A. Taher et al.

Letter

Amine-functionalized Metal-Organic Frameworks: An Efficient and Recyclable Heterogeneous Catalyst for the Knoevenagel Condensation Reaction

Α

Abu Taher Dong-Jin Lee Byoung-Ki Lee Ik-Mo Lee*

Department of Chemistry, Inha University, Incheon 402-751, Korea imlee@inha.ac.kr



R¹ = H, Me; R² = H, Cl, Br, HO, Me, MeO, NO₂; X = CN, COOEt

Received: 03.12.2016 Accepted after revision: 12.01.2016 Published online: 05.02.2016 DOI: 10.1055/s-0035-1561356; Art ID: st-2015-u0937-I

Abstract A highly efficient and reusable catalyst based on metal-organic frameworks (MOF) has been synthesized by post-functionalization and applied in Knoevenagel condensations of various aldehydes and ketones. The catalytic efficiency was demonstrated by the high conversion (over 85–98%) of the reactants under mild conditions. The catalyst maintained its unique framework after the reaction and could be recycled and reused several times without significant loss of activity.

Key words Knoevenagel condensation, metal-organic frameworks, heterogeneous catalysis, carbon–carbon bond, aldehyde, ketone

The Knoevenagel condensation¹ is one of the most important and widely used methods for the formation of carbon-carbon bonds in organic synthesis.² The condensation reaction occurs between carbonyl compounds and activated methylene compounds. This carbon-carbon bond coupling reaction is useful for the preparation of important intermediates in drug production. In addition, this reaction is employed as a classic test reaction to analyze the activity of a variety of solid base catalysts. The typical pK_a values of hydrogen atoms in β -dicarbonyl compounds are in the range of 9-11.³ This makes them ideal substrates for test reactions utilizing Knoevenagel condensations. Active methylene groups of compounds with different pK_a values can be reacted with benzaldehyde to test the activity of a basic catalyst. Owing to their importance from an industrial and synthetic point of view, a large number of methods for Knoevenagel condensations has been reported employing Lewis acids or bases,⁴ microwave assistance,⁵ or ultrasound irradiation.⁶ Furthermore, biotechnology-based approaches,⁷ solid-phase reactions,⁸ and methods using ionic liquids,⁹ green solvents such as water,¹⁰ or grindstones under solvent-free conditions have been developed.¹¹ All these protocols have drawbacks, such as use of expensive homogeneous catalysts, harsh thermal conditions, disposal of toxic solvents and catalysts, or long reaction times. As a result, the development of heterogeneous catalytic systems for chemical synthesis has attracted increasing attention, and these systems can lead to novel environmentally benign chemical procedures for academia and industry.¹²

The newly developed porous MOF structures are a promising new generation of heterogeneous catalytic materials¹³ affording studies in the coordination space provided by the 3D structure of the MOF due to (i) the well-ordered size and shape of the pores, (ii) the flexible and dynamic behavior in response to guest molecules, and (iii) the designable channel surface functionalities. Porous MOFs can be constructed rapidly from multidentate ligands through selfassembly, where the ligand topology and coordination tendencies depend on the metal ion. For the optimal catalytic activity, two types of strategies are used: (a) introduction of organic groups to provide guest-accessible functional organic sites¹⁴ and (b) formation of coordinatively unsaturated metal sites.¹⁵ If the metal is saturated coordinatively, the organic moiety incorporating the functionality for non-covalent interactions can bind the reactant(s) through H-bonding, or non-covalent stacking, leading to their activation. Herein, we report a highly active and recyclable catalyst obtained by post-functionalization of MOF for Knoevenagel condensations between an aldehyde or ketone and malononitrile or ethyl cyanoacetate, catalyzed by the primary amines embedded inside the well-known MOF [see Scheme 1 in the Supporting Information (SI)]. The activities were compared with those of the homogeneous counterparts benzylamine and aniline, and the heterogeneous IR-MOF-3 catalyst.

The azide-functionalized MOF-N₃ was prepared from an azide-containing organic linker using zinc nitrate hexahydrate in N,N-diethylformamide (DEF) as described earlier.¹⁶ The XRD pattern of as-synthesized MOF-N₃ (Figure 1, a) was similar to the literature.¹⁶ In the FT-IR spectra, the crystals showed a stretching band of the azide groups at 2100 cm⁻¹ with the C–O stretching band of zinc carboxylate at 1400 cm⁻¹ (Figure 1, b). These facts suggested that two azide groups were introduced on each organic linker in the frameworks of MOF-N₃.¹⁷ Then, we tried reduction of the azide groups by using triphenylphosphine (PPh₃) as reducing agent in DEF. The optical microscope observation illustrated that there was no apparent damage to the shape and the edges of the MOF crystals after modification (see Figure S1a in the SI). The progress of the reducing reaction of MOF-N₃ was monitored by FT-IR as shown in Figure 1, b. After 10 hours, the azide stretching band at 2100 cm⁻¹ disappeared completely, an NH stretching band at 3300 cm⁻¹ was observed, and C=O stretching at ca. 1700 cm⁻¹ showed no changes (Figure 1, b). Therefore, the C-O band was still maintained along with Zn (see Figure S2 in the SI) after modification indicating that the MOF framework was constructed by zinc ions and carboxylate anions.



Furthermore, the formation of amine functionalities in the MOF crystals was qualitatively confirmed by a ninhydrin test according to a literature procedure.¹⁷ A red color developed that the starting MOF-N₃ did not display (see Figure S1b in the SI). This observation strongly suggested that Downloaded by: University of Otago. Copyrighted material.

the azide groups of MOF-N₃ were reduced to the primary amine groups. The complete conversion of the azide groups was also confirmed by the ¹H NMR spectrum after digestion of the reacted crystals (see Figure S3 in the SI). The signal of the benzyl protons at 4.3 ppm was shifted to 3.8 ppm. The XRD pattern of the MOF-NH₂ crystals exhibited no apparent changes compared to the XRD pattern of the starting MOF-N₃ as shown in Figure 1, a. The MOF-NH₂ and the parent compound showed identical thermal stability (see Figure S4 in the SI). The BET surface area and pore volume of MOF-NH₂ were 516.18 $m^2 \cdot g^{-1}$ and 0.29 cm³ \cdot g^{-1}, respectively, and the modified MOF showed type I N₂-adsorption-desorption isotherms (see Figure S5 in the SI), again suggesting that the structure of the parent MOF remained intact after functionalization. To gain further insights, we also performed XPS analysis. Careful analysis showed the presence of a split peak with maxima at 400 and 401 eV for the azide groups¹⁸ (Figure 1, c). Maxima at 398 and 399 eV for the primary amine groups¹⁹ (Figure 1, d) suggested the complete conversion of the azide functionalities to amines.

The Knoevenagel condensation of aldehydes with compounds containing activated methylene groups is a robust reaction often used to test the catalytic activities of basic catalysts.²⁰ This reaction is catalyzed by alkali metal hydroxides or by homogeneous organic bases, such as primary, secondary and tertiary amines.²¹ On the other hand, recycling and catalyst recovery have been problems in their use in the production of fine chemicals. Initially, the Knoevenagel condensation of benzaldehyde was performed using various amounts of the catalyst MOF-NH₂ to screen the loading. The yield of the reaction gradually increased with increasing catalyst loading (0–0.15 mmol of –NH₂ groups, see Figure S7 in the SI). In addition, high catalytic activity was still observed with a very low catalyst loading. Although the reaction yield reached almost 100% with 0.10 mmol of -NH₂ groups in MOF-NH₂, 0.13 mmol and 0.15 mmol gave 100% yield in the reaction of benzaldehyde at 80 °C in DMF. Therefore, 0.13 mmol loading of –NH₂ groups in MOF-NH₂ was determined to be the optimal loading under such reaction conditions. Furthermore, solvents were screened to reach higher efficiency in the condensations (Figure 2, a). Water and toluene were poor solvents, and the crystal structure of MOF-NH₂ was deformed when water was used as a solvent (see Figure S8 in the SI). The Knoevenagel condensation of benzaldehyde reached only 55-65% conversion in DMA, DME and ethanol. The results showed that DMF proved the best solvent regarding the catalytic activity. With the optimized conditions in hand, the reactions of various aromatic substituted aldehydes or ketones with malononitrile or ethyl cyanoacetate were investigated and the results are listed in Table 1.24

A. Taher et al.

 Table 1
 Knoevenagel Condensation of Various Aldehydes and Ketones

 Catalyzed by MOF-NH₂ in DMF^a



R¹ = H, Me; R² = H, Cl, Br, HO, Me, MeO, NO₂; X = CN, COOEt

Entry	Product	Time (h)	Yield (%) ^b Mp (°C)		
				Found	Reported
1 ^c	CN CN	4.5	51	84	84 ²²
2	CN CN	4.5	98	84	84 ²²
3	CI CN	4	97	159	162 ²²
4	HOCN	5	90	187	188 ²²
5	HO	4.5	86	164	164 ²³
6	O ₂ N CN	4	97	160	160 ²²
7	O ₂ N CN	3.5	85	107	107 ²³
8	CN CN	7	88	91	92 ²²
9	CN	6.5	92	134	135 ²³
10	MeO	7	87	133	113 ²³
11	CN COOEt	5	98	51	50 ²²
12	CI COOEt	6.5	91	88	88 ²²

Table 1 (continued)

Entry	Product	Time (h)	Yield (%) ^b Mp (°C)		
				Found	Reported
13	CI COOEt	5	90	91	93 ²²
14	HO COOEt	6	96	173	173 ²²
15	O ₂ N COOEt	4	95	130	131 ²²
16	O ₂ N COOEt	6.5	90	143	144 ²²
17	Br COOEt	6.5	86	83	84 ²²

^a Reaction conditions: aldehyde or ketone (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol), MOF-NH₂ (0.13 mmol of $-NH_2$ groups), DMF (6 mL), 80 °C.

^b Isolated yields.
^c Control experiment using MOF-N₃: MOF-N₃ and MOF-NH₂ were calculated to have the same amount of Zn²⁺ ions, selectivity 100%.

Control experiments using MOF-N₃ under exactly the same reaction conditions were carried out, showing that the MOF-N₃ material was less effective than MOF-NH₂ (Table 1, entries 1 and 2). The catalytic activity of MOF-N₃ presumably results from coordinatively unsaturated zinc sites.²⁵ All reactions proceeded smoothly to give the corresponding Knoevenagel condensation products in high yield with 100% selectivity under those conditions (entries 2-17). The catalytic activity of MOF-NH₂ for benzaldehyde, 4chlorobenzaldehyde, 4-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, acetophenone, 4-methylbenzaldehyde, and 4-methoxylbenzaldehyde with malononitrile was high in DMF (entries 2-10). The electron-withdrawing groups (EWG) promoted this condensation efficiently and reduced the reaction time (entries 3, 6, 7) as compared to the electron-donating groups (EDG) (entries 4, 5, 9 and 10). In addition, the catalytic system could be extended to various aldehydes and ketones in reaction with ethyl cyanoacetate, and showed high activity in DMF (entries 11-17). The Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate was close to quantitative in yield (98%, entry 11). Electron-withdrawing derivatives, such as 4-chlorobenzaldehyde, 1-(4-chlorophenyl)ethanone, 4-nitrobenzaldehyde, 1-(4-nitrophenyl)ethanone, and 1-(4-bromophenyl)ethanone (entries 12, 13, 15,

Letter

A. Taher et al.

D

16, and 17), along with the electron-donating derivatives, such as 4-hydroxybenzaldehyde (entry 14), showed satisfactory yields of 86–98%. Interestingly, the EWG gave the products in shorter time as compared to the EDG. Furthermore, the catalyst also performed well for ketones to give the corresponding condensation products in up to 90% yield (entries 8, 13, 16 and 17). These results demonstrate that MOF-NH₂ successfully promoted the Knoevenagel condensation reactions of various aldehydes and ketones, having either EWGs or EDGs.

The activity of MOF-NH₂ was compared to that of benzylamine, aniline and IRMOF-3 at 80 °C in DMF (Figure 2, b), considering that the total number of amino groups was equal in all cases. These results clearly demonstrate that the reactivity of the benzylamino groups is enhanced when incorporated into the MOF structure, and the reactivity of the benzylamine is superior to that of aniline. Therefore, the high activity of MOF-NH₂ is most likely due to an enhancement of the basicity of the benzylamino groups upon incorporation into the MOF framework, along with the coordinatively unsaturated zinc sites.²⁵ Furthermore, this enhancement would be due to the structure of pores and the surface functionalization of the MOF frameworks (see Figures S5 and S6 in the SI).



Figure 2 Knoevenagel condensation of benzaldehyde with malononitrile catalyzed by MOF-NH₂. (a) Screening of different solvents. (b) Comparative catalytic study with the same catalyst loading (0.13 mmol $-NH_2$ groups). (c) Hot filtration test. (d) Recyclability test. In all cases the reaction conditions are the same as given in Table 1.

The crucial issue with regard to a heterogeneous catalyst is the possibility that active molecules can migrate from the solid to the liquid phase by leaching. These leached molecules would become responsible for a significant contribution to the catalytic activity. Two reactions with benzaldehyde were carried out, with continuous monitoring of the conversion after 1.5 hours. One reaction was carried out in presence of the catalyst until the conversion was 41%, and then the solid part of the reaction mixture was filtered off. The liquid phase was then transferred to another clean reaction vial and allowed to react further, but no significant change in conversion was observed (Figure 2, c). After 4.5 hours, 43% conversion was noted which indicates that no active species was present in the reaction vial. In addition, the reusability of the catalyst was examined.

The major advantage of the catalyst was the easy recovery by filtration or centrifugation. The recycling of the catalyst was examined by the coupling of benzaldehyde with malononitrile (Figure 2, d). Similar yields (100–98%) were obtained by performing five runs without any significant loss of activity. The XRD patterns of the catalyst after reuse were indistinguishable from those of the fresh catalyst (see Figure S8 in the SI), suggesting that no structural deterioration or organic and metal complex decomposition had occurred after the catalytic reaction and filtration. Therefore, MOF-NH₂ most likely maintained a similar structural framework that could be helpful for using it as a heterogeneous catalyst.

The present work focused on a well-known and important type of metal-organic framework, MOF-NH₂, which possesses exceptionally high catalytic activity. The repeated reactions performed with the recycled catalyst maintained similar yields without significant loss of activity or selectivity. Interestingly, MOF-NH₂ showed the highest catalytic activities among benzylamine, aniline and IRMOF-3 in all cases. The advantages of the present method are the simplicity of work-up, high yields and recyclability. Moreover, the exceptional reactivity of the novel composites prompted our concurrent inquiry into applications of these catalytic matrices in a multitude of catalytic reactions and engineering processes.

Acknowledgment

This work is supported by Inha University Research Grant (Inha 2014)

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561356.

References and Notes

- (1) Knoevenagel, E. Ber. Dtsch. Chem. Ges. 1894, 27, 2345.
- (2) (a) Knoevenagel, E. Ber. Dtsch. Chem. Ges. 1898, 31, 2585.
 (b) Jones, G. Org. React. (N. Y.) 1967, 15, 204. (c) Tietze, L. F.; Beifuss, U. In Comprehensive Organic Synthesis; Vol 2; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, 341.
- (3) Solomons, T. W. G.; Fryhle, C. Organic Chemistry; Wiley: New York, 2009.

Syn<mark>lett</mark>

A. Taher et al.

- (4) (a) Rao, P. S.; Venkataratnam, R. V. Tetrahedron Lett. 1991, 32, 5821. (b) Prajapati, D.; Sandhu, J. S. J. Chem. Soc., Perkin Trans. 1 1993, 739. (c) Lehnert, W. Tetrahedron Lett. 1970, 11, 4723. (d) Dai, G.; Shi, D.; Zhou, L.; Huaxue, Y. Chin. J. Appl. Chem. 1995, 12, 104. (e) Gill, C.; Pandhare, G.; Raut, R.; Gore, V.; Gholap, S. Bull. Catal. Soc. India 2008, 7, 153.
- (5) (a) Mogilaiah, K.; Reddy, C. S. *Synth. Commun.* **2003**, 33, 3131.
 (b) Mallouk, S.; Bougrin, K.; Laghzizil, A.; Benhida, R. *Molecules* **2010**, *15*, 813. (c) Bhuiyan, M. M. H.; Hossain, M. I.; Ashraful, M.; Mahmud, M. M. J. Chem. **2012**, *2*, 30.
- (6) (a) McNulty, J.; Steere, J. A.; Wolf, S. *Tetrahedron Lett.* **1998**, *39*, 8013. (b) Palmisano, G.; Tibiletti, F.; Penoni, A.; Colombo, F.; Tollari, S.; Garella, D.; Tagliapietra, S.; Cravotto, G. Ultrason. Sonochem. **2011**, *18*, 652.
- (7) (a) Pratap, U. R.; Jawale, D. V.; Waghmare, R. A.; Lingampalle, D. L.; Mane, R. A. New J. Chem. 2011, 35, 49. (b) Wang, C.; Guan, Z.; He, Y. Green Chem. 2011, 13, 2048.
- (8) (a) Xia, Y.; Yang, Z.-Y.; Brossi, A.; Lee, K.-H. Org. Lett. 1999, 1, 2113. (b) Guo, G.; Arvanitis, E. A.; Pottorf, R. S.; Player, M. P. J. Comb. Chem. 2003, 5, 408.
- (9) (a) Ying, A.-G.; Liu, L.; Wu, G.-F.; Chen, X.-Z.; Ye, W.-D.; Chen, J.-H.; Zhang, K.-Y. *Chem. Res. Chin. Univ.* **2009**, *25*, 876. (b) Khan, F. A.; Dash, F. J.; Satapathy, R.; Upadhyay, S. K. Tetrahedron Lett. **2004**, *45*, 3055. (c) Verdia, P.; Santamarta, F.; Tojo, E. *Molecules* **2011**, *16*, 4379.
- (10) (a) Bigi, F.; Conforti, M. L.; Maggi, R.; Piccinno, A.; Sartori, G. *Green Chem.* **2000**, *2*, 101. (b) Wang, S.; Ren, Z.; Cao, W.; Tong, W. *Synth. Commun.* **2001**, *31*, 673. (c) Oskooie, H. A.; Heravi, M. M.; Derikvand, F.; Khorasani, M.; Bamoharram, F. F. *Synth. Commun.* **2006**, *36*, 2819.
- (11) (a) Pasha, M. A.; Manjula, K. J. Saudi Chem. Soc. 2011, 15, 283.
 (b) Rong, L.; Li, X.; Wang, H.; Shi, D.; Tu, S.; Zhuang, Q. Synth. Commun. 2006, 36, 2407. (c) Ren, Z.; Cao, W.; Tong, W. Synth. Commun. 2002, 32, 3475.

 (12) (a) Dimitratos, N.; Lopez-Sanchez, J. A.; Hutchings, G. J. Chem.
 Sci. 2012, 3, 20. (b) Anastas, P. T.; Kirchhoff, M. M.; Williamson, T. C. Appl. Catal. A. 2001, 221, 3.

Letter

- (13) (a) Kitagawa, S.; Kitaura, R.; Noro, S. Angew. Chem. Int. Ed. 2004,
 43, 2334. (b) Dhakshinamoorthy, A.; Alvaro, M.; Garcia, H.
 Chem. Commun. 2012, 48, 11275.
- (14) Custelcean, R.; Gorbunova, M. G. J. Am. Chem. Soc. 2005, 127, 16362.
- (15) Kitaura, R.; Onoyama, G.; Sakamoto, H.; Matsuda, R.; Noro, S.; Kitagawa, S. *Angew. Chem. Int. Ed.* **2004**, 43, 2684.
- (16) Goto, Y. H.; Shinkai, S. S.; Sada, K. J. Am. Chem. Soc. **2008**, 130, 14354.
- (17) Nagata, S.; Sato, H.; Sugikawa, K.; Kokado, K.; Sada, K. CrystEng-Comm **2012**, 14, 4137.
- (18) Haensch, C.; Hoeppener, S.; Schubert, U. S. Nanotechnology 2008, 19, 035703.
- (19) Adenier, A.; Chehimi, M. M.; Gallardo, I.; Pinson, J.; Vila, N. Langmuir 2004, 20, 8243.
- (20) Freeman, F. Chem. Rev. 1980, 80, 329.
- (21) Macquarrie, D. J.; Jackson, D. B.; Clark, J. H. In Supported catalysts and their application; Sherrington, D. C.; Kybett, A. P., Eds.; RSC: Cambridge, 2001.
- (22) Gupta, R.; Gupta, M.; Paul, S.; Gupta, R. Bull. Korean Chem. Soc. **2009**, 30, 2419.
- (23) Pal, R. Int. J. Adv. Chem. 2014, 2, 27.
- (24) Knoevenagel Condensations Using MOF-NH₂; General Procedure

Catalyst corresponding to 0.13 mmol $-NH_2$ groups (based on the total amount of amino groups in the catalytic material) was added to a solution of malononitrile or ethyl cyanoacetate (1 mmol) and aldehyde or ketone (1 mmol) in DMF (6 mL) at 80 °C under a nitrogen atmosphere. After the reaction was complete, the yield was monitored by GC analysis.

(25) Xamena, F. X. L.; Cirujano, F. G.; Corma, A. Microporous Mesoporous Mater. 2012, 157, 112.