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Multi-component synthesis of 2-amino-6-(alkylthio)pyridine-3,5-dicarbonitriles using Zn(II) and Cd(II) metal–organic frameworks (MOFs) under solvent-free conditions

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ABSTRACT

Multi-component synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines has been developed by using the reaction of aldehydes, malononitrile, and thiophenols in the presence of a Zn(II) or a Cd(II) metal–organic framework (MOF) as the heterogeneous catalyst. This protocol tolerates different functional groups on the substrates and does not require the use of any organic solvent. Moreover, the Zn(II) and Cd(II) MOF catalysts can be recovered and reused for a number of runs without loss of activity.

Among the nitrogen-containing heterocycles, densely substituted pyridine derivatives are one of the most important classes of compounds as they widely occur as key structural subunits in numerous natural products that exhibit many interesting biological activities.[1] In addition, these heterocyclic compounds have found a variety of applications in medicinal and pharmaceutical sciences.[2] Among these pyridine derivatives, 2-amino-6-(arylthio)pyridine-3,5-dicarbonitrile is a privileged scaffold for developing pharmaceutical agents because various compounds with this structural motif display significant and diverse biological activities. For example, adenosine receptors are associated with Parkinson's disease, hypoxia, asthma, epilepsy, cancer, and cardiovascular diseases.[3] These pyridine compounds have been shown to be active inhibitors of the adenosine receptors and, therefore, can be used for treating these diseases.[3] They are also inhibitors of cholinesterases and may be used for treating neurodegenerative diseases.[4] These compounds have also been studied as potential anti-HBV,[5] anti-bacterial, antibiofilm, and anti-infective agents,[6] and as potassium channel openers with applications in treating urinary incontinence.[7] Moreover, some of these derivatives also inhibit prion replication and may be used for treating Creutzfeldt–Jacob disease.[8] A few examples of recently reported biologically significant 2-amino-6-(alkylthio)pyridine-3,5-dicarbonitrile derivatives are collected in Figure 1. Compound **1** is an agonist for adenosine A_1 receptor,[3c] while compound **2** is a highly potent agonist for human adenosine A_{2B} receptor.[3b] Compounds **3**[8b] and **4**[8a] have been proposed as potential therapeutics for prion disease due to their ability in inhibiting prion replication.[8]

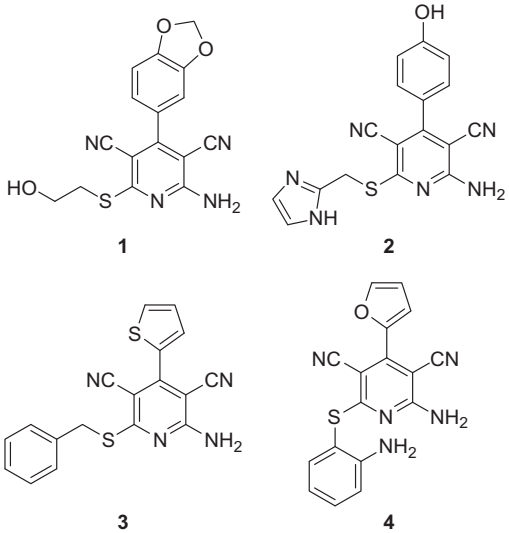

Figure 1. Examples of biologically active 2-amino-6-(arylthio)pyridine-3,5-dicarbonitriles

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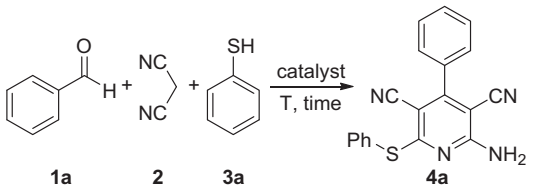
Owing to the broad spectrum of biological activities exhibited by these 2-amino-6-thiopyridine-3,5-dicarbonitrile derivatives, many synthetic methods have been developed for the construction of these compounds.[9] Among these reported methods, the Lewis/Brønsted base-catalyzed three-component reaction of aldehydes, malononitrile, and thiophenols is the most common approach.[9] The reported Lewis/Brønsted base catalysts include DBU,[9f] Et_3N,[9b,9d] piperidine,[9e,9h] KF/alumina,[9j,9k] K_2CO_3/$KMnO_4$,[9p] etc. Besides bases, Lewis acid, Brønsted acid, nanoparticles, and ionic liquids, such as $ZnCl_2$,[9g] boric acid,[9l] silica nanoparticles,[9i] nano MgO,[9m] [bmim]OH,[9c] and [bmim]Br,[9o] are also occasionally used. Good to high yields of the desired 2-amino-3,5-dicarbonitrile-6-thio-pyridines may be obtained using these methods. Nevertheless, most of these methods require the use of hazardous organic solvents, and some of them need exotic reaction conditions such as the use of microwave irradiation or an ionic liquid. Because of our continuing interest in developing green methods for the synthesis of biologically significant molecules,[10] the development of an environmentally benign and practical synthetic route for accessing these important pyridine derivatives became our goal.

Metal–organic frameworks (MOFs),[11,12] have been shown to be a class of emerging catalysts with many promising characters. These new heterogeneous catalysts usually are very stable and may be easily recycled and reused after the application. Recently we have reported the synthesis of two new iso-structural Zn- and Cd-based MOFs $M(4,4'\text{-Bpe})_2(H_2O)_4\cdot(m\text{-BDS})$ ($M = Zn^{2+}$ and Cd^{2+}; 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.[13] In continuation of our interest in MOF-catalyzed reactions, we recently explored the synthesis of 2-amino-6-(arylthio)pyridine-3,5-dicarbonitriles using a multi-component reaction of aldehyde, malononitrile, and thiophenol catalyzed by these Zn(II) and Cd(II) MOFs. Once again we demonstrated the remarkable catalytic activity of these robust MOF catalysts. Herein we wish to report our findings.

Benzaldehyde (**1a**), malononitrile (**2**), and thiophenol (**3a**) were adopted as the model substrates for investigating the multi-component synthesis of 2-amino-6-(arylthio)pyridine-3,5-dicarbonitriles. The Zn(II) and Cd(II) MOFs developed in our lab were used as the catalysts.[13] The results of the optimizations are summarized in Table 1.

Initial screenings were performed using toluene as a solvent. In the absence of catalyst, the product was obtained in only 30% yield after refluxing for 16 h (Table 1, entry 1), In contrast, in the presence of only a catalytic amount (2.0 mol %) of the Zn(II) and Cd(II) MOFs, after 10 h, the desired product was obtained in high yields of 82 and 84%, respectively (Table 1, entries 2 and 3). When the reactions were performed under solvent-free conditions, the reaction times were decreased to 30 minutes with the same catalyst loading (Table 1, entries 4 and 5).[14] This is a great advantage of this new catalytic system in terms of green chemistry since no toxic organic solvent is required for realizing the desired transformation.

Table 1
Reaction condition optimizations[a]

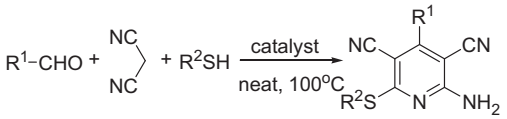


1a **2** **3a** **4a**

Entry	MOF	*T* (°C)	Solvent	Time (h)	Yield (%)[b]
1[c]	–	reflux	Toluene	16	30
2	Zn	reflux	Toluene	10	82
3	Cd	reflux	Toluene	10	84
4	Zn	100	Neat	0.5	86
5	Cd	100	Neat	0.5	87

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.20 mmol), **2** (0.30 mmol), and **3a** (0.10 mmol) and the MOF catalyst (0.0020 mmol, 2.0 mol %).
[b] Yield of the isolated product after column chromatography.
[c] Without any catalyst.

Table 2
Multi-component synthesis of 2-amino-6-thiopyridine-3,5-dicarbonitriles catalyzed by Zn-MOF and Cd-MOF[a]



1 **2** **3** **4**

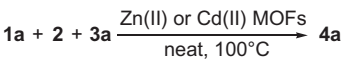
Entry	MOF	R^1	R^2	Time (min)	Yield (%)[b]
1	Zn	Ph	Ph	30	86
2	Zn	4-FC_6H_4	Ph	30	80
3	Zn	4-ClC_6H_4	Ph	30	86
4	Zn	4-$NO_2C_6H_4$	Ph	30	87
5	Zn	4-MeC_6H_4	Ph	45	79
6	Zn	4-$MeOC_6H_4$	Ph	45	73
7	Zn	2-Thiophenyl	Ph	40	83
8	Zn	*n*-C_5H_{11}	Ph	60	61
9	Zn	Ph	4-ClC_6H_4	40	87
10	Zn	Ph	4-MeC_6H_4	30	80
11	Zn	Ph	4-$MeOC_6H_4$	30	81
12	Cd	Ph	Ph	30	87
13	Cd	4-FC_6H_4	Ph	30	82
14	Cd	4-ClC_6H_4	Ph	30	87
15	Cd	4-$NO_2C_6H_4$	Ph	30	88
16	Cd	4-MeC_6H_4	Ph	45	81
17	Cd	4-$MeOC_6H_4$	Ph	45	73
18	Cd	2-Thiophenyl	Ph	40	85
19	Cd	*n*-C_5H_{11}	Ph	60	61
20	Cd	Ph	4-ClC_6H_4	40	87
21	Cd	Ph	4-MeC_6H_4	30	81
22	Cd	Ph	4-$MeOC_6H_4$	30	84

[a] Unless otherwise specified, all reactions were carried out with **1** (0.2 mmol), **2** (0.3 mmol), and **3** (0.1 mmol) and the MOF catalyst (0.002 mmol, 2.0 mol %) under neat conditions.
[b] Yield of the isolated product after column chromatography.

In order to demonstrate the scope of this reaction, a series of substituted aldehydes and thiophenols were then studied and the results are summarized in Table 2. As is evident from the results shown in Table 2, this method is highly compatible with many substituted benzaldehydes. Benzaldehydes with both an electron-donating and an electron-withdrawing group, such as, 4-fluoro, 4-chloro, 4-nitro, 4-methyl, and 4-methoxy groups, all give the desired products in excellent yields (Table 2, entries 2–6 and 13–17). In addition, good to high yields were also obtained for a heteroaromatic aldehyde (thiophene-2-carbaldehyde, entries 7 and 18) and an aliphatic aldehyde (*n*-hexanal, entries 8 and 19) when they were applied in this reaction. Similarly, the substituents on thiophenol show almost no effects on the reaction: 4-Chloro, 4-methyl, and 4-methoxy substituted thiols afforded the corresponding pyridine derivatives in good to excellent yields with both catalysts (Table 2, entries 9–11 and 20–22).

The other advantage of these heterogeneous MOF catalysts lies in the fact that they may easily be recovered by simple filtrations and can be reused for many cycles without significant loss of the catalytic activities. As our results in Table 3 show, when the reaction of benzaldehyde (**1a**), malononitrile (**2**), and thiophenol (**3a**) was used as a model reaction, both the Zn(II) and the Cd(II) MOF's can be recovered in high yields and reused for five cycles with almost no loss of the catalytic activity for the first three cycles (Table 3, entries 1–10).

Table 3
Catalyst recycling and stability study[a]



Entry	MOF	T (°C)	Cycle	Catalyst recovery (%)	Time (min)	Yield (%)[b]
1	Zn[c]	100	I	99	30	86
2	Zn[d]	100	II	97	30	85
3	Zn[e]	100	III	94	40	83
4	Zn[f]	100	IV	93	50	81
5	Zn[g]	100	V	90	60	79
6	Cd[c]	100	I	>99	30	87
7	Cd[d]	100	II	98	30	85
8	Cd[e]	100	III	96	30	84
9	Cd[f]	100	IV	94	40	81
10	Cd[g]	100	V	91	50	80

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.20 mmol), **2a** (0.30 mmol), and **3a** (0.10 mmol) and the MOF catalyst (0.0020 mmol, 2.0 mol %) under neat conditions.
[b] Yield of the isolated product after column chromatography.
[c] The scale of this reaction was 8.0 mmol.
[d] The scale of this reaction was 7.0 mmol.
[e] The scale of this reaction was 6.0 mmol.
[f] The scale of this reaction was 5.0 mmol.
[g] The scale of this reaction was 4.0 mmol.

In summary, we have demonstrated that the Zn(II) and Cd(II) MOFs are efficient, robust, and recyclable catalysts for the multi-component reaction of aldehydes, malononitrile, and thiophenols. This reaction offers a new convenient and green method for the synthesis of the biologically significant 6-(alkylthio)-2-amino-pyridine-3,5-dicarbonitrile derivatives. These MOF-mediated green reactions are mild and easy to operate with the advantage of the solvent-free reaction conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.139.

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14. General Experimental Procedures: To a mixture of benzaldehyde (**1a**, 21.2 mg, 0.20 mmol), malononitrile (**2**, 19.8 mg, 0.30 mmol), and thiophenol (**3a**, 11.0 mg, 0.10 mmol) was added the Zn(II) MOF (1.5 mg, 0.0020 mmol, 2.0 mol %) or the Cd(II) MOF (1.6 mg, 0.0020 mmol, 2.0 mol %). The mixture was then kept at 100 °C for 30 min until the full conversion of the starting materials was achieved (monitored by TLC). The reaction mixture was then filtered and washed with hot ethanol to recover the catalyst. The filtrate was stripped off the solvent and then purified using column chromatography to give the desired product **4a** (28.1 mg, 86% for Zn(II) MOF and 28.5 mg, 87% for Cd(II) catalyst, respectively).