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MCM-41 Mesoporous Silica: Efficient and Reusable Catalyst for the Synthesis of 2,4,5-Trisubstituted Imidazoles Under Solvent-Free Conditions

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A simple, high-yielding synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketone/1,2-hydroxyketone and aldehydes in the presence of NH_4OAc is described. Under solvent-free conditions, aryl and heteroaryl substituted imidazoles are formed in yields ranging from 70 to 90%.

Keywords benzil, benzoin, click reaction, MCM-41, trisubstituted imidazoles

INTRODUCTION

The synthesis, reactions, and biological properties of substituted imidazoles constitute a significant part of modern heterocyclic chemistry. Multisubstituted imidazoles, an important class of pharmaceutical compounds, exhibit a wide spectrum of biological activity.[1] Highly substituted imidazoles like lepidilines[2] exhibit micromolar cytotoxicity against several human cancer cell lines. Trifenagrel[3] is a potent 2,4,5-triarylimidazole that reduces platelet aggregation in several animal species and humans. Substituted imidazoles are substantially used in ionic liquids[4] that have been given a new approach to "green chemistry." The imidazole compounds are also used in photography as photosensitive compounds. Recently, multicomponent reactions (MCRs) have attracted considerable attention since they are performed without the need to isolate any intermediate and save both energy and raw materials and also reduce time.[5] 2,4,5-Trisubstituted imidazoles are generally synthesized by three-component cyclo-condensation of a 1,2-diketone/1,2-hydroxyketone with an aldehyde and ammonium acetate, in a process that comprises the use of microwaves,[6] refluxing in acetic acid,[7] silica sulfuric acid,[8] $NiCl_2{\cdot}6H_2O/Al_2O_3$,[9] $ZrCl_4$,[10] ionic liquids,[11] and CAN.[12] Although there are several papers reporting the synthesis of trisubstituted imidazoles using 1,2-diketones, there are few reports in the literature using α-hydroxyketones as statrting material. Herein we describe the synthesis of trisubstituted imidazoles by the one-pot condensation of benzil, benzoin with a substituted benzaldehyde, and ammonium acetate in the presence of MCM-41 as the catalyst. In the past 10 years a new class of mesoporous silica materials has become available, materials constituted of a two-dimensionally ordered array of cylindrical pores of uniform size disposed parallel to each other and separated by thin walls. The pore diameter is adjustable between 2 and 4 nm in the case of MCM-41 silicas. The silica materials are obtained as a fine powder after removal of the surfactant by calcination. Mesoporous silica materials are promising candidates for catalytic applications. For these applications it is mandatory to understand the properties of the inner surfaces as well as the state of the guest molecules. MCM-41, one member of the M41S family, possesses a regular hexagonal array of uniform pore openings with a broad spectrum of pore diameters between 15 and 100 Å.[13] The mesoporous structure can be controlled by a sophisticated choice of templates (surfactants) and changing reaction parameters (e.g., temperature, compositions). The pores of this novel material are nearly as regular as, yet considerably larger than, those present in crystalline materials such as zeolites, thus offering new opportunities for applications to catalysis. For economic and ecological reasons, organic synthetic chemists face an increasing obligation to optimize their synthetic methods in order to produce the desired products in high yields and selectivities through a safe and environmentally acceptable process. Thus, the challenge was to replace them by solid MCM-41, which is easier to separate from the products, and possesses reusability, high acid strength, and hydrophilic and hydrophobic properties.

In continuation of our ongoing research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds,[14] herein we report a simple, economic, and efficient one-pot method for the synthesis of 2,4,5-triaryl-1*H*-imidazoles from benzoin or benzil, ammonium

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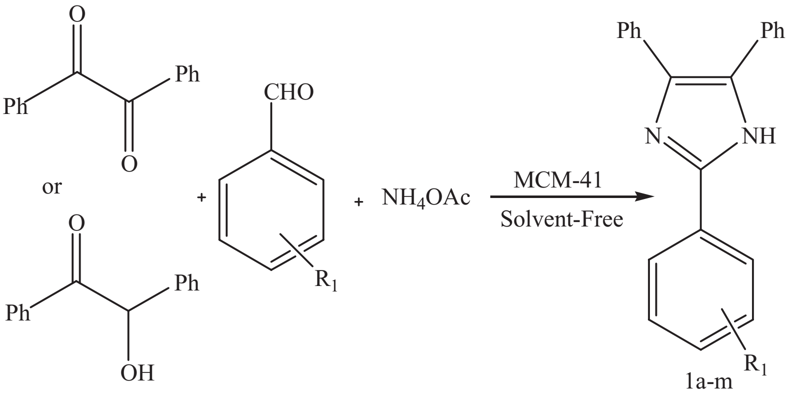


SCH. 1.

acetate, and aromatic aldehydes using MCM-41 as the catalyst under solvent-free conditions (Scheme 1).

EXPERIMENTAL

Materials and Methods

Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ^{1}H-Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AQS AVANCE 300-MHz spectrometer using trimethylsilane (TMS) as an internal standard ($CDCl_3$ solution). Infrared (IR) spectra were recorded using KBr disks on the FT-IR Bruker Tensor 27. All products were well characterized by comparison with authentic samples by thin-layer chromatography (TLC) and spectral and physical data.

General Procedure for the Synthesis of 2,4,5-Triarylimidazoles 1a–m

A mixture of benzil or benzoin (1.0 mmol), aldehyde (1.0 mmol), ammonium acetate (4 mmol), and MCM-41 (0.05 g) was stirred at 80°C for the appropriate time mentioned in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude product was dissolved in ethanol and the catalyst was separated by filtration. The filtrate was evaporated under reduced pressure to remove ethanol,and the resulting product was washed with water, dried with $MgSO_4$, and evaporated to give the crude product. Further purification was achieved by recrystallization from ethanol.

Selected Spectral Data

Compound **1b**: 2-(2-Chloro-phenyl)-4,5-diphenyl-1*H*-imidazole: IR (KBr): 3425, 1600, 1483, 1438, 694 cm^{-1}, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.30–7.48 (m, 9H, ArH), 7.50 (s, 4H, ArH), 8.50–8.52 (dd, 1H, $J = 1.67$ and $J = 8$ Hz, ArH), 10.31 (br, 1H, NH) ppm. MS: *m/z* 330 [M$^+$], 315, 294, 267, 253, 227, 207, 190, 165, 147, 123,104.

Reusability of MCM-41

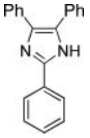
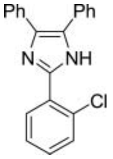
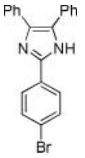
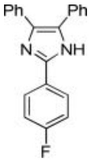
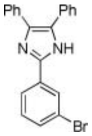
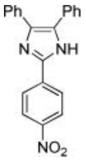
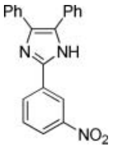
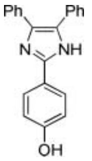
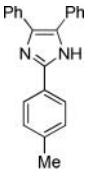
Next, we investigated the reusability of MCM-41. At the end of the reaction, the catalyst could be recovered by a simple filtration, washed with methanol and subjected to a second run of the reaction process. In Table 2, the comparison of efficiency of MCM-41 in synthesis of **1a** after four times is reported. As shown in Table 2, the first reaction using recovered MCM-41afforded a similar yield to that obtained in the first run. In the second, third, and fourth runs, the yields were gradually decreased.

RESULTS AND DISCUSSION

In this study, to evaluate and optimize the catalytic system, we screened different mesoporous compounds for their ability to catalyze the synthesis of 2,4,5-trisubstituted imidazole compounds (Table 3). MCM-41, immobilized Mn(II) complex with oxygen donor ligand (2,2′ bipyridine 1,1′ dioxide (bpdo)) within nanoreactors of MCM-41,[15] Al-MCM-41,[16] $[Zn(bpdo)_2Cl_2]$/MCM-41, $[Cu(bpdo)_2.2H_2O]^{+2}$/MCM-41, and $[Zn(bpdo)_2{\cdot}2H_2O]^{+2}$/Na-montmorillonite-KSF catalysts were examined in the present study. In the case of supported reagents the presence of complex in the channels leads to a decrease in the surface area and the silanol groups. As shown in Table 3, these catalysts afforded the desired product but only in moderate yields (Table 3, entries 1, 2, 3, 4, and 5). Interestingly, it was found that MCM-41 could efficiently catalyze this reaction to affored the desired products in good yields in a relatively short time. It proved to be an efficient catalyst and gave exclusively 2,4,5-triphenylimidazole **1a** in 90% yield in 15 min under solvent-free conditions (Table 3, entry 6).

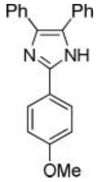
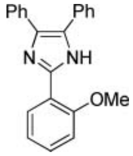
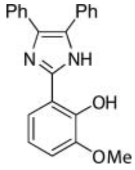
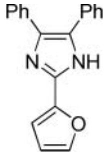
The results obtained from MCM-41 catalyzed synthesis of trisubstituted imidazoles are given in Table 1. These results were obtained by stirring a mixture of aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (4 mmol), and MCM-41 (0.05 g) under solvent-free conditions for 15 min. After completion of the reaction, the mixture was cooled to room temperature. The crude product from the reaction mixture was dissolved in ethanol and the catalyst was separated by filtration. After evaporating the

TABLE 1
MCM-41 catalyzed synthesis of 2,4,5-trisubstituted imidazoles

Ref.	(°C) (Lit)	Mp Found	(%) Benzoin	Yield Benzil	(Min) Benzoin	Time Benzil		Products	R_1	Entry
17	267–269	269–270	85	90	35	15	1a		H	1
17	190–191	189–190	75	80	35	15	1b		2-Cl	2
18	188–189	190–193	80	85	35	15	1c		4-Br	3
17	232–233	229–231	85	88	35	15	1d		4-F	4
19	302–303	302–303	78	85	35	15	1e		3-Br	5
17	199–201	197–198	88	90	35	15	1f		4-NO_2	6
17	300	298–303	80	86	35	15	1g		3-NO_2	7
17	232–233	233–235	75	85	35	15	1h		4-OH	8
17	233	230	80	85	35	15	1i		4-Me	9

(Continued on next page)

TABLE 1
MCM-41 catalyzed synthesis of 2,4,5-trisubstituted imidazoles *(Continued)*

Ref.	(°C) (Lit)	Mp Found	(%) Benzoin	Yield Benzil	(Min) Benzoin	Time Benzil		Products	R_1	Entry
20	202–203	203–204	80	88	35	15	1j		4-OMe	10
17	210–211	210–212	75	80	35	15	1k		2-OMe	11
11	170	168–170	70	75	35	15	1l		2-OH-3-OMe	12
10	185–187	189–191	70	70	35	15	1m		Furfural	13

[a] The yields refer to isolated products

solvent, pure product was obtained. It should be mentioned that the desired products could be easily separated in this condition. MCM-41 is not soluble in ethanol at room temperature but the products are. While the mixture cooled to room temperature the products appeared from solution and could be separated by a simple filtration. Under the same conditions, this approach can be repeated for synthesis of these imidazoles when the benzoin was used instead of benzil as a starting material (Scheme 1). Thus, benzoin effectively participated in the condensation with aldehyde and ammonium acetate in the presence of MCM-41 to give corresponding trisubstituted imidazoles but the yields were found to be lower than for benzil (70–85%). The reaction profile is very clean and no side products are formed. Aldehydes bearing either electron-withdrawing or electron-donating groups perform equally well in the reaction. Steric effects did not influence the yield significantly; for example, in the reaction of *p*-methoxy (Table 1, entry 10) and *o*-methoxy (Table 1, entry 11) benzaldehyde, the corresponding condensation

TABLE 2
Reuseability of the MCM-41 for synthesis 2,4,5-triphenylimidazole **1a.**

Entry	Time (min)	Yield[a](%)
1	15	80
2	30	75
3	40	60
4	50	55

[a] Isolated yield

TABLE 3
Synthesis of 2,4,5-triphenylimidazole **1a** using in the different catalysts

Entry	Catalyst (0.05 g)	Time (min)	Yield[a] (%)
1	$[Mn(bpdo)_2Cl_2]$/MCM-41	30	70
2	$[Cu(bpdo)_2.2H_2O]^{+2}$/MCM-41	20	65
3	$[Zn(bpdo)_2.Cl_2]$/MCM-41	25	65
4	$[Zn(bpdo)_2.2H_2O]^{+2}$/Na-montmorillonite-KSF	20	30
5	Al-MCM-41	20	75
6	MCM-41	15	90

[a] The yields refer to isolated products

products were obtained in 88% and 80% yields, respectively. Additionally, heterocyclic aldehyde (Table 1, entry 13) delivers the corresponding imidazoles in high yield. All the synthesized imidazoles have been characterized on the basis of elemental and spectral studies.

The substitution of traditional homogeneous catalysts for heterogeneous ones could form a more environmentally friendly substitute in catalyzed organic reactions. Such catalysts offer many advantages compared to their homogeneous counter parts: no need for solvents or the use of less toxic ones (e.g., hydrocarbons), milder reaction conditions, easier separation of the catalyst from the reaction mixture by filtration, and its possible regeneration and reuse, reducing the creation of waste and thus harm to the environment.

CONCLUSION

In summary, this article describes a convenient and efficient process for the synthesis of trisubstituted imidazoles through the three-components coupling of benzil or benzoin, aldehydes, and ammonium acetate using MCM-41 as a solid support. This methodology offers very attractive features such as reduced reaction times, higher yields, and economic viability of the catalyst, when compared with the conventional method as well as with other catalysts, and will have wide scope in organic synthesis. The simple procedure combined with easy of recovery and reuse of this catalyst makes this method economic, benign, and a waste-free chemical process for the synthesis of trisubstituted imidazoles. The catalyst can be prepared easily with readily available inexpensive reagents, and is heterogeneous and nonhazardous. We believe that this procedure is convenient, economic, and a user-friendly process for the synthesis of trisubstituted imidazoles of biological and medicinal importance. Since the reaction proceeds relatively rapidly and selectively under mild condition to covalently link components, it can be considered a click reaction.

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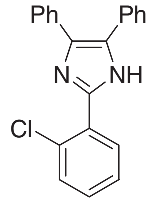
APPENDIX

^{1}HNMR (500 MHz, $CDCl_3$): $\delta = 7.30$–7.48 (m, 9H, Ar), 7.50(s, 4H, Ar), 8.50–8.52(d.d, 1H, J = 1.67, J = 8 Hz, Ar), 10.31 (s, br, 1H, NH) ppm. FTIR (KBr, cm^{-1}, υ): 3425, 1600, 1483, 1438.694. MS: m/z 330 [M$^+$], 315, 294,267, 253, 227, 207, 190, 165, 147, 123,104, 89.



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