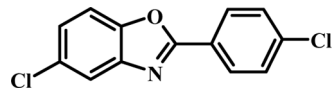
EXPERIMENTAL

Melting points were determined using a 9200-Barnstead Electrothermal apparatus, the accuracy of which was checked using standard compounds of known melting points. Infrared (IR) spectra were recorded on a Fourier transform (FT)–IR Tensor 27 spectrophotometer. Gas chromatography (GC) and GC-Mass spectra were recorded on Aglient apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ solvent on a Bruker instrument at 500 MHz.

Preparation of Benzoxazoles in the Presence of MCM-41: General Procedure

MCM-41 (0.02 g) was added to a mixture of 2-aminophenol (1 mmol) and benzoyl chloride (1 mmol). The mixture was heated and stirred under solvent-free conditions, and the reaction was monitored by thin-layer

Table 2. Synthesis of benzoxazoles catalyzed by MCM-41 in solvent-free condition

Entry	Compound	X	Y	Product	Time (min)	Yield[a]
1	a	H	H		30	94
2	b	H	CH_3		30	94
3	c	H	Cl		25	93
4	d	CH_3	H		35	90
5	e	Cl	H		30	90
6	f	CH_3	Cl		30	88
7	g	Cl	CH_3		35	89
8	h	CH_3	CH_3		35	90
9	i	Cl	Cl		25	94

[a]Yields refer to the isolated pure products.

chromatography (TLC) using EtOAc–hexane (4:1) as eluent. After completion of the reaction, the MCM-41 was separated by simple filtration by diluting it with ethyl acetate. The recovered MCM-41 was reused in

Table 3. Reusability of catalyst in the model reaction (30 min)

Entry	Number of uses	Yield (%)[a]
1	Fresh	94
2	1	94
3	2	90
4	3	87

[a]Yields refer to the isolated pure products.

subsequent reactions. The filterate was concentrated, and the residue was purified by column chromatography over silica gel using EtOAc–hexane (4:1) as eluent to obtain pure benzoxazole derivatives. To establish the generality of the present reaction, several structurally diverse 2-aminophenpols and benzoyl chlorides (Table 2) were subjected to condensation with each other under the catalytic influence of MCM-41 in solvent-free conditions, and benzoxazoles were obtained in high yields. All products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples.

Recycling of the Catalyst

The catalyst could be recycled by evaporating the of solvent from the residue, washing it with diethyl ether, drying it at 130°C for 1 h, and reusing it in another reaction. The recycled catalyst was used for four reactions without appreciable loss in its catalytic activities in the case of the model reaction.

Spectroscopic Data and Melting Points for Compounds in Table 1

2-Phenyl-benzoxazole

Mp 102°C, FT-IR (KBr) ν_{max}: 3060, 2926, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.29, 8.30 (d, 2H), 7.28, 7.39 (m, 4H), 7.56, 7.81 (m, 3H) ppm; MS m/z (relative intensity): 195 (M^+).

2-(4-Methyl-phenyl)-benzoxazole

Mp 112–114°C; FT-IR (KBr) ν_{max}: 3055, 2918, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.09, 8.07 (d, 2H), 7.77 (t, 2H), 7.42, 7.38 (m, 4H), 2.40 (s, 3H) ppm; MS m/z (relative intensity): 209 (M^+).

2-(4-Chloro-phenyl)-benzoxazole

Mp 148–151°C; FT-IR (KBr) ν_{max}: 3056, 2924, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.23, 8.25 (d, 2H), 7.54, 7.56 (d, 2H), 7.81, 7.82 (m, 1H), 7.62, 7.64 (m, 1H), 7.40, 7.42 (m, 2H) ppm; MS m/z (relative intensity): 229 (M^+).

2-Phenyl-5-methyl-benzoxazole

Mp 103–105°C, FT-IR (KBr) ν_{max}: 3055, 2918, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.28, 8.30 (d, 2H), 7.60 (s, 1H), 7.55, 7.57 (m, 3H), 7.49, 7.50 (d, 1H), 2.58 (s, 3H) ppm; MS m/z (relative intensity): 209 (M^+).

2-Phenyl-5-chloro-benzoxazole

Mp 110–113°C, FT-IR (KBr) ν_{max}: 3055, 2918, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.30, 8.32 (d, 2H), 7.62 (s, 1H), 7.55, 7.57 (m, 3H), 7.49, 7.50 (d, 1H), 7.20, 7.21 (d, 1H) ppm; MS m/z (relative intensity): 229 (M^+).

2-(4-Chloro-phenyl)-5-methylbenzoxazole

Mp 148–150°C; FT-IR (KBr) ν_{max}: 3075, 2919, 1618 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.21, 8.23 (d, 2H), 7.59 (s, 1H), 7.53, 7.55 (d, 2H), 7.48, 7.50 (d, 1H), 7.21, 7.22 (d, 1H), 2.53 (s, 3H) ppm; MS m/z (relative intensity): 243 (M^+).

2-(4-Methyl-phenyl)-5-chlorobenzoxazole

Mp 132–135°C, FT-IR (KBr) ν_{max}: 3050, 2924, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.16, 8.18 (d, 2H), 7.77 (d, 1H), 7.52 (d, 1H), 7.36, 7.39 (d, 2H), 7.34 (d, 1H), 2.49 (s, 3H) ppm; MS m/z (relative intensity): 243 (M^+).

2-(4-Methyl-phenyl)-5-methylbenzoxazole

Mp 138–141°C; FT-IR (KBr) ν_{max}: 3024, 2916, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.16, 8.18 (d, 2H), 7.58 (d, 1H), 7.47, 7.48 (m, 3H),

7.36, 7.37 (d, 1H), 7.17, 7.19 (d, 1H), 2.52 (s, 3H), 2.48 (s, 3H) ppm; MS m/z (relative intensity): 223 (M^+).

2-(4-Chloro-phenyl)-5-chlorobenzoxazole

Mp 195–197°C; FT-IR (KBr) ν_{max}: 3061, 2924, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.21, 8.23 (d, 2H), 7.78, 7.79 (d, 1H), 7.55, 7.57 (m, 3H), 7.30 (d, 1H), 7.39, 7.54 (d, 1H) ppm; MS m/z (relative intensity): 263 (M^+).

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