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COMMUNICATION

Mesoporous silica MCM-41 as a highly active, recoverable and reusable catalyst for direct amidation of fatty acids and long-chain amines†

Kenichi Komura,* Yu Nakano and Mamoru Koketsu

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Direct amidation of fatty acids with long-chain amines was successfully performed by mesoporous silica MCM-41, which showed the highest catalytic activity among other used homo- and heterogeneous catalysts. It was found that MCM-41 can be easily recovered from the reaction mixture followed by simple calcination treatment and reused without loss of its catalytic activity.

Amidation reaction is one of the most fundamental synthetic tools in organic chemistry,¹ which is generally conducted by using an excess amount of either carboxylic acid or amine in the presence of catalyst, and activation of acids by SOCl_2 or organic condensation agents such as DCC.² However, these classic methods involve some drawbacks, *i.e.* utilisation of corrosive and expensive reagents, emission of by-products and/or waste salts or gases, the removal of catalyst and tedious work-ups for purification. To overcome these issues, attempts directed at developing more practical and efficient methods have been postulated. For example, Yamamoto *et al.* reported the amidation by an arylboronic acid with electron-withdrawing substituents,^{3,4} and they have also developed a heterogeneous version using a polystyrene resin bounded 4-boronopyridinium salts.⁵ The combinations of $\text{Me}_2\text{NSOCl}_2$ and *N,N*-dimethylamine or tetrabenzylpyrophosphate (TBPP) and DMAP have been found to be effective catalysts developed by Tanabe *et al.*⁶ and Crooks *et al.*,⁷ respectively. Mukaiyama and co-workers recently have designed original dehydrating agents,⁸ tetrakis(alkoxy)silane $\text{Si}(\text{OR})_4$, and applied them to condensation reactions.^{9,10} We also have reported the direct amidation of fatty acids and long-chain amines catalyzed by multivalent metal salts such as $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyst.¹¹ Although these methods circumvent the utilization of corrosive and excess of reagents, considering the enhanced demands for environmentally benign chemistry, there still remains a task of improving the reusability of the catalyst and the facilitation of work-up. Thus a heterogeneous catalyst should be a promising candidate; in particular, an inorganic

catalyst has great potential to envisage a practical green and economic reaction system. If the amidation quantitatively occurs from the mixture containing an equimolar amount of acid and amine, only amide product can be obtained after removing the solvent through facile separation of the catalyst; furthermore, if the catalyst can be reused without loss of activity, this would offer an overwhelming advantage of being economic. Therefore, the development of a recyclable and reusable heterogeneous catalyst for amidation reactions has been paid much attention. Recently, Clark *et al.* reported the marvellous amide synthesis.¹² They claimed that the activated silica gel sufficiently catalyzed direct amidation, and this reaction system does not require removing formed water during catalysis. Akamanchi *et al.* have reported a solid catalyst for amide synthesis using the sulfated tungstate.¹³ Indeed, they have reported on a variety of combinations of acids and amines over activated silica gel catalyst; however, catalytic activity for fatty acids or long-chain amines is still unknown. Generally, the reactivity of a substance bearing a long aliphatic chain is lower than that of low molecular weight one, thus it is still a challenging task to achieve a heterogeneous catalytic system to produce *N*-alkyl fatty acid amides which are valuable chemicals often found in photographic materials, polyolefin foaming agents, stabilizers of polymers, and so on.¹⁴

Here, we wish to report the green and atom economical heterogeneous amidation using an equimolar amount of fatty acids and long-chain amines over mesoporous silica MCM-41 as a highly active, recyclable and reusable catalyst.

Results and discussion

Table 1 summarizes the results of the amidation using an equimolar amount of palmitic acid and hexylamine over various catalysts. We have operated the reactions in toluene solvent using a typical condensation apparatus (Dean–Stark) to remove the formed water by an azeotropic reflux. In the absence of any catalysts, the reaction did not proceed well giving 20% yield (entry 1). The use of typical condensation catalysts such as H_2SO_4 and *p*-toluenesulfonic acid also gave poor results with 14% and 19% yields, respectively (entries 2 and 3). The decrease of the yield by H_2SO_4 is due to the formation of stable ammonium salt between the amine. Multivalent metal salts such as $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ showed high catalytic activity at *m*-xylene reflux

Department of Materials Science and Technology, Faculty of Engineering, Gifu University, Gifu City, 501-1193, Japan.
E-mail: kkomura@gifu-u.ac.jp; Tel: +08-58-293-2600

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Table 1 Amidation of palmitic acid with *n*-hexylamine using various catalysts^a

Entry	Catalyst	Yield ^b /%
1	None	20
2	H ₂ SO ₄ ^c	14
3	<i>p</i> -TsOH ^d	19
4	FeCl ₃ ·6H ₂ O ^d	24
5	Nafion [®]	26
6	Silica gel ^f	68
7	Silica gel ^g	87
8	H–Y zeolite ^h	26
9	[Al]MCM-41 ⁱ	76
10	MCM-41	94

^a Reaction was performed by using palmitic acid (3 mmol) and *n*-hexylamine (3 mmol) in toluene (15 ml) in the presence of catalyst (20 wt%) at reflux temperature for 6 h. ^b Yield was determined by GC. ^c 8.4 mol% of H₂SO₄ was used. ^d 5.0 mol% of catalyst was used. ^e 0.2 g of resin was used. ^f Silica gel 60 (Merck) was used. ^g Activated at 700 °C of silica gel 60 (Merk). ^h SiO₂/Al₂O₃ = 5.6. ⁱ SiO₂/Al₂O₃ = 103.

in our recent report; however, at toluene reflux the yield of amide was not satisfactory at 24% (entry 4), and this trend is in good agreement with our previous results.¹¹ The ion exchanged resin (proton type) as an organic heterogeneous catalyst, Nafion[®], did not show sufficient catalytic activity, giving a 26% yield (entry 5). According to the report by Clark *et al.*, we have also demonstrated the amidation by silica gel as a solid catalyst, resulting in a moderate yield of amide (68%). However, as it can be expected, the silica gel catalyst activated at 700 °C offered the excellent yield (87%) of amine (entry 7). This result encouraged us to apply solid acid catalysts such as zeolite, since zeolite is a microporous aluminosilicate with a strong acidity.¹⁵ However, the utilisation of typical solid acid H–Y zeolite bearing three dimensional pore systems in 0.74 nm diameter¹⁶ was not suitable for this amidation, giving in 26% yield (entry 8). This is due to the limitation of the size of substrates to enter and diffuse into the pore, thus we chose a mesoporous aluminosilicate ([Al]-MCM-41) having Brønsted acid sites to enhance the diffusion of substrates. The catalytic activity was almost the same as the silica gel catalyst, affording the amide in 76% yield (entry 9). Interestingly, we found that quantitative amide formation in 94% yield was observed with MCM-41 catalyst which has large surface area (884 m² g⁻¹) and uniformed pores (pore diameter = 3.04 nm estimated by BJH method) (entry 10). MCM-41 is one of the mesoporous materials having uniformed hexagonal pores with *P6mm* space group and has been widely utilized by many researchers based on its unique characters.¹⁷ Actually, MCM-41 is constructed by amorphous SiO₂ units; however, it is known that their pore walls have homogeneously exposed silanol groups which can often be utilize for covalent grafting or physical adsorption to design functional catalysts.¹⁸ It is remarkable that the weak acid site (SiOH) rather than typical Brønsted acid site (Si–OH–Al) of the solid catalyst should be suitable to accomplish a sufficient amidation reaction. Clark *et al.* also claimed the importance of weak acidity for efficient amide formation.¹² Thus, the exposed silanols of MCM-41 gave an appropriate environment for catalysis; further it is notable that the large surface area of MCM-41 should also be responsible for the enhancement of catalytic activity.

Table 2 Results of the amidation of fatty acids with long-chain amines over MCM-41 catalyst^a

Entry	Acids	Amines	Yield ^b /%
1	Palmitic acid	<i>n</i> -Hexylamine	94
2	Palmitic acid	<i>n</i> -Octylamine	>99
3	Palmitic acid	<i>n</i> -Decylamine	>99
4	Palmitic acid	<i>n</i> -Dodecylamine	>99
5	Palmitic acid	<i>n</i> -Tetradecylamine	>99
6	Palmitic acid	<i>n</i> -Hexadecylamine	>99
7	Octanoic acid	<i>n</i> -Hexylamine	90
8	Decanoic acid	<i>n</i> -Hexylamine	89
9	Dodecanoic acid	<i>n</i> -Hexylamine	85
10	Myristic acid	<i>n</i> -Hexylamine	88
11	Stearic acid	<i>n</i> -Hexylamine	>99
12	Oleic acid	<i>n</i> -Hexadecylamine	>99

^a Reaction was carried out by using acid (3 mmol) and amine (3 mmol) in the presence of 20 wt% of MCM-41 in toluene (15 ml) at reflux for 6 h. ^b Yield was determined by GC.

Mesoporous silica MCM-41 showed excellent catalytic activity for amide formation from the mixture of fatty acid and long-chain amine, as given in Table 1. We then examined the amidation of various combinations of fatty acids and long-chain amines over MCM-41 catalyst (Table 2). Interestingly, almost all amides combined with palmitic acid and long-chain aliphatic amines from C6 (hexylamine) to C16 (hexadecylamine) were quantitatively obtained in >99% yields (entries 1 to 6). In our recent reports, the yield of the product was strongly depended on the chain length of the substrate: with increasing the carbon number usually decreasing its yield.^{11,19} However, it is obvious that MCM-41 has a high potential for catalysis. Further, the amidation between various fatty acids with different chain-length (C8 to C18) and hexylamine can be also performed in excellent yields over MCM-41 catalyst (entries 7 to 11). Notably, when an oleic acid bearing the unsaturated moiety was used as a substrate in the reaction with hexadecylamine (C16), the corresponding amide can be obtained in quantitative yield without any side reactions such as isomerization of the alkene moiety (entry 12).

Amidation of fatty acids and long-chain amines proceeded well with the MCM-41 catalyst resulting in the quantitative yields. Instead of long-chain amines, lower molecular weight amines were used as substrates. Results are given in Table 3. The values in parentheses are yields of amide in the absence of MCM-41 catalyst (control experiments). The use of aromatic amines such as aniline produces the corresponding amide in 93% isolated yield, and it is obvious, comparing with the control experiment, that MCM-41 shows excellent behavior as a catalyst (entry 1). An excellent result was also obtained in the reaction of benzylamine to afford the amide in 92% yield, although moderate formation of amide was detected in the control experiment (entry 2). However, the steric hindrance of used amines severely affects the reaction: moderate yield and no reaction were observed in reactions of cyclohexylamine and *tert*-butylamine, respectively (entries 3 and 4), and only a trace of amide was detected in the reaction of a secondary long-chain amine (entry 5). In contrast, the reaction of an aliphatic cyclic amine gave the corresponding product quantitatively (entry 6), where this is likely to be due to the higher basicity

Table 3 Results of the amidation of palmitic acid with various amines over MCM-41 catalyst^a

Entry	Amines	Yield ^b /%
1	Aniline	93 (trace)
2	Benzylamine	92 (42)
3	Cyclohexylamine	59 (8)
4	<i>Tert</i> -butylamine	0 (0)
5	<i>N,N</i> -Diethylamine	3 (trace)
6	Pyrrolidine	94 (50)

^a Reaction was carried out by using acid (3 mmol) and amine (3 mmol) in the presence of 20 wt% of MCM-41 in toluene (15 ml) at reflux for 12 h. ^b Isolated yield. The values in parentheses are yields of control experiments (without MCM-41 catalyst).

of pyrrolidine, because the reaction moderately proceeded even in the absence of MCM-41 catalyst. These results suggest that MCM-41 effectively catalyzed the reaction for less sterically hindrance substrates.

The amidation of fatty acids and long-chain aliphatic amines catalyzed by MCM-41 gave an excellent opportunity for practical applications that are green, environmentally benign and atom economical. Then we have attempted to examine the recyclability and reusability of the MCM-41 catalyst and have demonstrated this by the reaction of palmitic acid with hexylamine as a model reaction. The results are given in Fig. 1. The MCM-41 catalyst can be completely recovered from the reaction mixture by filtration, and the collected catalyst was treated in two different manners prior to use in the next reaction; calcination at 550 °C under air flow (black bar in Fig. 1), or rinsed with chloroform and dried at 60 °C for overnight (white bar in Fig. 1). When treated by rinsing with CHCl₃, the yield of amide declined to 67% after the 1st reuse, however, further reuse until the 4th repeat did not significantly drop the yield. TG-DTA analysis of used catalyst revealed an exothermic peak at 300 °C corresponding to the decomposition and/or the combustion of organic compounds adsorbed on the pore wall surface. Thus we carried out calcination of the used MCM-41 and utilized it for repeat experiments, which resulted in excellent yields of amide until the 4th time reuse. This suggests that MCM-41 is

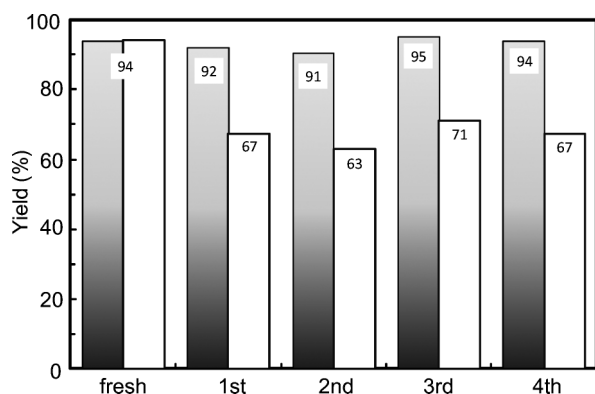


Fig. 1 Results of reuse experiments of MCM-41 catalyst. Reaction was performed with palmitic acid (3 mmol), *n*-hexylamine (3 mmol) and MCM-41 (20 wt%) in toluene (15 mL) at reflux for 6 h. Black bar: calcination; white bar: rinse with CHCl₃.

a marvellous catalyst which is highly active, recoverable and reusable.

Experimental

A round-bottom flask containing the mixture of fatty acid (3 mmol), amine (3 mmol) and MCM-41 (20 wt%) in toluene (15 ml) equipped with a Dean–Stark apparatus was heated at azeotropic reflux temperature for 6 h. After cooling to ambient temperature, the suspended MCM-41 was removed by filtration and rinsed with CHCl₃. A small portion was taken from the collected filtrate to determine the conversion and yield by gas chromatography (Shimadzu 18A, column: Ultra ALLOY⁺-65). Purification was carried out by column chromatography using hexane–EtOAc (3/1) as an eluent, and the isolated products were identified by both ¹H and ¹³C NMR (ECA-500 NMR, JEOL). Note: The utilization of toxic chloroform, through extremely undesirable, was necessary to estimate accurate yields of amides by GC due to their poor solubility.

Conclusions

Amide compounds can be excellently prepared by MCM-41 catalyst from the mixture of an equimolar amount of long-chain aliphatic acids and amines. The MCM-41 catalyst is non-toxic and safe, and further it can be recovered and reused without loss of its catalytic activity. Hence, this offers a great advantage for a green chemical process with highly atom economy. Further research is ongoing and we will report in near future.

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