

단 신

새롭고 효과적인 촉매로서의 메조포러스 분자체인 MCM-41을 사용한 빠른 Knoevenagel 축합반응

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(2008. 5. 20 접수)

Rapid Knoevenagel Condensation Using Mesoporous Molecular Sieve MCM-41 as a Novel and Efficient Catalyst

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(Received May 20, 2008)

주제어: Knoevenagel 축합반응, MCM-41, 에틸 시아노아세티에트, 말로노니트릴

Keywords: Knoevenagel Condensation, MCM-41, Ethyl Cyanoacetate, Malononitrile

INTRODUCTION

The synthesis of arylidene derivatives has attracted considerable attention from organic chemists for many years, because many of them have significant biological activity. More over, benzylidene malononitriles were reported to be effective anti-fouling agents, fungicides and insecticides. They are important intermediates for the synthesis of various organic compounds.¹

Knoevenagel condensation of carbonyl compounds on molecules containing an active methylene group is an important method for the preparation of substituted alkenes. Several important key products, such as nitriles used in anionic polymerization and α,β -unsaturated ester intermediates employed in the synthesis of several therapeutic drugs, e.g., nifedipine and nitrendipine, etc have been synthesized via this condensation.^{1,2} Ylidenenitriles have increasing applications in industry, medicine, agriculture and biological science, and are precursors to heterocycles.³ The reaction is catalyzed by primary and secondary amines or their corresponding ammonium salts in harmful solvents or with Lewis acids,

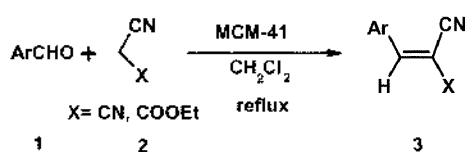
as $\text{TiCl}_4/\text{base}$,^{4a}, ZnCl_2 ,^{4b}, CdI_2 ,^{4c} and other catalysts.^{4a-b} Most of these methods have not been entirely satisfactory owing to such drawbacks as low yields, long reaction times and effluent pollution.

In continuation of our program to develop reactions in eco-friendly conditions⁵ and our interest in the Knoevenagel reaction,⁶ in this communication we wish to disclose our results for this reaction using MCM-41 as catalyst.

RESULT AND DISCUSSION

Mesoporous molecular sieves, which was synthesized by Mobil group in 1992⁷, have a space enough to accommodate the guest molecules. The MCM-41 exhibits a hexagonal array of cylindrical pores, cubic ordered pores and lamellar structure. Chemists have found this material as a brilliant host for the accommodation guest molecules and used it in catalytic reactions.⁸ Then, we decided to investigate Knoevenagel condensation in the presence of MCM-41 as a solid acid catalyst.

To start our investigation, we performed the study of various solvents effect on the course of reaction



Scheme 1

of 4-chlorobenzaldehyde with malononitrile. This reaction was carried out in various solvents such as water, DMF, chloroform, Ethanol, CH_2Cl_2 and toluene and the best results in terms of yield and time obtained in CH_2Cl_2 .

After optimizing the reaction condition, various aromatic aldehydes reacted very well with malononitrile and ethylecyanoacetate as active methylene compounds to give the corresponding arylidenes in good to excellent yields (Scheme 1). More interestingly, the reaction is highly stereoselective affording alkenes in E-geometry. The results are summarized in Table 1. It is worthwhile to mention that Knoevenagel condensation with ketones in this condition does not occur. We used acetophenone as an example of ketones which did not react in these conditions even after prolonged reaction time (24h). The aromatic aldehydes readily condensed with malononitrile, while with ethylecyanoacetate, the reaction is slightly slow. This may be attributed to the fact that abstraction of a proton from the active methylene group of ethylecyanoacetate is more diffi-

cult due to its lower activity. As shown in Table 1, aromatic aldehydes containing both electron donating or withdrawing groups gave the desired products in good to excellent yields. Deactivated aldehydes such as nitrobenzaldehyde isomers and 4-chlorobenzaldehyde required shorter reaction time due to the electron withdrawing groups (Table 1, entries 2,3,8,9). Moreover, the steric hindrance seems to have significant effects on the reaction times and yields (Table 1, entries 6,13).

The use of MCM-41 as a recyclable catalyst in this reaction allowed us to perform the condensation under mild conditions. In this case, yields were excellent. In order to show the merit of the present work in comparison with some reported procedures, we compared the result of the synthesis of olefinic compounds in the presence of HZSM-5,¹⁵ Proline,¹⁶ RE-NaY zeolite¹⁷ and MCM-41 with respect to the reaction times and yield of products (Table 2). The results show that MCM-41 promotes the reaction more effectively than HZSM-5. Reaction in the presence of other catalysts in Table 2 required longer reaction times.

In summary, we have demonstrated the MCM-41 catalyzed condensation between various aldehydes and active methylene compounds. This method offers some advantages in terms of simplicity of performance, easy work-up, use of inexpensive,

Table 1. Knoevenagel condensation using MCM-41 as catalyst in CH_2Cl_2 .

Entry	Ar	x	Product	Time (min)	Yield (%)	m.p. (°C)	
						Found	lit
1	Ph-	CN	3a	30	92	85	84 ⁹
2	3-NO ₂ Ph-	CN	3b	20	90	102	104-105 ¹⁰
3	4-Cl Ph-	CN	3c	30	90	169	163 ¹¹
4	4-OH Ph-	CN	3d	30	93	184	185 ⁹
5	4-CH ₃ -C ₆ H ₄	CN	3e	50	92	137-138	135 ¹²
6	2-CH ₃ O-C ₆ H ₄	CN	3f	60	90	80	78 ⁹
7	4-CH ₃ O-C ₆ H ₄	CN	3g	50	92	113-114	115 ¹²
8	3-NO ₂ Ph-	COOEt	3h	90	83	136-7	128-132 ¹³
9	4-Cl Ph-	COOEt	3i	60	83	92-3	86 ¹⁰
10	4-OH Ph-	COOEt	3j	120	87	88	88 ⁹
11	4-CH ₃ -C ₆ H ₄	COOEt	3k	120	86	93-94	92 ⁹
12	2-CH ₃ O-C ₆ H ₄	COOEt	3l	140	83	70	69 ¹⁴
13	4-CH ₃ O-C ₆ H ₄	COOEt	3m	120	87	85	80-84 ⁹

(a) Isolated yields

Table 2. Comparison of the synthesis of trisubstituted alkenes using different catalysts.

Entry	Catalyst	Time	Yield(%)	Ref
1	HZSM-5	5-12 (h)	60-80	15
2	Proline	Over night	66-100	16
3	RE-NaY Zeolite	8-18 (h)	78-100	17
4	MCM-41	30-120 (min)	83-93	This work

available and easy to handle catalyst and high yields of products and relatively short reaction times.

EXPERIMENTAL

All products are known compounds and were characterized by mp, IR, ¹HNMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ¹HNMR 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 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 MCM-41

MCM-41 was prepared according to the procedure described previously.¹⁸ A typical procedure was as follow: 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 the teflon lined stainless steel autoclave to make crystallization under static condition 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.

General procedure for the Knoevenagel condensation

A mixture of carbonyl compound (1 mmol), ethylethanoacetate or malononitrile (1 mmol) and MCM-41 (0.1 g) was refluxed in CH₂Cl₂ for indicated time as required to complete the reaction (Table 1). Upon completion of the reaction, monitored by TLC, the reaction mixture was cooled to room temperature. The mixture was filtered off (removed the catalyst and catalyst was washed with methanol for reuse). Upon the evaporation of solvent, the crude product was recrystallized from ethanol to give the pure product.

Selected physical data

2-benzylidene malononitrile (3a). Mp: 85 °C. ¹HNMR (CDCl₃, 300 MHz) δ_H (ppm): 7.25-7.51 (m, 5 H), 7.95 (t, *J*=8.0 Hz, 1H). ¹³C NMR (CDCl₃, Me₄Si) δ_C (ppm): 68.61, 111.28, 111.48, 111.65, 112.41, 112.64, 127.18, 128.82, 131.92, 154.90.

2-(4-Nitrobenzylidene)malononitrile (3b). Mp: 102 °C. ¹HNMR (CDCl₃, 300 MHz) δ_H (ppm): 7.2 (2H, *J*=7.8, d), 7.9 (2H, *J*=7.8, d), 8.05 (t, *J*=7.9 Hz, 1H). ¹³C NMR (CDCl₃, Me₄Si) δ_C (ppm): 69.95, 111.55, 111.62, 122.19, 126.17, 130.35, 131.60, 131.98, 148.07, 155.92.

Ethyl-2-cyano-3-(4-hydroxyphenyl)acrylate (3j). Mp: 88 °C. ¹HNMR (CDCl₃, 300 MHz) δ_H (ppm): 1.71 (t, *J*=8.1, 3H), 4.01 (q, *J*=8.1, 2H), 5.15 (s, 1H), 7.2 (2H, *J*=7.8, d), 7.9 (2H, *J*=7.8, d), 8.06 (t, *J*=7.9 Hz, 1H). ¹³C NMR (CDCl₃, Me₄Si) δ_C (ppm): 14.15, 55.90, 87.38, 112.05, 115.42, 122.01, 123.21, 123.09, 126.07, 127.89, 153.54, 159.81.

Ethyl-2-cyano-3-(4-methoxyphenyl)acrylate (3m). Mp: 85 °C. ¹HNMR (CDCl₃, 300 MHz) δ_H (ppm): 1.71 (t, *J*=8.1, 3H), 3.71 (s, 3H), 4.01 (q, *J*=8.1, 2H), 7.2 (2H, *J*=7.8, d), 7.9 (2H, *J*=7.8, d), 8.15 (t, *J*=8.0 Hz, 1H). ¹³C NMR (CDCl₃, Me₄Si) δ_C (ppm): 14.25,

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

Yield (%) ^a	Time (min)	Run
92	30	first
91	30	second
85	40	third
83	45	fourth
80	60	fifth

(a) Isolated yields

55.96, 61.12, 87.45, 112.55, 115.62, 122.19, 123.31, 123.69, 126.17, 127.8, 154.65, 159.91.

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 weighted after filtration and before using and reusing for the next reaction. The results show that these catalysts are not soluble in methanol. In Table 3, the comparison of efficiency of MCM-41 in synthesis of 3a after five times is reported. As it is shown in Table 3, the first reaction using recovered 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.

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