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Hydrogen-bonding 2D metal-organic solids as highly robust and efficient heterogeneous green catalysts for Biginelli reaction

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Abstract

Two new Zn(II) and Cd(II) MOFs have been synthesized. These MOFs have been applied as heterogeneous catalysts for the green synthesis of a variety of dihydropyrimidinone derivatives through the Biginelli reaction and the desired products were obtained in high yields with short reaction time under mild solvent- free conditions. Moreover, the MOF catalysts may be readily recovered after the reaction and reused for many cycles.

Keywords

Metal-organic framework; Biginelli reaction; Heterogeneous catalyst; Solvent- free conditions; Green reactions

Heterogenization of homogeneous catalysts has been of great academic and industrial importance, because the heterogenized catalysts have the advantages to be recoverable, reusable and environmentally friendly. Although a variety of heterogenization approaches such as anchoring catalysts onto porous inorganic materials, organic polymers, dendrimers supports and metal-organic frameworks (MOFs) have been explored; most heterogenized catalysts suffer from the reduced catalytic activity and efficiency.^{1,2}

The Biginelli reaction,³ the three-component reaction between aldehydes, urea, and acetoacetate, is one of the most efficient ways to synthesize dihydropyrimidinone derivatives, which are important pharmacological compounds.⁴ Although a few lanthanide-containing MOF catalysts have been explored for this reaction, the yields are usually very low (<69%) even with a large loading of the catalysts (up to 20 mol %).⁵ Moreover, the reaction time has been quite long while the recyclability of these catalysts has been very poor or not established. The fact that these reported MOF catalysts are not comparable to

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Supplementary data Supplementary data (detailed experimental procedures and characterization data of the MOFs and the Biginelli products) associated with this article can be found, in the online version at doi:.

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their homogeneous Lewis acid counterparts⁶ in terms of the catalytic activity indicates that there is a great need to realize highly efficient heterogeneous catalysts for this important three-component reaction. It has been known that some simple zinc(II) and cadmium(II) salts, such as ZnCl₂ and CdCl₂, are good homogeneous catalysts for the Biginelli reaction,⁷ we thus intended to develop zinc and cadmium-based MOFs as the heterogeneous catalysts for the Biginelli reaction. Herein we report the synthesis and structures of two new iso-structural Zn- and Cd-based MOFs M(4,4'-bpe)₂(H₂O)₄·(*m*-BDS) (M = Zn²⁺ and Cd²⁺; 4,4'-bpe = 1,2-bis(4-pyridyl)ethylene; *m*-BDS = 1,3-benzenedisulfonic acid) and their application as robust and green catalysts for the Biginelli reaction.

The **Zn-** and **Cd-MOFs** were readily synthesized from hydrothermal reactions from their corresponding metal salts and organic linkers 4,4'-bpe and *m*-BDS as single crystals in high yield.⁸ Their crystal structures were characterized by single x-ray diffraction and purity of the phases were confirmed by powder XRD.⁹ **Zn-** and **Cd-MOFs** are iso-structural. As shown in Figure S1,⁹ the Cd ion is coordinated by two 4,4'-bpe and four water molecules in octahedral coordination geometry. These Cd(4,4'-bpe)₂(H₂O)₄ moieties are bridged by the free *m*-BDS molecules by hydrogen bonding to form two-dimensional hydrogen bonded framework (Figure 1).

Using benzaldehyde (**1a**), acetoacetate (**2a**), and urea (**3a**) as the model substrates, the Biginelli reaction was studied with these two catalysts, and the results are summarized in Table 1.

Without catalyst, no product was obtained after 6 h of reflux in EtOH (entry 1). When 2.5 mol % of the **Cd-MOF** was added, 66% of the desired product **4a** was obtained under similar conditions (entry 2). This discovery encouraged us to further explore green reaction conditions without the usage of the organic solvent for this reaction.¹⁰ To our pleasure, the reaction goes much faster under these conditions, and a high yield of 92% of the product was obtained in about 2 h (entry 3). Under these conditions, the **Zn-MOF** also leads to similar results (entry 4). Unlike molecular Zn²⁺ and Cd²⁺ Lewis acid catalysts,⁵ these two catalysts are not soluble in the reaction mixture and the reaction system is heterogeneous.

After the reaction, the catalyst can be readily recovered by a simple filtration followed by washing.

To demonstrate the advantage of these heterogeneous MOF catalysts, we studied the recyclability of these catalysts. As shown by the data collected in Table 1, both catalysts may be recovered in high yields after the reaction and reused for five cycles with almost no loss of the catalytic activity (entries 5-14). The catalyst loading of the **Zn-MOF** may also be reduced to 1.0 mol % or 0.5 mol % without affecting the product yield (entries 15-16), although slightly longer reaction time is necessary with the lower catalyst loadings.

With these promising results, we next studied the scope of this reaction. The results are summarized in Table 2. With the **Zn-MOF**, high yields (≥86%) of the corresponding dihydropyrimidinone derivatives **4** may be obtained within 2 h of reaction for aromatic aldehydes that bear both an electron-withdrawing and an electron-donating group on the phenyl ring (entries 1-8). A high yield (91%) may also be obtained for the products of thiourea (entry 9) and acetoacetone (entry 10). An aliphatic aldehyde may also be applied in this reaction and the reaction of hexanal gave the desired product in 71% yield in 8 h (entry 11). The **Cd-MOF** was found to have similar reactivity and substrate scope (entries 12-22).

In summary, we have demonstrated that the newly synthesized **Zn** and **Cd-MOFs** are highly efficient heterogeneous catalysts for the Biginelli reaction. High yields of the desired products may be obtained in short reaction times. These cheap and readily available

catalysts have high stability under the reaction conditions and may be easily recycled and reused without loss of reactivity. Furthermore, no organic solvent is necessary for the synthesis, which makes the synthesis really green. It is very unusual for such hydrogen bonded frameworks to have such a high stability that are even much superior to a lot of traditional MOFs during the catalytic reaction.¹¹ It is expected that the sulfonic groups significantly enforce the frameworks by their hydrogen interactions with the coordination water molecules. We are now exploring chiral sulfonic derivatives and incorporating them into enantiopure MOFs for their heterogeneous asymmetric catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Part of the single crystal structure of **Cd-MOF** $\text{Cd}(4,4'\text{-bpe})_2(\text{H}_2\text{O})_4\cdot(\text{m-BDS})$ indicating the 2D framework and hydrogen bonding.

Table 1

Reaction condition optimizations and catalyst recycling study^a

Entry	MOF	T (°C)	Cycle	Catalyst recovery (%)	Time (min)	Yield (%) ^b
1 ^c	none	reflux			480	0
2 ^c	Cd	reflux			480	66
3	Cd	80			110	92
4	Zn	80			110	92
5	Cd ^d	80	I	92	120	96
6	Cd ^d	80	II	90	130	96
7	Cd ^e	80	III	89	130	94
8	Cd ^f	80	IV	89	140	96
9	Cd	80	V	88	140	92
10	Zn ^d	80	I	97	110	94
11	Zn ^d	80	II	96	110	90
12	Zn ^e	80	III	96	115	88
13	Zn ^f	80	IV	95	115	88
14	Zn	80	V	95	120	87
15	Zn ^g	80			180	90
16	Zn ^h	80			360	86

^a Unless otherwise specified, all reactions were carried out with **1a** (1.0 mmol), **2a** (1.0 mmol), and **3a** (1.0 mmol) and the MOF catalyst (0.025 mmol, 2.5 mol %) under neat conditions.

^b Yield of the isolated product after recrystallization from EtOH.

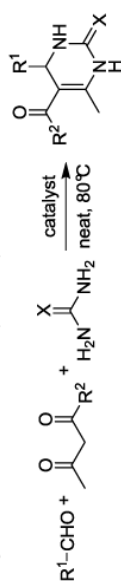
^c Carried out in EtOH.

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- ^d The scale of this reaction was 5.0 mmol.
- ^e The scale of this reaction was 3.0 mmol.
- ^f The scale of this reaction was 2.0 mmol.
- ^g Carried out with 1.0 mol % of the catalyst.
- ^h Carried out with 0.5 mol % of the catalyst.

Table 2

Biginelli Reaction Catalyzed by **Zn-MOF** and **Cd-MOF**^a

1	2	3	4
Entry	MOF catalyst	R ¹	R ² X Time (min) Yield (%) ^b
1	Zn	Ph	OEt O 110 94
2	Zn	4-FC ₆ H ₄	OEt O 110 91
3	Zn	4-ClC ₆ H ₄	OEt O 115 90
4	Zn	4-BrC ₆ H ₄	OEt O 120 90
5	Zn	4-CNC ₆ H ₄	OEt O 140 87
6	Zn	4-NO ₂ C ₆ H ₄	OEt O 140 86
7	Zn	4-MeC ₆ H ₄	OEt O 115 90
8	Zn	4-MeOC ₆ H ₄	OEt O 115 91
9	Zn	Ph	OEt S 120 91
10	Zn	Ph	Me O 110 91
11	Zn	<i>n</i> -C ₅ H ₁₁	OEt O 480 71
12	Cd	Ph	OEt O 110 93
13	Cd	4-FC ₆ H ₄	OEt O 110 91
14	Cd	4-ClC ₆ H ₄	OEt O 115 90
15	Cd	4-BrC ₆ H ₄	OEt O 120 89
16	Cd	4-CNC ₆ H ₄	OEt O 150 86
17	Cd	4-NO ₂ C ₆ H ₄	OEt O 140 87
18	Cd	4-MeC ₆ H ₄	OEt O 115 91
19	Cd	4-MeOC ₆ H ₄	OEt O 115 90
20	Cd	Ph	OEt S 120 90
21	Cd	Ph	Me O 110 91
22	Cd	<i>n</i> -C ₅ H ₁₁	OEt O 480 73

^a Unless otherwise specified, all reactions were carried out with **1** (1.0 mmol), **2** (1.0 mmol), and **3** (1.0 mmol) and the MOF catalyst (0.025 mmol, 2.5 mol %) under neat conditions.

^b Yield of the isolated product after recrystallization from EtOH.