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Silica-based sulfonic acid (MCM-41-SO_3H): a practical and efficient catalyst for the synthesis of highly substituted quinolines under solvent-free conditions at ambient temperature

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In this work, a variety of highly substituted quinolines were readily synthesized via Friedlander annulation using Brönsted acid silica-based sulfonic acid as a modified catalyst under solvent-free conditions at room temperature. This efficient procedure has the advantages of giving the target compounds in high yields, short reaction times, simple workup procedure, reusability of the catalyst, and environmentally benign conditions.

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1. Introduction

Recently, due to the economical and environmental advantages of recoverable and reuseable catalysts, a general trend of science and technology is transformation of successful homogeneous catalysts into heterogeneous catalytic systems. A general methodology allowing an efficient homogeneous catalyst recovery and reuse is its immobilization on an insoluble solid support. The catalytically active species are anchored covalently to the support to obtaion Brönsted and Lewis acids such as silica-based nanocatalysts. Therefore, the application of them as heterogeneous catalysts in organic transformations is a very important field of pioneers researches in the world to avoid wastes as well as improving the greenness of the processes[1].

Due to diverse biological activities, practical synthesis of fused heterocyclic compounds is of considerable interest in the fields of organic and pharmaceutical chemistry[2]. Quinoline-based

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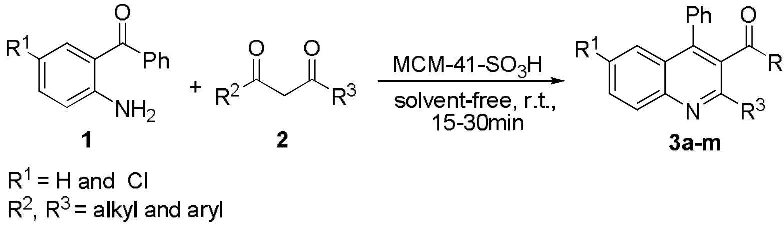
heterocyclic compounds are most widely used as antimicrobial, anticancer, antioxidant, anti-inflammatory, antihypertensive, and tyrosine kinase inhibitory agents[3-6].

Several methods have been reported for the synthesis of quinolines, such as Dobner[7], Skraup[8], Pfitzinger and Friedlander[9,10]. But, among them, Friedlander reaction is the most simple and straightforward method. Friedlander reaction includes the condensation of 2-aryl ketones and carbonyl derivatives with an activated α-methylene group followed by cyclodehydration. This reaction is catalyzed by both acids and bases. Reports showed that acid catalysts are more effective than base catalysts for this reaction. There has been some development for the synthesis of quinolines derivatives using acid catalysts such as *p*-toluenesulfonic acid[11], hydrochloric acid[12,13], $CeCl_3.7H_2O$[14], $SnCl_2$[15], sulfuric acid[16], silica sulfuric acid[17], triflouroacetic acid[18] and supported protic ionic liquid[19]. But, many of these procedures have been highlight led to suffer from various problems such as low yields, harsh reaction conditions, difficulties in workup, expensive reagents, long reaction times, and the use of toxic solvents. As a result, discovering and introducing of new milder and easier modified method for the synthesis of quinolines by using efficient and recyclable catalyst is of prime importance.

In view of the importance of high surface mesoporous and reusable catalysts in organic synthesis, and in continunig of our research in organic transformations[20], in this work, we wish to report a facile method for the synthesis of substituted quinolines **3a-m** by condensation of 2-aminoaryl ketones **1** and active methylene carbonyl compounds **2** in the presence of MCM-41-SO_3H in very short reaction times and high yields under solvent-free conditions at room temperature (Scheme 1).



Scheme 1. Synthesis of substituted quinolines **3a-m** in the presence of MCM-41-SO_3H.

2. Results and discussion

Initially, to optimize the reaction conditions, the condensation of 2-aminobenzophenone (**1a**) with ethylacetoacetate (**2a**), as a model reaction, was carried out for the synthesis of ethyl 4-phenylquinoline-3-carboxylate (**3a**) in the presence of a catalytic amount of MCM-41-SO_3H at room temperature. Then, several test reactions were performed and the effect of solvents and loading of the catalyst were studied. The results showed that, among the various screened reaction mediums, the reaction was faster under solvent-free conditions and higher yield was obtained (Table 1).

Table 1. Effect of solvent on the model reaction in the presence of a catalytic amount of MCM-41-SO_3H at room temperature

Entry	Solvent	Time (min)	Yield (%)[a]
1	EtOH	100	84
2	CH_2Cl_2	150	58
3	toluene	120	68
4	CH_3CN	130	62
5	1,2-dichloroethane	145	52
6	EtOAc	115	71
7	solvent-free	15	93

[a]Isolated yield

The optimization results show that the reaction in the presence of MCM-41-SO_3H was preceded in short time and with high yield at room temperature. This study established that 15 mg of catalyst was equally efficient to perform the reaction for the synthesis of quinolines. Higher catalyst loadings did not improve the reaction yield (Fig. 1). Thus, solvent-free, room temperature and 15 mg of MCM-41-SO_3H are optimal conditions.

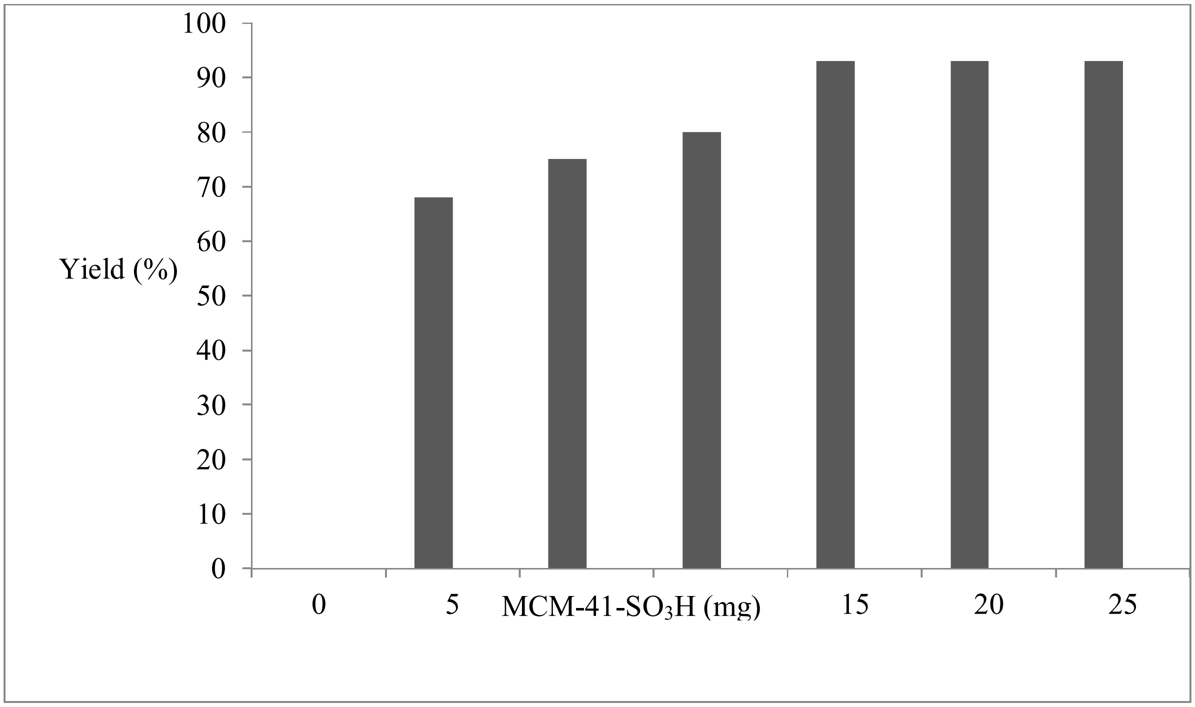


Fig. 1. The effect of the catalyst amount on the reaction yields

Furthermore, to show the superiority in efficiency of MCM-41-SO_3H, it was compared with other heterogeneous or homogeneous catalytic systems under the same or similar reaction conditions (Table 2). The results obtained in this study confirmed the superiority of the present catalyst in terms of its amount, yields, reaction times and temperature.

Table 2. The comparison of the catalytic activity of MCM-41-SO_3H with various catalysts applied in quinolines synthesis

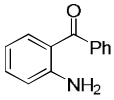
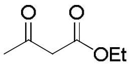
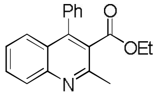
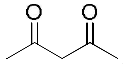
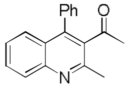
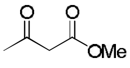
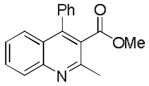
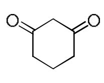
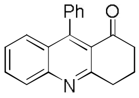
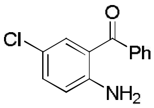
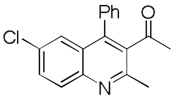
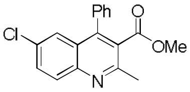
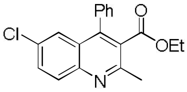
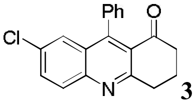
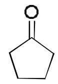
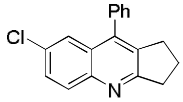
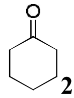
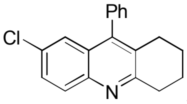
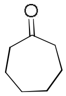
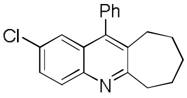
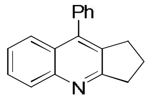
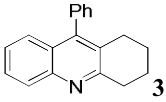
Entry	Catalyst	Reaction conditions	Time (min)	Yield (%) [Lit.]
1	CF_3COOH	solvent-free, 100°C	8	92 [18]
2	silica sulfuric acid	solvent-free, 100°C	55	87 [17]
3	$CeCl_3.7H_20$	CH_3CN, r.t.	30	95 [14]
4	Al-SBA-15	toluene, 100°C	120	62 [21]
5	nano-Al_2O_3	$CHCl_3$, reflux	180	98 [22]
6	(BSPY)HSO_4/MCM-41	solvent-free, 100°C	70	93 [19]
7	MCM-41-SO_3H	solvent-free, r.t.	15	93 [present work]

* With respect to the *o*-amino aryl ketone

In order to evaluate the scope and limitations of this acid-catalyzed process, we have extended it to various cyclic and acyclic β-dicarbonyl compounds, and cyclic ketones such as cyclopentanone, cyclohexanone and cycloheptanone. As indicated in Table 3, the reaction proceeds efficiently with various kinds of β-dicarbonyl compounds and cyclic ketones at room temperature. After separation of catalyst, the pure solid products **3a-m** were obtained by re-crystallization from EtOH and H_2O.

Another important advantage of this protocol is recyclability of MCM-41-SO_3H. As indicated in Table 3 (Entry 1), the catalyst could be recovered and reused in subsequent reactions for several times without considerable loss of catalytic activity, under the same reaction conditions using fresh starting materials. Therefore, this process could be interesting for industrial large-scale synthesis of highly substituted quinolines.

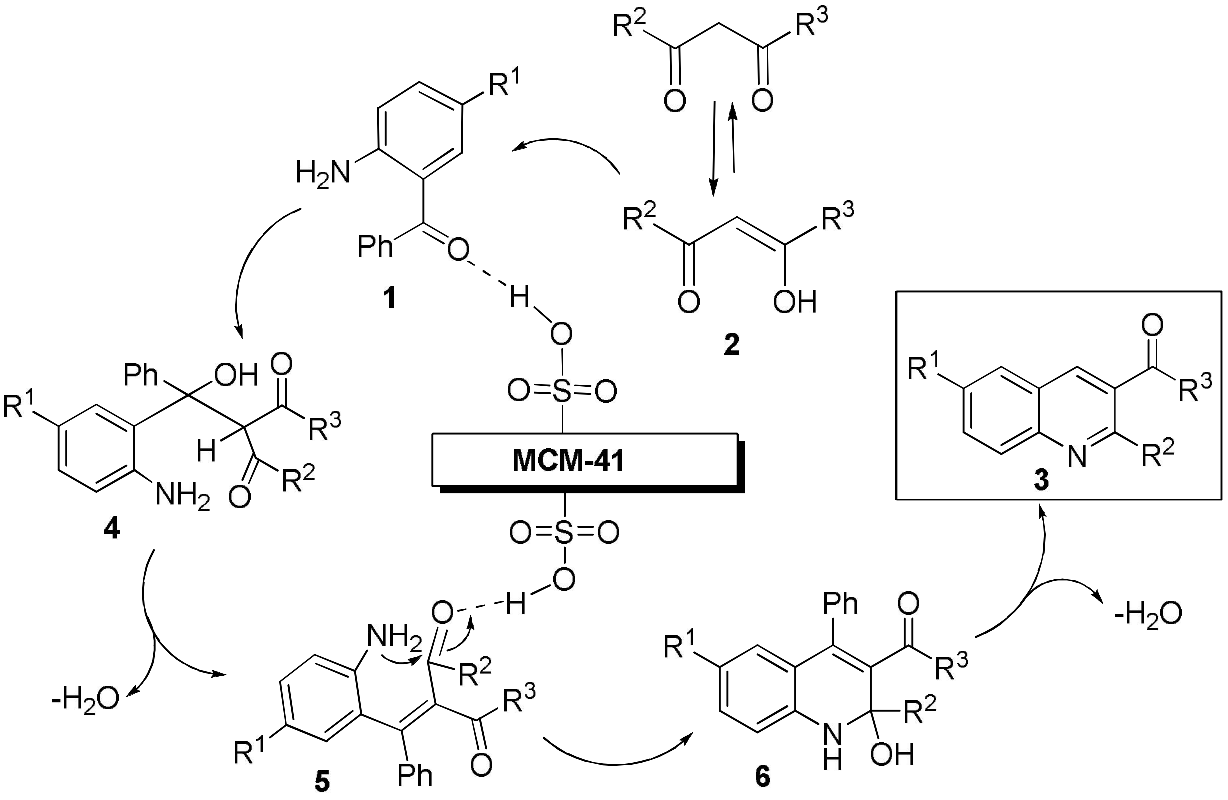
Table 3. Synthesis of substituted quinolines **3a-m** in the presence of MCM-41-SO_3H under solvent-free conditions at room temperature

Entry	1	2	Product	Time (min)	Yield (%)[a]	Mp (ºC)	
						Found	Reported
1	 **1a**	 **2a**	 **3a**	15	93[b]	98-100	100-101[26]
2	**1a**	 **2b**	 **3b**	15	92	112-114	112-115[18]
3	**1a**	 **2c**	 **3c**	15	90	130-132	131-133[25]
4	**1a**	 **2d**	 **3d**	15	96	152-153	151-153[23]
5	 **1b**	**2b**	 **3e**	15	91	149-151	154[25]
6	**1b**	**2c**	 **3f**	15	94	132-134	133-135[24b]
7	**1b**	**2a**	 **3g**	20	91	101-103	102-105[25]
8	**1b**	**2d**	 **3h**	15	94	186-188	185-189[18]
9	**1b**	 **2e**	 **3i**	25	72	105-108	106-108[24b]
10	**1b**	 **2f**	 **3j**	30	66	160-163	162-164[17]
11	**1b**	 **2g**	 **3k**	25	94	192-195	193-195[13]
12	**1a**	**2e**	 **3l**	20	67	137-140	138-141[25]
13	**1a**	**2f**	 **3m**	30	61	159-161	162-164[25]

[a] Isolated yield.

[b] Yields of the subsequent runs by using the same recovered catalyst were 91, 90, 82, 80 and 75, respectively.

The possible mechanism for the reaction was proposed in Scheme 2. MCM-41-SO_3H as a protic acid catalyst, activates the carbonyl group of 2-aminobenzophenone **1**[24]. Then, nucleophilic attack of enolate form of **2** to carbonyl group of **1** results in the information of intermediate **4**. After dehydration of **4**, compound **5** was formed. Then, an intermolecular nucleophilic attack of NH_2 group to carbonyl, and the second elimination of H_2O molecule from intermediate **6**, cyclization was occurred and final products **3a-m** were prepared.



Scheme 2. Possible mechanism for the synthesis of **3a-m**

3. Conclusion

In summary, we have described a practical and convenient procedure for the synthesis of highly substituted quinolines *via* Friedlander reaction with broad substrate scope, by condensation of 2-aminoarylketones with α-methylene carbonyl compounds in the presence of MCM-41-SO_3H as a modified catalyst at room temperature under solvent-free conditions. The simplicity of operation, green experimental procedure, mild reaction conditions, short reaction times, reusability of the catalyst and the environmentally benign nature of the reaction allows easy application to a wide range of substrates.

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4. Experimental

Materials and Methods

All solvents, chemicals and reagents were purchased from Merck, Fluka and Sigma-Aldrich chemical companies. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mesoporous MCM-41 and MCM-41-SO_3H catalysts were prepared according to the literature procedures[27-29].

All of the products were known and identified by comparison with those authentic samples.

General procedure for the synthesis of quinolines ***3a-m***

A mixture of 2-aminobenzophenone (**1**) (1 mmol), ketone or β-diketone (**2**) (1 mmol) and MCM-41-SO_3H (15 mg) was stirred under solvent-free conditions at room temperature. After completion of the reaction as monitored by TLC, hot EtOH was added to reaction mixture and the catalyst was separated by filtration. Pure solid products were obtained by re-crystallization from EtOH and H_2O.

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