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Selective synthesis of α-substituted β-keto esters from aldehydes and diazoesters on mesoporous silica catalysts

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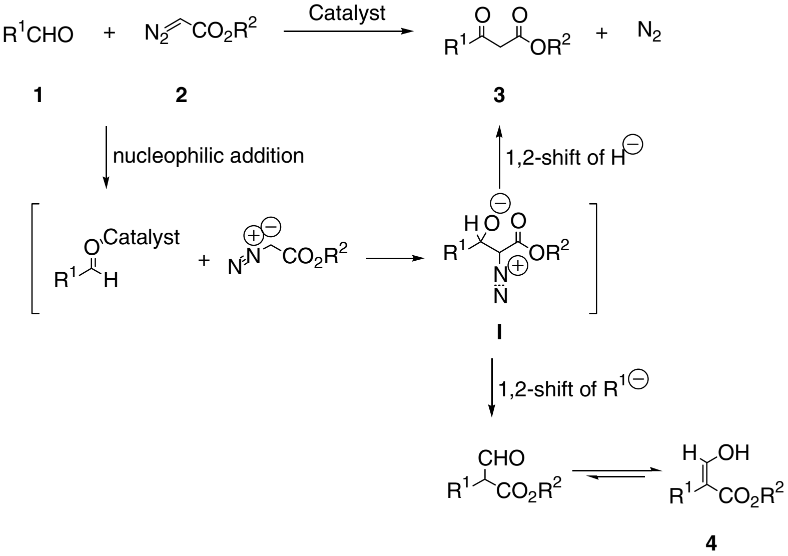
ABSTRACT

The titled reactions are effectively catalyzed on mesoporous silica MCM-41 but not on amorphous silica prepared from the same starting materials as those of MCM-41. The ordered porous structure was essential to generate the acid catalysis. Planting of Al or Ti ion improved not only the catalytic activity but also the tolerance to basic functional groups of substrates. The catalytic activity of Al- or Ti-MCM-41 was better than that of $SnCl_2$ and $NbCl_5$ in the homogeneous phase. In particular, Al (or Ti)-MCM-41 was characteristically active for the reaction of aldehydes with α-substituted diazoesters to give 2-substituted-3-oxo propionic acid esters.

β-Keto esters are one of the most important intermediates for synthesis of useful organic compounds. Although many synthetic routes have been proposed, there are only a few catalytic approaches.[1] Acid-catalyzed reaction of aldehyde and diazoester is regarded as a useful way to access β-keto esters because only nitrogen is generated as a by-product (Scheme 1). In 1909, Schlotterbeck reported that this type of reaction proceeded at 333–363 K without any catalysts; however, the examples were limited in some halogenated aliphatic aldehydes or *p*-nitrobenzaldehydes and the yields of desired products were less than 40% in most cases.[2] $SnCl_2$ was found to be effective for the reaction of aldehydes with diazoester;[3] for example, with 10 mol % of $SnCl_2$, hydrocinnamaldehyde and ethyl diazoacetate were converted to the corresponding β-keto ester in 86% yield. The $SnCl_2$-catalyzed reaction



Scheme 1. The reaction pathways of aldehydes and diazoesters.

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was unfortunately not useful for the reaction of aromatic aldehydes.[3] Recently, $NbCl_5$ was reported as a new catalyst, on which a variety of β-keto ester were obtained in 75–92% yield from ethyl diazoacetate and aliphatic or aromatic aldehydes.[4] Several heterogeneous catalysts were also investigated. Aromatic or aliphatic aldehydes reacted with ethyl diazoacetate to yield β-keto ester in 75–85% yield on alumina,[5] though the amount of alumina employed was very great. H-β-Zeolite[6] and Cu-exchanged Mont K10[7] were also found to be active for the reaction. The reflux condition at 353 K was required on the catalysts to give satisfactory yields in the reaction of aromatic or aliphatic aldehydes with ethyl diazoacetate.

In the above study on $SnCl_2$,[3] BF_3, $ZnCl_2$, $ZnBr_2$, $AlCl_3$, $GeCl_2$, and $SnCl_4$ were also examined as a catalyst and good yields were reported only on $SnCl_2$, $GeCl_2$, and BF_3. The activity of $AlCl_3$ and $SnCl_4$ was again reported by Hossain et al. to be low.[8] In the zeolites catalysts, the activity was in the order H-β > H-Y > H-ZSM-5.[6] The reports in homogeneous and heterogeneous phases might suggest that strong acids would not be suitable for this type of reaction. On the other hand, $La(OTf)_3$ was reported to catalyze the reaction of aldehydes and diazoester to produce epoxides through the Darzens-type reaction.[9] All the reports indicate that the selection of the acidity and metal ion is a key to carry out the two successive reactions for the β-keto ester formation, the nucleophilic addition of diazoester and the hydride transfer in the resulting intermediate (Scheme 1).

The novel acidic properties of mesoporous silica material MCM-41 (M41) have been reported from the present[10] and the other groups.[11] The acidity is known to be not strong but unique to promote various selective catalyses. Our efforts were therefore devoted to clarify the catalytic activity of M41 for the β-keto ester formation from aldehydes and diazoesters. In this Letter, we will report the effect of mesopores on the catalytic activity, its enhancement by addition of metal ion, and finally the reactions of α-substituted diazoesters.

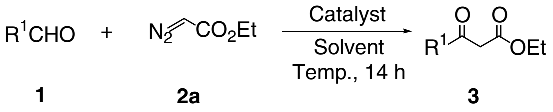
M41 was prepared in the reported manner by using $C_{12}H_{25}N(CH_3)_3Br$ as the template and colloidal silica as the silica source.[12] The BET surface area and the BJH pore diameter were 1010 $m^2\,g^{-1}$ and 2.12 nm, respectively. The hexagonal structure of resulting M41 was confirmed from the XRD pattern and the Si/Al atomic ratio was 237, in which the origin of Al is impurity of the raw material, colloidal silica. Metal ion-planted M41s (M-M41s) were prepared by the template-ion exchange (TIE) method.[13] M41 and M-M41s were used in the catalytic reaction after evacuation at 373 K for 1 h.

We first examined the effect of solvent in the reaction of 0.5 mmol of *n*-butanal (**1a**) and 0.75 mmol of ethyl diazoacetate (**2a**) on 50 mg of M41.[14] The reaction easily proceeded at room temperature. As shown in Table 1, halogenated aromatic or aliphatic hydrocarbons such as chlorobenzene, dichloromethane, and 1,2-dichloroethane induced better yields than hydrocarbons including octane and toluene, and the best yield of 82% was attained by using dichloromethane (entry 4). Polar solvents, THF and CH_3CN, were not effective. The effectiveness of halogenated hydrocarbon as a solvent in this reaction was already recognized in the previous reports.[3,4,6,8] Next the effect of reaction temperature was studied on M41 in halogenated hydrocarbon solvents. Upon temperature rising to 353 K in CH_2ClCH_2Cl, the yield became lower to 30% from 78% at 298 K (entries 5 and 8). On the other hand, at 273 K the yield was only 23% in CH_2Cl_2 (entry 9). All experiments were hereinafter carried out at room temperature in CH_2Cl_2.

The reactivity of other aliphatic aldehydes such as acetoaldehyde (**1b**), *n*-heptanal (**1c**), and hydrocinnamaldehyde (**1d**) was examined and corresponding β-keto esters could be obtained in good to excellent yields (entries 10–12). For **1b**, 1,2,3-trichloropropane was the suitable solvent resulting in the high yield.[15] The yield of reaction product of cyclohexanecarboxaldehyde (**1e**) (entry 13) was somewhat smaller than those of the linear aliphatic aldehydes. It would be due to the steric hindrance around carbonyl carbon.

Table 1

Yields of β-keto esters on M41-catalyzed reactions of aldehydes and ethyl diazoacetate



Entry	R^1	Catalyst	Solvent	Temp (K)	Yield (%)
1	^{n}Pr (**1a**)	M41	Octane	298	55[a]
2	^{n}Pr	M41	Toluene	298	51[a]
3	^{n}Pr	M41	Chlorobenzene	298	62[a]
4	^{n}Pr	M41	CH_2Cl_2	298	82[a]
5	^{n}Pr	M41	$ClCH_2CH_2Cl$	298	78[a]
6	^{n}Pr	M41	THF	298	11[a]
7	^{n}Pr	M41	CH_3CN	298	49[a]
8	^{n}Pr	M41	$ClCH_2CH_2Cl$	353	30[a]
9	^{n}Pr	M41	CH_2Cl_2	273	23[a]
10	Me (**1b**)	M41	$ClCH_2CHClCH_2Cl$	298	>99[a]
11	^{n}Hex (**1c**)	M41	CH_2Cl_2	298	79[a,b]
12	$Ph(CH_2)_2$ (**1d**)	M41	CH_2Cl_2	298	82[c]
13	^{c}Hex (**1e**)	M41	CH_2Cl_2	298	73[c]
14	^{n}Pr	SiO_2[d]	CH_2Cl_2	298	Trace[a]

Effect of solvents, reaction temperature and sorts of aldehydes (Typical reaction conditions: M41, 50 mg; **1**, 0.50 mmol; **2a**, 0.75 mmol; solv., 2.5 mL; 14 h.).

[a] GC Yield.

[b] The reaction was carried out for 1 h.

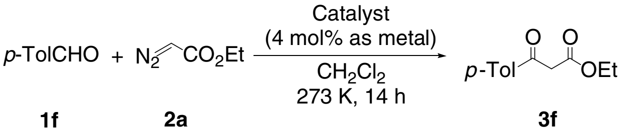
[c] Isolated yield.

[d] Prepared in vigorous stirring from colloidal silica and $C_{12}H_{25}N(Me)_3Br$ without hydrothermal treatment. The BET surface area was 122 $m^2\,g^{-1}$. 415 mg of the SiO_2 was used in the catalytic run.

To reveal the effect of pore structure of M41, SiO_2 was separately prepared under the vigorous stirring by using the same raw materials as those employed in the preparation of M41. The components in obtained SiO_2 were the same as those of M41 within the experimental errors, and the major difference between M41 and SiO_2 was the presence/absence of pore structures. This SiO_2 was entirely inert for the present reaction (entry 14). It should be noted in the entry 14 that the BET surface area of SiO_2 employed was 122 $m^2\,g^{-1}$ and therefore 415 mg of the sample was used as the catalyst to unify the surface areas applied for the reaction. The result indicates that first the Al impurity contained in M41 is not the origin of the catalytic activity, and second the presence of

Table 2

Change in the catalytic activity of M41 with the loading of metal ions[a]



Entry	Catalyst				Conv. of **1f**[b] (%)	Yield[b] (%)	Select (%)
		[M]/mmol g^{-1}	Si/M	Weight/mg			
1	M41	0.065	[Al]237	50	63	53	84
2	Al-M41	0.33	35	53	94	86	91
3	Ti-M41	0.35	35	50	84	75	89
4	Sc-M41	0.27	42	74	82	45	55
5	La-M41	0.29	40	61	79	72	91

[a] Typical reaction conditions: **1f**, 0.50 mmol; **2a**, 0.75 mmol; CH_2Cl_2, 2.5 mL; 273 K; 14 h.

[b] Determined by GC analysis.

mesoporous structures is significant for the appearance of catalysis.

The reaction of *p*-tolualdehyde with ethyldiazoacetate **2a** was examined on M41 (Table 2) in more detail. The Hossain's report[8] indicated that Brønsted acids conducted the 1,2-shift of the aromatic group on the intermediate **I** to obtain 3-hydroxy-2-arylacrylates (Scheme 1, **4**), whereas weak Lewis acids such as $SnCl_2$ had high selectivity to the synthesis of β-keto ester **3** though the yields were low to moderate. As shown in Table 2, entry 1, M41 showed high selectivity (84%) and moderate conversion (63%) in the reaction of *p*-tolualdehyde (**1f**) with **2a**. The catalytic activity of M41 for aromatic aldehyde was good but the possibility of its improvement with addition of metal ion was investigated here. As summarized in Table 2, the planting of Al, Ti, and La onto M41 greatly improved the yields of **3f** and further the selectivity also became better from 84% to 89–91%. It would be worth to note that the highest yield of 86% was obtained on Al-M41 and we needed neither the reflux condition nor large amount of catalyst used[5–7] (Table 2, entry 2).

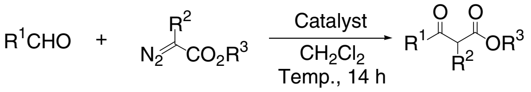
The excellent catalytic activity of Al-M41 led us to investigate systematically the reactions of various substrates (Table 3). Entries 1[16] and 2 concluded that the catalytic activity of Al-M41 was better than or similar to that of M41 (Table 1) for the condensation of aliphatic aldehyde **1c** or **1d** with **2a**. The aromatic aldehydes were applicable partners in the β-keto ester synthesis on Al-M41 and gave 3-oxo-3-aryl propionic acid esters in 50–86% yields (entries 3–5). In addition, the reactions of α-substituted diazoacetates with aldehydes afforded 3-oxo-2-phenyl propionic or 3-oxo-2-methyl acid esters in good yields (entries 6–8).[17] They can provide a direct way for the catalytic synthesis of 3-oxo-2-substituted propionic acid esters. 2-Pyridinecarboxaldehyde (**1l**) and 4-nitrobenzaldehyde (**1m**) did not give good yields on Al-M41 (entries 9 and 10), while the use of Ti-M41 instead of Al-M41 improved the yields. Although the active sites of M41, Al-M41, and Ti-M41 catalysts still remain unclear, appropriate Lewis acidity of Ti ion would prevent the substrates bearing basic functional groups from occasionally coordinating to acid sites and deactivating the catalytic activities.

Finally two important findings should be noted. Firstly, the reusability of the present catalyst was examined. The Al-M41 catalyst was recovered by filtration after the reaction of **1c** with **2a**, dried at 353 K for 1 h, and evacuated at 373 K for 1 h (the same treatment as that in the 1st run). The results of 2nd and 3rd runs are shown in Table 3, entry 1. The yields after 10 min were slightly lower than that of 1st run, but those after 60 min were all >99%. The results indicate that the present Al-M41 was reusable without significant loss of the catalytic activity. Secondly, the catalytic activity of Al-M41 (and Ti-M41) was compared with that of the reported catalysts. $SnCl_2$[3] and $NbCl_5$[4] were employed here as the reference catalysts, and the results determined in this study are summarized in Table 3. At first it should be noted that the results in the present $SnCl_2$-catalyzed reactions are in good agreement with those of the literature[3] (entries 2 and 5). The catalytic activity of Al-M41 for the reaction of aliphatic aldehydes with **2a** (entries 1 and 2) was greater than or almost the same as that of $SnCl_2$. The difference between the yields on the former and the latter became larger in the reactions of aromatic aldehydes (entries 3–5). The catalytic activity of $SnCl_2$ for the syntheses of **3i**–**m**, not reported in the literature, was much lower than that of M-M41 as shown in entries 6–10. In the case of $NbCl_5$ (5 mol %), the yields of β-keto esters were always low without exception. We should add that unfortunately we could not reproduce the Yadav's results[4] in the present experiments, though the reactions were performed under strict anhydrous conditions by using purified $NbCl_5$ and reagents.

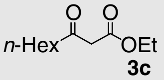
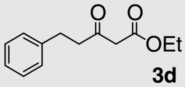
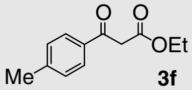
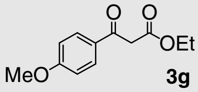
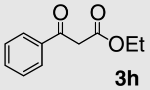
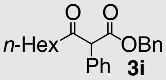
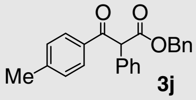
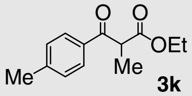
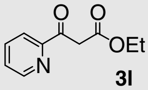
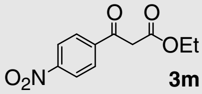
In summary, mesoporous silica M41 and Al- or Ti-loaded M41 were highly active for the synthesis of β-keto esters from a wide variety of aldehydes and diazoesters. The catalytic activity was much higher than that of $SnCl_2$ and $NbCl_5$, and furthermore M41 and its modified ones required only mild reaction conditions such as room temperature and short reaction time. Substituted diazoesters could also be used as substrates; as a result, 3-oxo-2-substi-

Table 3

Synthesis of various substituted β-keto ester on MCM-41



1 **2** **3**

Entry	Product	Temp (K)	Yield (%)		
			Al-M41[a]	$SnCl_2$[b]	$NbCl_5$[c]
1[d]	 **3c**	298	>99,[e] >99[f] 86,[e,g] >99[f,g] 80,[e,h] >99[f,h]	76	34
2[i]	 **3d**	298	82	85	71
3[d]	 **3f**	273	86	41	49
4[i]	 **3g**	298	50	30	39
5[d]	 **3h**	298	78	49	20
6[i]	 **3i**	298	41	5	6
7[i]	 **3j**	298	59	9	16
8[i]	 **3k**	298	55	48	12
9[i]	 **3l**	298	19, 53[j]	10	14
10[i]	 **3m**	298	16, 65[j]	17	11

[a] Typical reaction conditions: Al-M41, 50 mg; **1**, 0.50 mmol; **2**, 0.75 mmol; CH_2Cl_2, 2.5 mL; 14 h.

[b] By using 10 mol % of $SnCl_2$ as a catalyst.

[c] By using 5 mol % of $NbCl_5$ as a catalyst.

[d] GC yield.

[e] Reaction time, 10 min.

[f] Reaction time, 60 min.

[g] 2nd run. Since the amount of Al-M41 recovered after the 1st run was 36 mg, the following reaction conditions were applied: **1**, 0.36 mmol; **2**, 0.54 mmol, CH_2Cl_2, 1.8 mL.

[h] 3rd run. Recovered Al-M41, 25 mg; **1**, 0.25 mmol; **2**, 0.38 mmol; CH_2Cl_2, 1.3 mL.

[i] Isolated yield.

[j] By using 50 mg of Ti-M41 ([Ti] = 0.90 mmol g^{-1}, Si/Ti = 16) as a catalyst.

tuted propionic acid esters were directly obtained through the reaction.

References and notes

1. Several preparation methods of β-keto esters such as Claisen condensations were described below: (a) Benetti, S.; Romagnoli, R.; Risi, C. D.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065–1114; (b) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Benjamin: New York, 2001; pp 569–573; (c) Iida, A.; Takai, K.; Okabayashi, T.; Misaki, T.; Tanabe, Y. *Chem. Commun.* **2005**, 3171–3173; (d) Sato, T.; Itoh, T.; Fujiwara, T. *Chem. Lett.* **1982**, 1559–1560.
2. (a) Schlotterbeck, F. *Chem. Ber.* **1909**, *42*, 2565–2573; (b) Curtius, T.; Buchner, E. *Chem. Ber.* **1885**, *18*, 2371–2377.
3. Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260.
4. Yadav, J. S.; Subba Reddy, B. V.; Eeshwaraiah, B.; Reddy, P. N. *Tetrahedron* **2005**, *61*, 875–878.
5. Dhavale, D. D.; Patil, P. N.; Mali, R. S. *J. Chem. Res. (S)* **1994**, 152–153.
6. Balaji, B. S.; Chanda, B. M. *Tetrahedron* **1998**, *54*, 13237–13252.
7. Phukan, P.; Mohan, J. M.; Sudalai, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3685–3689.
8. (a) Mahmood, S. J.; Hossain, M. M. *J. Org. Chem.* **1998**, *63*, 3333–3336; (b) Dudley, M. E.; Morshed, M. M.; Brennan, C. L.; Islam, M. S.; Ahmad, M. S.; Atuu, M.; Branstetter, B.; Hossain, M. M. *J. Org. Chem.* **2004**, *69*, 7599–7608.
9. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Eur. J. Org. Chem.* **2002**, 1562–1565.
10. (a) Tanaka, Y.; Sawamura, N.; Iwamoto, M. *Tetrahedron Lett.* **1998**, *39*, 9457–9460; (b) Iwamoto, M.; Yasuhiro, T.; Sawammura, N.; Namba, S. *J. Am. Chem. Soc.* **2003**, *125*, 13032–13033; (c) Ishitani, H.; Iwamoto, M. *Tetrahedron Lett.* **2003**, *44*, 299–301.
11. (a) Itoh, A.; Kodama, T.; Maeda, S.; Masaki, Y. *Tetrahedron Lett.* **1998**, *39*, 9461–9464; Itoh, A.; Kodama, T.; Masaki, Y. *Chem. Pharm. Bull.* **2007**, *55*, 861–864; (c)(b) Yamamoto, T.; Tanaka, T.; Funabiki, T.; Yoshida, S. *J. Phys. Chem. B* **1998**, *102*, 5830–5839.
12. Abe, T.; Tachibana, Y.; Uematsu, T.; Iwamoto, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1617–1618.
13. Iwamoto, M.; Tanaka, Y. *Catal. Surv. Jpn.* **2001**, *5*, 25–36.
14. *Typical procedure for* β-*ketoester preparation*: a solution of aldehyde **1** (0.50 mmol) with tetradecane (0.10 mmol, internal standard) in 2.0 mL distilled CH_2Cl_2 was added to the evacuated M41s. Then, 0.75 mmol of diazoester **2** with 0.5 mL of CH_2Cl_2 were dropwised into the suspension (30 min). After 14 hour, the reaction media was diluted by CH_2Cl_2 and the catalyst was removed by the filtration. Yield was determined by preparative TLC or GC.
15. **3b** was 65% yield when CH_2Cl_2 was used as a solvent.
16. Ethyl diazoacetate **2a** was added at a stroke.
17. *Physical data of representative compounds:* **3i**: ^{1}H NMR (400 MHz; $CDCl_3$/TMS) δ (ppm) 0.83 (t, 3H, J = 7.0), 1.14–1.21 (m, 6H), 1.45–1.57 (m, 2H), 2.08 (t, 0.6H, J = 8.0), 2.44 (t, 1.4H, J = 7.2), 4.76 (s, 0.7H), 5.19 (s, 2H), 7.15–7.19 (m, 1H), 7.27–7.38 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ (ppm) 13.98, 22.42, 23.56, 26.63, 28.51, 28.83, 31.39, 31.43, 32.80, 41.64, 64.92, 65.76, 67.26, 127.02, 127.14, 127.80, 128.05, 128.26, 128.35, 128.38, 128.56, 128.83, 129.47, 131.33, 132.50, 135.40, 168.45, 203.65. Anal. for $C_{22}H_{26}O_3$ (338.19). Calcd: C, 78.07; H, 7.74; O, 14.18. Obsd: C, 77.67; H, 8.00; O, 14.89. Compound **3j**: ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ (ppm) 2.27 (s, 3H), 5.16 (s, 2H), 5.64 (s, 1H), 7.10–7.40 (m, 12H), 7.81 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ (ppm) 21.5, 60.41, 67.23, 126.32, 126.75, 127.27, 127.43, 127.90, 128.10, 128.24, 128.75, 129.13, 133.06, 135.56, 144.41, 168.77, 192.69. Anal. for $C_{23}H_{20}O_3$ (338.19). Calcd: C, 80.21; H, 5.85; O, 13.94. Obsd: C, 79.30; H, 6.02; O, 16.23. The amounts of carbon and hydrogen were analyzed in a usual manner with a CHNS-932 system of LECO Corporation. The oxygen content was separately determined with a CHNS-932 system using a VFT-900 furnace operated at 1573 K.