



Al-MCM-41 catalyzed three-component Strecker-type synthesis of α -aminonitriles

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ABSTRACT

Mesoporous aluminosilicate (Al-MCM-41) efficiently catalyzed the three-component Strecker-type reaction of benzylacetone and aniline with trimethylsilyl cyanide in CH_2Cl_2 at room temperature to afford the corresponding α -aminonitrile in excellent yields (up to 97%). Mesoporous silica (MCM-41), amorphous $\text{SiO}_2\text{-Al}_2\text{O}_3$, and H-Y and H-ZSM-5 zeolites also catalyzed this reaction, but gave the desired product in lower yields. The Al-MCM-41 catalyzed three-component Strecker-type reaction was applicable to a wide range of ketones, aldehydes, and amines. Furthermore, the Al-MCM-41 catalyst could be applied to a fixed-bed flow reactor: The desired α -aminonitrile derivative was constantly produced in nearly 80% yields for 48 h.

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1. Introduction

Three-component Strecker-type reaction from carbonyl compounds, amines, and trimethylsilyl cyanide (TMSCN) is an important reaction in organic synthesis because the products, α -aminonitrile derivatives, are versatile intermediates, which can be transformed into various building blocks, including α -amino acids, 1,2-diamines, and nitrogen-containing heterocycles.¹ Various Lewis acids such as $\text{Yb}(\text{OTf})_3$,^{2a} $\text{Pr}(\text{OTf})_3$,^{2b} $\text{Cu}(\text{OTf})_2$,^{2c} LiClO_4 ,^{2d} BiCl_3 ,^{2e} NiCl_2 ,^{2f} RuCl_3 ,^{2g} CeCl_3 ,^{2h} InI_3 ,²ⁱ RhI_3 ,^{2j} $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ or $\text{GdCl}_3 \cdot 6\text{H}_2\text{O}$,^{2k} iodine,^{2l} and (bromodimethyl)sulfonium bromide,^{2m} homogeneously catalyze the Strecker-type reaction. On the other hand, several heterogeneous catalysts, which are more advantageous in terms of catalyst/product separation and continuous production, have been proposed for the reaction. The examples include polymer-supported scandium triflate,^{3a} montmorillonite,^{3b} sulfuric acid on silica,^{3c,d} heteropoly acid,^{3e-g} sulfamic acid,^{3h,i} and poly(4-vinyl pyridine)- SO_2 complex.^{3j} A few catalyst-free methods are also known.⁴ However, the starting carbonyl compounds are mostly limited to aldehydes; there are few examples on the successful three-component reaction starting from ketones. Matsumoto et al. performed the three-component reaction using ketones under extremely high pressure conditions (600 MPa).⁵ Olah et al. have reported this type of reaction from fluorinated ketones using $\text{Ga}(\text{OTf})_3$ or TMSOTf as a catalyst.^{6,7} Khan et al. have also reported the

efficient $\text{Fe}(\text{Cp})_2\text{PF}_6$ catalyzed Strecker-type reaction from ketones as well as aldehydes under solvent-free conditions.⁸ In both cases, however, the reactions are promoted by homogeneous catalytic systems. Therefore, there is still scope to develop an efficient heterogeneous catalyst for preparing a wide range of α -aminonitriles.

Ordered mesoporous materials are very attractive as heterogeneous solid catalysts for fine chemicals synthesis because their large pore sizes and pore volumes allow facile diffusion of bulky reactants and products that are often involved in such a reaction.⁹ The additional attractive feature of mesoporous materials is their high surface areas, which provide a high concentration of active sites often introduced by incorporating metal ions into the siliceous framework. For instance, aluminum substituted mesoporous silicas show acid catalysis for numerous fine chemicals syntheses.¹⁰ Recent examples include acetalization,¹¹ esterification,¹² β -keto ester synthesis,¹³ cyanosilylation,¹⁴ allylation,¹⁵ and Mukaiyama aldol reaction.¹⁶ Herein, we report that mesoporous aluminosilicate (Al-MCM-41) is a highly efficient heterogeneous catalyst for the three-component Strecker-type reaction of various ketones including less reactive acyclic ketones with amines and TMSCN. Using the catalyst in a flow reactor, α -aminonitriles can be continuously produced without catalyst separation from the products.

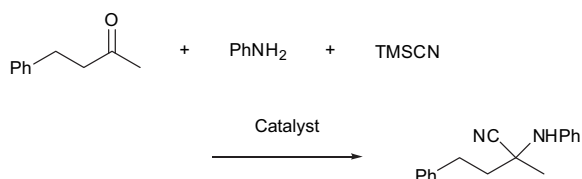
2. Results and discussion

We initially used benzylacetone and aniline (1.2 equiv) as substrates to investigate the effect of catalysts on the three-component

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Strecker-type reaction with TMSCN (1.2 equiv) in CH_2Cl_2 . The results are summarized in Table 1. It is noteworthy that the reaction hardly proceeded in the absence of a catalyst (Table 1, entry 1). Silica gel was not effective for the reaction, whereas mesoporous silica (MCM-41) afforded the desired α -aminonitrile in a 61% yield (Table 1, entries 2 and 3). Additionally, substitution of a part of silicon in MCM-41 with aluminum improved the yield, and the desired product was obtained in 97% yield when Al-MCM-41 with a Si/Al ratio of 20 (denoted by Al-MCM-41 (20)) was used (Table 1, entry 6). On the other hand, amorphous silica/alumina ($\text{SiO}_2\text{-Al}_2\text{O}_3$; Si/Al=20) and zeolites such as H-Y and H-ZSM-5 gave moderate yields (Table 1, entries 7–9). If one considers the specific surface areas of Al-MCM-41 (20) and $\text{SiO}_2\text{-Al}_2\text{O}_3$ being 993 and $157\text{ m}^2\text{ g}^{-1}$, respectively, one can see that the high yield produced by Al-MCM-41 (20) is primarily due to its high surface area. For the Al-MCM-41 (20) catalyst, the yield increased with the amount of catalyst, but the use of 50 mg was enough to obtain the best result (Table 1, entries 10–13). Among the solvents tested in the Al-MCM-41 catalyzed reaction, CH_2Cl_2 was the most suitable. Toluene and acetonitrile¹⁷ were also a good solvent, but DMF and THF gave somewhat lower yields (Table 1, entries 14–17).

Table 1
Three-component Strecker-type reaction of benzylacetone with aniline and TMSCN by various catalysts^a



Entry	Catalyst ^b	Amount of catalyst (mg)	Solvent	Yield ^c (%)
1	None		CH_2Cl_2	2
2	SiO_2	50	CH_2Cl_2	5
3	MCM-41	50	CH_2Cl_2	61
4	Al-MCM-41 (100)	50	CH_2Cl_2	82
5	Al-MCM-41 (50)	50	CH_2Cl_2	89
6	Al-MCM-41 (20)	50	CH_2Cl_2	97 (95) ^d
7	$\text{SiO}_2\text{-Al}_2\text{O}_3^e$	50	CH_2Cl_2	40
8	H-Y	50	CH_2Cl_2	64
9	H-ZSM-5	50	CH_2Cl_2	28
10	Al-MCM-41 (20)	100	CH_2Cl_2	92
11	Al-MCM-41 (20)	20	CH_2Cl_2	82
12	Al-MCM-41 (20)	10	CH_2Cl_2	79
13	Al-MCM-41 (20)	5	CH_2Cl_2	74
14	Al-MCM-41 (20)	50	Toluene	94
15	Al-MCM-41 (20)	50	CH_3CN	87
16	Al-MCM-41 (20)	50	DMF	71
17	Al-MCM-41 (20)	50	THF	71

^a Reaction conditions: benzylacetone (1 mmol), aniline (1.2 mmol), TMSCN (1.2 mmol), catalyst, solvent (2 mL), room temperature, under an argon atmosphere, 24 h.

^b Figures in parentheses are the molar ratio of Si/Al (input).

^c Each yield was determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard, unless otherwise noted.

^d Isolated yield after gel permeation chromatography (GPC).

^e Amorphous silica–alumina.

To verify whether the catalysis of Al-MCM-41 in this reaction is heterogeneous or not, we conducted the following experiment. A mixture of benzylacetone (1.0 mmol), aniline (1.2 mmol), TMSCN (1.2 mmol), triphenylmethane (internal standard), and Al-MCM-41 (20) (50 mg) in CH_2Cl_2 (3.0 mL) was stirred at room temperature. After 1 h, Al-MCM-41 (20) was filtered off, and the filtrate was stirred again under the same conditions for 23 h. However, the increase in the yield was negligible (32% at 1 h and 33% at 24 h), indicating that Al-MCM-41 truly works as a heterogeneous catalyst.

Table 2 summarizes the scope of amines as well as carbonyl compounds. Depending on the combination of ketone and amine, the reaction proceeded fairly well even in the absence of the catalyst. In each case, however, the use of Al-MCM-41 gave the product in a higher yield. When benzylamine and *p*-anisidine were used, the corresponding α -aminonitrile derivatives, in which the amino groups were protected with *N*-benzyl and *N*-PMP (*p*-methoxyphenyl) groups, respectively, were obtained in excellent yields (Table 2, entries 2 and 3). In contrast, the use of pyrrolidine as an amine did not give the desired α -aminonitrile, but produced the corresponding cyanohydrin trimethylsilyl ether quantitatively (Table 2, entry 4). Cyclic ketones such as cyclohexanone, 2-methylcyclohexanone, and cyclopentanone afforded the desired products in good to high yields within 3 h (Table 2, entries 5–7). In the case of sterically hindered pinacol, aromatic ketone, and α,β -unsaturated ketone, the yields of the corresponding α -aminonitriles were moderate (Table 2, entries 8–10). On the other hand, the reaction starting from benzophenone did not proceed at all (entry 11). On the contrary, the three-component reaction of aldehydes such as *n*-hexanal, cyclohexanecarbaldehyde, and benzaldehyde with benzylamine and TMSCN proceeded sufficiently without catalyst, although the use of the Al-MCM-41 catalyst improved the yields of the desired aminonitriles (Table 2, entries 12–17).

To obtain insights into the reaction mechanism, we carried out two experiments shown in Scheme 1. First, we performed the reaction between cyanohydrin trimethylsilyl ether derived from benzylacetone and aniline in the presence of the Al-MCM-41 catalyst (Eq. 1). However, the corresponding α -aminonitrile was not formed at all. Therefore, it is unlikely that the present three-component reaction proceeds via cyanohydrin silyl ethers. Second, the reaction between imine derived from benzylacetone and TMSCN in the presence of Al-MCM-41 produced α -aminonitrile (Eq. 2), but the reaction was much slower than the three-component reaction; the yield of α -aminonitrile was only 29% in 24 h. Therefore, it is also unlikely that the three-component reaction proceeds via imine although the intermediacy of imine has been assumed, for instance in the homogeneous $\text{Fe}(\text{Cp})_2\text{PF}_6$ catalyzed reaction.⁸ If these results are taken into account, it is reasonable to assume that the three-component reaction over the Al-MCM-41 catalyst proceeds by way of an *N,O*-acetal intermediate,¹⁸ which is formed from ketones and amines (Scheme 2). Ketones activated by the acidic proton of Al-MCM-41 react with amines to form *N,O*-acetals, which undergo nucleophilic attack by TMSCN, as the case of ring opening reactions of semicyclic *N,O*-acetals with silicon-based nucleophiles,¹⁹ leading to α -aminonitriles. Since MCM-41 showed appreciable catalysis for this three-component reaction (Table 1, entry 3), the weak acid site like the surface silanol group ($\text{p}K_{\text{a}}=7.2$)²⁰ should be sufficient to activate ketones.

Finally, we performed the continuous Strecker-type reaction of benzylacetone, aniline, and TMSCN using a fixed-bed flow reactor in order to demonstrate the merit of Al-MCM-41 as a solid catalyst, as well as examine the catalytic stability. The catalytic activity was maintained for at least 48 h, and the desired α -aminonitrile derivative was constantly produced in nearly 80% yields (Fig. 1). This proves that Al-MCM-41 is stable enough to serve as a solid catalyst under the present reaction conditions.

In conclusion, we have demonstrated that Al-MCM-41 is a highly active heterogeneous solid catalyst for the three-component Strecker-type reaction. Using the Al-MCM-41 catalyst and TMSCN as a cyanide source, various α -aminonitriles are obtained from a wide range of ketones and amines in high yields under mild reaction conditions. The merit of the Al-MCM-41 catalyst is the presence of a high concentration of the acid sites easily accessible to large molecules per weight of the catalyst. This report extends the application range of mesoporous aluminosilicates as heterogeneous catalysts in organic synthesis, especially for fine chemicals.

Table 2
Three-component Strecker-type reaction of various carbonyl compounds and amines catalyzed by Al-MCM-41^a



Entry	R ¹	R ²	R ³	R ⁴	Time (h)	Yield ^b (%)	Yield ^c (%)
1	PhCH ₂ CH ₂	Me	Ph	H	24	97 (95) ^d	2
2	PhCH ₂ CH ₂	Me	PhCH ₂	H	24	98 (97) ^d	25
3	PhCH ₂ CH ₂	Me	4-MeOC ₆ H ₄	H	24	95 (93) ^d	6
4	PhCH ₂ CH ₂	Me	-(CH ₂) ₄ -	H	24	0	0
5	-(CH ₂) ₅ -		PhCH ₂	H	3	91 ^e	74
6	-CHMe(CH ₂) ₄ -		PhCH ₂	H	3	78	55
7	-(CH ₂) ₄ -		PhCH ₂	H	3	76	— ^f
8	<i>t</i> -Bu	Me	PhCH ₂	H	24	48	4
9	Ph	Me	PhCH ₂	H	24	73	5
10	PhCH=CH	Me	PhCH ₂	H	24	40	8
11	Ph	Ph	PhCH ₂	H	24	0 ^g	— ^f
12	PhCH ₂ CH ₂	H	PhCH ₂	H	0.25	96 ^e	— ^f
13	<i>n</i> -C ₆ H ₁₃	H	PhCH ₂	H	0.25	90 ^e	84
14	<i>cyclo</i> -C ₆ H ₁₁	H	PhCH ₂	H	0.25	91 ^e	85
15	<i>t</i> -Bu	H	PhCH ₂	H	2	84 ^e	75
16	Ph	H	PhCH ₂	H	0.5	100	93
17	PhCH ₂ CH ₂	H	-(CH ₂) ₄ -	H	3	100	79

^a Reaction conditions: carbonyl compound (1 mmol), amine (1.2 mmol), TMSCN (1.2 mmol), CH₂Cl₂ (2 mL), room temperature, under an argon atmosphere.

^b Yields in the presence of Al-MCM-41 (20) (50 mg for ketones and 10 mg for aldehydes). Each yield was determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard, unless otherwise noted.

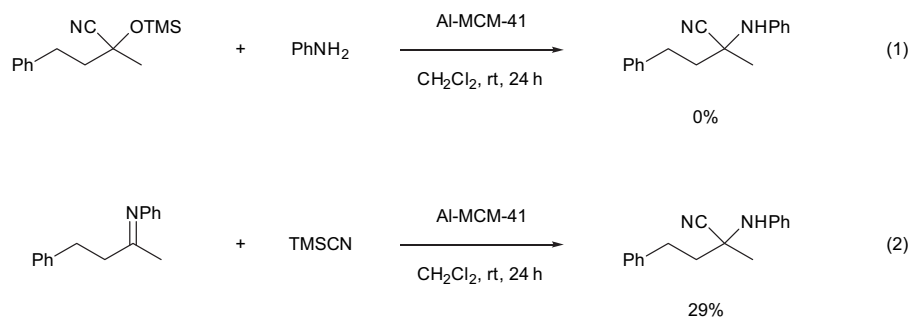
^c Yields in the absence of Al-MCM-41 (20). Each yield was determined in the same manner as footnote [b].

^d Isolated yield after gel permeation chromatography (GPC).

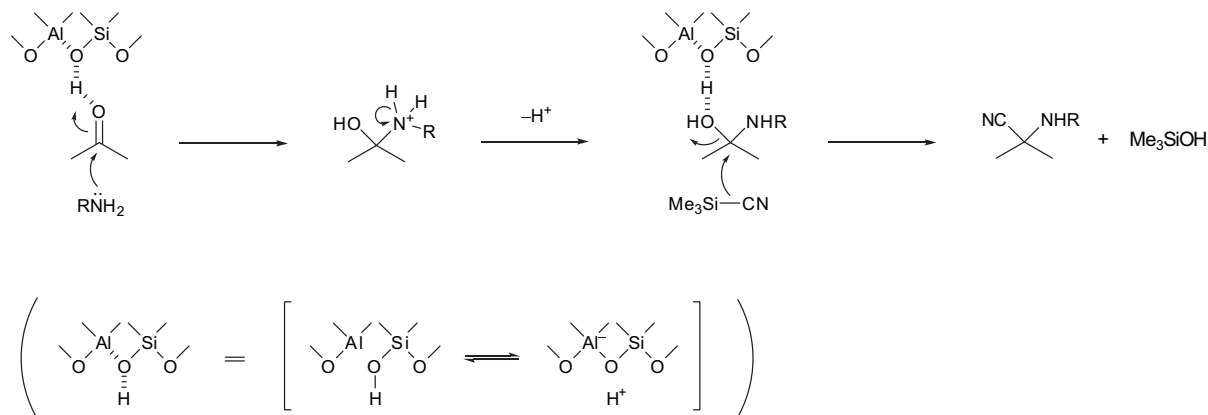
^e Isolated yield after silica gel column chromatography.

^f Not determined.

^g No reaction.



Scheme 1. Preparation of α -aminonitriles from cyanohydrin trimethylsilyl ether (Eq. 1: cyanohydrin TMS ether (1 mmol), aniline (1.2 mmol), Al-MCM-41 (50 mg)) and from imine (Eq. 2: imine (1 mmol), TMSCN (1.2 mmol), Al-MCM-41 (50 mg)).



Scheme 2. Possible reaction mechanism of the three-component Strecker-type reaction catalyzed by Al-MCM-41.

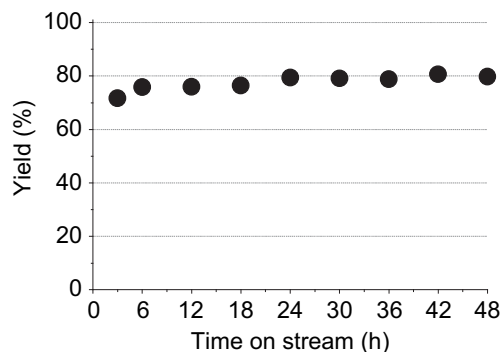


Figure 1. α -Aminonitrile yield during a continuous flow reaction. Reaction conditions: benzylacetone (7.4 wt %), aniline (1.05 equiv), and TMSCN (1.1 equiv) in CH_2Cl_2 . Al-MCM-41 (20) (100 mg, loaded in a 4 mm I.D. \times 30 mm Pyrex glass tube), flow rate (1.25 g h^{-1}), room temperature.

3. Experimental section

3.1. Preparation of catalysts

Al-MCM-41 (Si/Al=20) was prepared by a direct hydrothermal synthesis method according to the literature²¹ using cetyltrimethylammonium bromide (CTMABr) as a template. The Si and Al sources were colloidal silica and sodium aluminate, respectively. The molar ratio of CTMABr:SiO₂:NaAlO₄:NaOH:NH₃:H₂O was 1.1:20:1.0:5.5:1.1:940. The gel mixture was initially stirred for 1 h at room temperature, and then heated to 97 °C. After 1 day, the mixture was cooled to room temperature and the pH of the reaction mixture was adjusted to 10.2 by adding 30 wt % acetic acid. The heating and pH adjustment procedures were repeated twice. The resulting solid was filtered, washed with deionized water, dried at 97 °C, and then calcined in air at 550 °C for 18 h. The BET surface area and the pore volume were $993 \text{ m}^2 \text{ g}^{-1}$ and $1.08 \text{ cm}^3 \text{ g}^{-1}$, respectively. The preparation and characterization of Al-MCM-41 (Si/Al=50 and 100), MCM-41, amorphous SiO₂-Al₂O₃, H-Y, and H-ZSM-5 are shown in the [Supplementary data](#).

3.2. General procedure of three-component Strecker-type reactions

Dichloromethane was distilled from calcium hydride. TMSCN was purchased from Tokyo Chemical Industry Co., Ltd. and distilled prior to use. Benzaldehyde, cyclohexanone, and aniline were used after distillation and the other reagents were used as received.

3.2.1. The reaction procedure in entry 1 in Table 2. To a suspension of Al-MCM-41 (20) (50 mg), which was pretreated in vacuo at 120 °C for 1 h, benzylacetone (148 mg, 1.0 mmol), and aniline (110 μL , 1.2 mmol) in CH_2Cl_2 (2 mL) was added TMSCN (160 μL , 1.2 mmol). The reaction mixture was stirred at room temperature under an argon atmosphere. After 24 h, the catalyst was removed via filtration and the solvent was evaporated in vacuo. ¹H NMR analysis (400 MHz) of the product using 1,1,2,2-tetrachloroethane as an internal standard showed that 2-methyl-2-phenylamino-4-phenylbutanenitrile was obtained in 97% yield. The product was isolated by GPC (238 mg, 95%) and gave satisfactory ¹H NMR, ¹³C NMR, and IR spectra. The spectral data for new α -aminonitriles are included in the [Supplementary data](#).

3.2.2. The reaction procedure in Figure 1. The reactor was a Pyrex glass tube (4 mm inner diameter and 30 mm long), which was loaded with Al-MCM-41 (20) (100 mg) pretreated in vacuo at 120 °C for 1 h. The liquid feed, which contained benzylacetone (7.4 wt %), aniline (4.9 wt %), TMSCN (5.4 wt %) (molar ratio of

benzylacetone:aniline:TMSCN=1.0:1.05:1.1), triphenylmethane as an internal standard (2.5 wt %), and CH_2Cl_2 (for balance), was continuously introduced into the reactor at room temperature with a syringe pump (Harvard type 55-1111, Harvard Apparatus Inc.) at a flow rate of 1.25 g h^{-1} . The weight hourly space velocity (WHSV) was 12.5 h^{-1} . The liquid products were collected for 10 min every 6 h and analyzed by ¹H NMR.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tet.2010.01.001](https://doi.org/10.1016/j.tet.2010.01.001).

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