Fe/Al-MCM-41: Quinoxaline 계 화합물의 효율적인 합성

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(접수 2010. 5. 12; 수정 2010. 8. 20; 게재확정 2010. 12. 22)

Fe/Al-MCM-41: An Efficient and Reusable Catalyst for the Synthesis of Quinoxaline Derivatives

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(Received May 12, 2010; Revised August 20, 2010; Accepted December 22, 2010)

요 약. Fe/Al-MCM-41을 촉매로 사용하여, 1,2-diamines과 1,2-dicarbonyl 화합물을 축합반응을 통하여 quinoxaline 계 화합물을 좋은 수율로 합성하였다.

주제어: Quinoxaline, 1,2-디케톤, *o*-페닐렌디아민, Fe/Al-MCM-41

ABSTRACT. Fe/Al-MCM-41was found to be an effective catalyst for the synthesis of quinoxaline derivatives from the condensation of the 1,2-diamines and 1,2-dicarbonyl compounds in good yields. The catalyst is recyclable and reusable.

**Keywords:** Quinoxaline, 1,2-Diketones, *o*-phenylenediamines, Fe/Al-MCM-41

INTRODUCTION

Quinoxalines are important heterocycles in medicinal chemistry.[1] Quinoxalines display a broad spectrum of biological activity[2] which has made them privileged structures in combinatorial drug discovery libraries.[3] They have also found applications as dyes,[4a] efficient electroluminescent materials,[4b] organic semiconductors,[4c] dehydroannulenes,[4d] cavitands[4e] and chemically controllable switches.[4f] They have been reported for their applications in dyes,[5] pharmaceuticals,[6] and have also been used as building blocks for the synthesis of organic semiconductors.[7] Quinoxaline ring is a part of various antibiotics such as Echinomycin, Levomycin and Actinoleutin[15] that are known to inhibit growth of gram positive bacteria and are active against various transplantable tumors.[8] Despite remarkable efforts made in the last decade, the development of an effective method for the synthesis of quinoxaline ring is still an important challenge. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines.[9-12] Most common method is the condensation of aromatic 1,2-diamine with 1,2-dicarbonyl compound in refluxing ethanol or acetic acid.[13] However, many improved methods have been reported for the synthesis of quinoxalines using catalytic amounts of various metal precursors such as Pd(OAc)$_2$, RuCl$_2$-(PPh$_3$)$_3$-TEMPO, MnO$_2$, acids and zeolites.[14] In addition, microwave,[15] solid phase synthesis,[16] bicatalyzed (bismuth and copper) oxidative coupling of peroxides and ene-1,2-diamines[17] were also reported. Very recently, molecular iodine was used as catalyst for the synthesis of quinoxaline derivatives by Shivaji *et al*.[18a] in acetonitrile medium and by Rajesh *et al*.[18b] in dimethyl sulfoxide medium.

Many of these methods suffer from one or more limitations such as harsh conditions, low yields, long reaction times, critical product isolation procedures and co-occurrence of several side products. The main disadvantage of the existing methods is that the catalyst cannot be recovered and reused. Hence, there is still a need to develop improved methods for the synthesis of quinoxaline derivatives paying attention to avoid toxic reagents, economic viability and operational simplicity. In connection with our recent interests aimed at the development of efficient protocols for the preparation of biological active heterocycles,[19] we herein report an efficient method for the synthesis of quinoxaline derivatives from the condensation of the 1,2-diamines and 1,2-dicarbonyl compounds in good yields (*Scheme* 1).

Since the discovery of mesoporous molecular sieves MCM-41 by Mobile[20] in 1992, it has attracted consider-
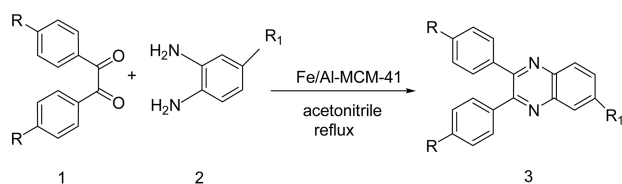
Scheme **1.**

able attention for its potential use in catalytic reactions. The main characteristics of this material is large surface areas and very narrow pore size distributions.[21,22] In fact, it has a space enough to accommodate the guest molecules that are used in catalytic reactions.[23,24] They have attracted the attention of many researchers. Molecular sieves are widely used in acid catalyzed reactions for the production of petrochemicals and fine chemicals. The incorporation of trivalent atoms (Al, Fe) into the walls of MCM-41 creates Brønsted acid sites and allows the preparation of materials with various acidity, which possess different catalytic and adsorptive properties.[25,26] Iron-loaded MCM-41

materials are remarkable for their molecular and electronic diversity and have quite significance in many areas *e.g.* catalysis, medicine, material science *etc*. These iron-loaded MCM-41 materials have received much attention because of their redox properties and unusual activity in organic reactions,[27,28] which shows higher acidity compared to conventional mineral acids,[29] and Lewis acids.[30] The use of iron-loaded mesoporous materials as catalyst can also eliminate the hurdles like pore size constraint, recyclability, and thermal and hydrothermal stability posed by other support materials. In our attempts to develop new catalyst systems, we are selected Fe/Al-MCM-41as a new catalyst for the synthesis of quinoxaline derivatives.

RESULT AND DISCUSSION

In a typical procedure, *o*-phenylenediamine (1 mmol) and benzil (1 mmol) in the presence of a catalytic amount of Fe/Al-MCM-41 in CH_3CN at reflux temperature for 10

Table **1.** Synthesis of quinoxalines using Fe/Al-MCM-41under refluxing condition

Entry	R	R^1	Product	Yield(%)^a	Mp (°C) Observed	Mp (°C) Reported
1	H	H	**3a**	96	128-130	128-129[31]
2	H	CH$_3$	**3b**	97	118-119	117-118[31]
3	H	NO$_2$	**3c**	93	193-195	193-194[31]
4	OCH$_3$	H	**3d**	93	152-153	151-152[31]
5	OCH$_3$	NO$_2$	**3e**	94	193-194	192-194[31]
6	F	NO$_2$	**3f**	94	176-177	174-176[31]

^{a}Yields refer to isolated products.

min afforded the desired quinoxaline (**3a**) in 96% yield (Entry 1, *Table* 1).

In order to show the generality and scope of this new protocol, we used various 1,2-diamine and 1,2-dicarbonyl compounds in the presence of Fe/Al-MCM-41, and the results are summarized in *Table* 1. Most of the reactions proceeded very cleanly at reflux temperature and no undesirable side-reactions were observed. The variations in the yields were very little and both substituted aromatic diamines such as 4-nitro and 4-methyl gave the condensed products in excellent yields with substituted 1,2-diketones.

We performed the effect of various solvents on the synthesis of **3a**. This reaction was carried out in various solvents such as CH_3CN, Ethanol, CH_2Cl_2, chloroform, and DMSO, and the best solvent was CH_3CN in terms of yield and time, as shown in *Table* 2.

We found that the reaction was slow in the absence of catalyst to provide the products in moderate yields after long reaction times. We also compared synthesis of uinoxalines over bimetallic (Fe and Al) substituted MCM-41 in comparison to Al-MCM-41 and MCM-41 as shown in *Table* 2. It is obvious that the best yield was achieved with Fe/Al-MCM-41.

Reusability of Fe/Al-MCM-41

Next, we investigated the reusability and recycling of Fe/Al-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

***Table* 3.** Reuse of the Fe/Al-MCM-41 for synthesis of **3a**

Yield (%)[a]	Time(min)	Entry
96	10	First run
94	10	Second run
92	10	Third run
89	10	Fourth run
88	10	Fifth run

[a]Isolated yields

did not dissolve in methanol, the catalysts were weighed after filtration and drying, and it turned out that the catalysts are not soluble in methanol. In *Table* 3, efficiency of Fe/Al-MCM-41 in synthesis of **3a** for the five runs is reported. As shown in *Table* 3, the first reaction using recovered Fe/Al-MCM-41 afforded similar yield to those obtained in the first run. In the second, third, fourth and fifth runs, the yield were gradually decreased.

In order to show the merit of the present work in comparison with some reported protocols, we compared the

***Table* 4.** Comparison the results of the synthesis of (**3a**) using different catalysts

Entry	Catalyst	Time (min)	Yield (%)	References
1	polyaniline-sulfate salt	20	95	[32]
2	I_2	35	95	[33]
3	[TMPSA] HSO_4	15	90	[34]
4	Zn[(L)proline]	10	95	[35]
5	$CuSO_4.5H_2O$	15	96	[36]
6	Mont K-10	150	100	[37]
7	Fe/Al-MCM-41	10	97	This work

[a]Isolated yields.

***Table* 2.** Synthesis of **3a** with Fe/Al-MCM-41 in the presence of different solvent via various Mesoporous Materials

Entry	Solvent	Catalyst	Temperature	Time(h)	Yield(%)[a]
1	CH_3CN	MCM-41	reflux	50	96
2	CH_3CN	Al-MCM-41	reflux	15	95
3	CH_3CN	Fe/Al-MCM-41	reflux	10	97
4	Ethanol	MCM-41	reflux	60	91
5	Ethanol	Al-MCM-41	reflux	30	92
6	Ethanol	Fe/Al-MCM-41	reflux	20	93
7	CH_2Cl_2	MCM-41	reflux	80	93
8	CH_2Cl_2	Al-MCM-41	reflux	40	90
9	CH_2Cl_2	Fe/Al-MCM-41	reflux	30	90
10	chloroform	MCM-41	reflux	90	91
11	chloroform	Al-MCM-41	reflux	50	90
12	chloroform	Fe/Al-MCM-41	reflux	40	91
13	DMSO	MCM-41	reflux	60	90
14	DMSO	Al-MCM-41	reflux	30	91
15	DMSO	Fe/Al-MCM-41	reflux	20	92

[a]Isolated products.

results of the synthesis of **3a** (entry1 in *Table* 1) in the presence of several catalysts with respect to the reaction times (*Table* 4). The best condition was obtained in the presence of Fe/Al-MCM-41.

EXPERIMENTAL

All products are known compounds and were characterized by mp, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk 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 quinoxaline derivatives: General procedure

To a mixture of an appropriate *o*-phenylenediamine (1mmol) and a 1,2-dicarbonyl compound (1 mmol) in CH_3CN (5 mL) a catalytic amount of MCM-41 (0.1 g) was added and the mixture was heated in oil bath for 10 min. The progress of the reaction was monitored by TLC. After completion of the reaction, CH_3CN was removed under reduced pressure then diethylether was added to the solidified mixture in order to separation of catalyst from the mixture since the catalyst is not soluble in organic solvent. The residue was then diluted with 5% $NaHCO_3$ (5 mL) and the product was extracted with diethyl ether (2×5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the pure product was obtained without any further purification.

Physical and spectral data of the selected products

2,3-diphenylquinoxaline (3a): mp=128-130 °C (Lit. 128-129 °C)[39]; ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm): 8.17 (dd, J=3.43, 6.30 Hz, 2H), 7.65 (dd, J=3.43, 6.30 Hz, 2H), 7.44 (m, 4H), 7.29 (m, 6H); IR (KBr) ν_{max} (cm^{-1}): 3050, 1549, 1350, 768, 730.

6-Methyl-2,3-diphenylquinoxaline (3b): mp=118-119 °C (Lit. 117-118 °C)[39]; ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm): 8.09 (d, J=8.55 Hz, 1H), 7.85 (s, 1H), 7.57 (dd, J=1.72, 8.56 Hz, 1H), 7.41 (m, 4H), 7.22 (m, 6H), 2.55 (s, 3H); IR

(KBr) ν_{max} (cm^{-1}): 3069, 1667, 1596, 1215, 880, 722, 633.

6-Nitro-2,3-diphenylquinoxaline (3c): mp=193-195 °C (Lit. 193-194 °C)[39]; ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm): 9.18 (d,J = 2.38 Hz, 1H), 8.66 (dd, J = 2.61, 9.10 Hz, 1H,), 8.54 (d, J = 9.17 Hz, 1H), 7.87 (m, 4H), 7.54 (m,6H); IR (KBr) ν_{max} (cm^{-1}): 3050, 2930, 1632, 1343, 1140, 699.

2,3-Bis(4-methoxy-phenyl) quinoxaline (3d): mp= 152-153 °C (Lit. 151-152 °C)[39]; ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm): 8.25(dd, J = 3.67, 6.32 Hz, 2H), 7.89 (dd, J = 3.39,6.41 Hz, 2H), 7.63 (d, J = 8.81 Hz, 4H), 6.91 (d,J = 8.66 Hz, 4H), 3.91 (s, 6H); IR (KBr) ν_{max} (cm^{-1}): 3000, 2945, 1609, 1518, 1351, 1062, 881.

2,3-Bis(4-methoxy-phenyl)-6-nitroquinoxaline (3e): mp=193-194 °C (Lit. 192-194 °C)[39]; ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm): 9.17 (d, J = 2.44 Hz, 1H), 8.55 (dd, J = 2.46, 9.28 Hz, 1H), 8.35 (d, J = 9.15 Hz, 1H), 7.67 (m,4H), 6.93 (d, J = 8.2 Hz, 4H), 3.94 (s, 6H); IR (KBr) ν_{max} (cm^{-1}): 2920, 1342, 1171, 1036, 844.

2,3-Bis (4-flouro-phenyl) 6-nitroquinoxaline (3f): mp =176-177 °C (Lit. 174-176 °C)[39]; ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm): 9.19 (d, J=2.41 Hz, 1H), 8.63 (dd, J= 2.44 Hz, 1H), 8.29 (d, J=9.27 Hz, 1H), 7.56 (m, 4H), 7.09 (m, 4H). IR (KBr) ν_{max} (cm^{-1}): 3093, 1603, 1523, 1354, 12331, 860.

Catalyst preparation

Al-MCM-41 (Si/Al=100, 50 and 25) samples were synthesized hydrothermally using a gel composition of SiO_2: xAl_2O_3:0.2CTAB:0.89H_2SO_4:120H_2O (*x* varies with Si/ Al ratio). Sodium metasilicate and aluminium sulphate were used as the sources for silicon and aluminium, respectively. Cetyl trimethyl ammonium bromide (CTAB) was used as the structure directing agent. In a typical synthesis, 10.6 g of sodium metasilicate in water was combined with appropriate amount of aluminium sulphate in distilled water and the pH of the solution was adjusted to 10.5 with constant stirring to form a gel. After 30 min, an aqueous solution of CTAB was added to it and the mixture was stirred for 1 h at room temperature. The suspension was then transferred into a 300 ml stainless steel autoclave, sealed and heated in a hot air oven at 160 °C for 48 h. After cooling to room temperature, the product formed was filtered, washed with deionised water and dried. Fe/Al-MCM-41 were synthesised by adopting the same procedure in which ferric nitrate was used as the source for iron. The dried materials were calcined at 550 °C for 1 h in nitrogen atmosphere and 5 h in air in order to maintain the crystallinity. The calcined materials were converted into H-form by repeated ion-exchange with

aqueous 1M NH4Cl solution followed by calcination at 550 ℃ for 5-6 h.

CONCLUSION

In summary, we describe a simple, efficient, and eco-friendly method for the synthesis of quinoxalines from various 1,2-diketones and 1,2-diamines using inexpensive and readily available Fe/Al-MCM-41 as a catalyst. The ambient conditions, good product yields, easy workup procedure and minimal environmental impact make it a useful and attractive process for the synthesis of these compounds.

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