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Zr-MCM-41 Nanoreactors: A Highly Efficient, Reusable and Novel Catalyst for the Synthesis of N-Heteroaryl Formamides under Solvent-Free Conditions

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ABSTRACT

N-Formylation of primary heteroaryl amines has efficiently been carried out in excellent yields by using catalytic amount of Zr-MCM-41 nanoreactors in formic acid under solvent-free conditions. The process is remarkably simple, environmentally benign and works well for electron-deficient primary heteroarylamines. The catalyst could be recycled and reused without a noticeably decrease in its activity.
KEYWORDS: Zr-MCM-41, heteroaryl amine, formic acid, *N*-heteroaryl formamide

1. INTRODUCTION

Formylation of amines is an important reaction in synthetic organic chemistry. Formamides, an important class of amine derivatives, have widely been used in the synthesis of pharmaceutically active compounds [1] and formamidines [2]. In addition, formamides have been also extensively employed in organic synthesis as protecting group of amines in peptides synthesis [3], precursors to isocyanides [4], Vilsmeier reaction [5], Lewis base catalysts in organic transformation such as asymmetric allylation [6], hydrosilylation [7]of carbonyl compounds.

In the literature, various approaches are available for *N*-formylation using different reagents such as chloral [8], formic acid-DCC [9], formic acid-EDCL [10], ammonium formate [11], CDMT [12], paraformaldehyde [13], methyl benzoate[14], formic acid-SiO_2 [15], thiamine hydrochloride [16], formic acid-sodium formate [17], Amberlite IR-120 [18], TiO_2-P25 [19], formic acid-polyethylene glycol (PEG-400) [20] and other solid-supported reagents [21]. Very recently the formylation of aliphatic and aromatic amines with formic acid by using Lewis acids such as $ZnCl_2$, $FeCl_3$, $AlCl_3$, $NiCl_2$ and $[Cp^*IrI_2]_2$ has been reported [22]. Many of these methods suffer from various drawbacks such as use of expensive an toxic formylation agents and catalysts, use of organic solvents, large excess of formic acid, long reaction times and removal of by-products. However, the success of this method is limited only to aromatic and aliphatic amines.

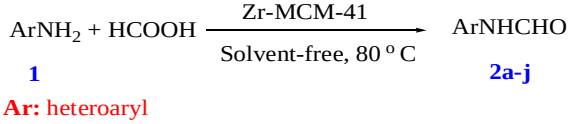
Considerable attention has been given to mesoporous materials such as MCM-41 family because of their unique properties [23-25]. They have high specific surface areas, high pore volumes, and tunable pore sizes with a narrow distribution. However, Si-based MCM-41 exhibits only mild acidity, which is much weaker than that of the microporous zeolites. The incorporation of zirconium into the MCM-41 framework increases both the Lewis and Brönsted acidity [26].

In continuation of our interest in the development of synthetic methods using solvent-free conditions[27], we report herein the challenge to carry out *N*-formylation reaction applicable to heteroarylamines in the presence of Zr-MCM-41 [28] as an efficient and reusable catalyst under solvent-free conditions.

2. RESULTS AND DISCUSSION

In our initial experiments, the reaction of 2-aminopyrimidine (1 mmol) and formic acid (2 mmol) was selected as a model reaction, and its behavior was studied in the presence of Zr-MCM-41 under solvent-free conditions. Moreover, to optimize the temperature in the mentioned reaction, we have carried out a model study using 0.01-0.04 g of catalyst at various temperatures under solvent-free conditions. Our investigation demonstrated that the best results were obtained when using 0.02 g of Zr-MCM-41 per 1 mmol of starting material at 80 °C. These conditions were efficiently accelerated the reaction of 2-aminopyrimidine and formic acid towards the formation of desired product under solvent-free conditions. Moreover, we have studied the molar ratio of formic acid to heteroarylamine on model reaction. The results revealed that when the reaction was carried out in the presence of 2 mol of formic acid relative to 1 mol amine, we got excellent yields of product in a short span.

To show the generality of this method the optimized system was used for the synthesis of other *N*-heteroaryl formamides from the reaction of heteroaryl amines with formic acid utilizing Zr-MCM-41 under solvent-free conditions at 80 °C (Scheme 1). All reactions were complete within 5-40 min, as indicated in Table 1. In this reaction, the hetroaryl amines bearing both electron-donating and electron withdrawing groups reacted with formic acid completely and afforded the corresponding products (**2**) in excellent yields.



Scheme 1. Zr-MCM-41 catalyzed N-formylation of heteroaryl amines with formic acid

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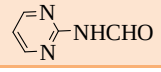
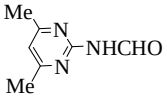
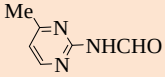
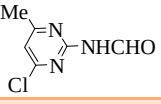
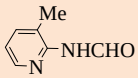
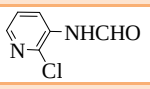
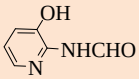
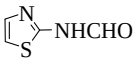
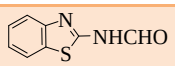
Table 1. Synthesis of *N*-heteroaryl formamides catalyzed by Zr-MCM-41

Entry	Product	2	Time (min)	Yield (%)	M.P (°C)
1		2a	15	91	146-148
2		2b	40	88	120-122
3		2c	20	89	155-156
4		2d	25	91	298-300
5		2e	5	90	135-136
6		2f	10	91	128-129
7		2g	5	86	148-149
8		2h	30	89	160-162
9		2i	40	92	248-250

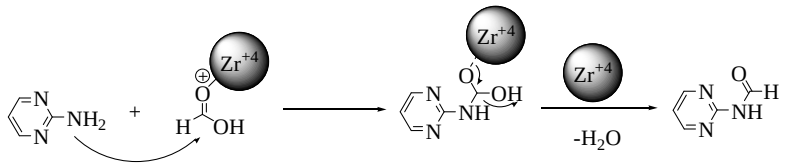
From the green chemistry point of view, efficient recovery and reuse of the catalyst is highly desirable, thus the recovery and reusability of Zr-MCM-41 was investigated. After the reaction was completed, ethyl acetate was added until the solid crude product was dissolved. Then, Zr-MCM-41 as the catalyst was isolated from the mixture of reaction by simple filtration and reused again after washing with ethyl acetate. The reusability of Zr-MCM-41 was examined efficiently (without any activation) by using 2-aminopyrimidine as a model substrate. The recovered Zr-MCM-41were reused directly for four consecutive cycles and all the results are tabulated in Table 2.

The surface acidity of the mesoporous solids is significantly influenced by the incorporation of zirconium ions into the framework. The addition of zirconium creates Brönsted acid sites and also enhances the acid strength of both the Lewis and Brönsted acid sites. The diameter of Zr^{4+} is much larger than that of Si^{4+} and when smaller Si^{4+} ions are replaced by larger Zr^{4+} ions in the framework of the solid the bond length of Zr–O–Si clearly differs from that of Si–O–Si. This must lead to the deformation of some structures and the generation of microstrain in the lattice cell. This feature can be useful for reactions that require both types of acid sites. Therefore, a plausible mechanism for the formation of *N*-heteroaryl formamides is shown in Scheme 2. The reaction is thought to proceed in a stepwise manner. Firstly, we assumed that the reaction may proceed via the nucleophilic addition of amine to formic acid catalyzed by Zr-MCM-41. Subsequent dehydration was carried out in the presence of Zr-MCM-41 to give the final product.

Table 2. Recyclability of the catalyst for the synthesis of xanthenes

No of Cycles[a]	Fresh	Run 1	Run 2	Run 3
Yields[b]	94	94	92	91
Time (min)	15	15	15	15

[a]Reaction conditions: 2-aminopyrimidine (1 mmol) and formic acid (2 mmol): Catalyst (0.02 g), Temperature: 80 °C, [b]Isolated yields



Scheme 2. Plausible mechanism for the synthesis of N-heteroaryl formamides

All products were well characterized by ^{1}H NMR, ^{13}C NMR, FT IR, mass spectra, Elemental Analyses and melting point. Identification of products **2a–j** was carried out on the basis of spectroscopic information. For example, in the ^{1}H NMR spectrum of compound **2j** the aromatic moieties gave two well-resolved doublet of doublet spin systems at about δ 7.12 and 8.45 ppm. The CHO and NH protons appeared as two broad signals at about δ 8.56 and 11.86 ppm, respectively. Upon addition of D_2O into the NMR tube, the broad signal at δ 11.86 ppm disappears. Elemental analysis, FT-IR and Mass spectra are in agreement with the proposed structure.

3. Experimental

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DRX-500 Avance spectrometers. Chemical shifts (δ) are reported in parts per million andare referenced to the NMR solvent. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 mass selective detector. Elemental analyses were carried out by a CHN–O–Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the synthesis of *N*-heteroaryl formamide (2a-j)

To a mixture of heteroarylamine (1 mmol) and formic acid (2 mmol) was added Zr-MCM-41 powder (0.02 g). The reaction mixture was magnetically stirred on a preheated oil bath at 80 ^{o}C for the appropriate time as indicated in Table 2. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled at room temperature. Then, ethyl acetate (10 mL) was added. Catalyst was recovered by centrifuging the organic layer and reutilized for the same reaction. The organic layer was washed with saturated $NaHCO_3$ and dried (Na_2SO_4), filtered and concentrated under vacuum to provide crude product which was purified by column chromatography on silica gel to afford the corresponding white products.

***N*-(4,6-Dimethyl-2-pyrimidinyl)formamide (2b)**

IR (KBr): 3171, 3063, 2999, 2835, 1709, 1605, 1549, 1447, 1371, 1232, 868 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.34 (s, 6H, 2 x *CH$_3$*), 6.94 (s, 1H, *pyrimidine-H5*), 9.37 (d , 1H, *J* = 9.90 Hz, *CHO*), 10.76 (d , 1H, *J* = 9.90 Hz, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 24.21, 116.41, 158.02, 163.97, 168.75 ppm; MS (EI): m/z 151 (M^+), 150, 149, 132, 124, 123, 108, 104; Anal. calcd. For $C_7H_9N_3O$: C, 55.63; H, 5.96; N, 27.81. Found: C, 55.60; H, 6.01; N, 27.87.

***N*-(4-Methyl-2-pyrimidinyl)formamide (2c)**

IR (KBr): 3143, 3090, 2991, 2818, 1693, 1599, 1570, 1518, 1404, 1373, 1308, 1219, 841 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.40 (s, 3H, *CH$_3$*), 7.07 (d, 1H, *J* = 5.05 Hz, *pyrimidine-H5*), 8.44 (d, 1H, *J* = 5.05 Hz, *pyrimidine-H6)* 9.38 (d , 1H, *J* = 9.55 Hz, *CHO*), 10.86 (d , 1H, *J* = 9.55 Hz, *NH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 24.44, 117.28, 158.23, 158.86, 163.98, 169.42 ppm; MS (EI): m/z 137 (M^+), 109, 94, 82, 67; Anal. calcd. For $C_6H_7N_3O$: C, 52.55; H, 5.11; N, 30.65. Found: C, 52.50; H, 5.15; N, 30.71.

***N*-(4-Chloro-6-methyl-2-pyrimidinyl)formamide (2d)**

IR (KBr): 3287, 3070, 2884, 2738, 1686, 1598, 1351, 1085, 846 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.20 (s, 3H, *CH$_3$*), 5.77 (s, 1H, *pyrimidine-H5*), 8.31 (s, 1H, *CHO*), 12.70 (br, 1H, *NH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 18.89, 102.92, 153.17, 153.33, 154.20, 160.89 ppm; MS (EI): m/z 173 $(M+2)^+$, 171 (M^+), 125, 109, 97, 84, 68, 43; Anal. calcd. For $C_6H_6ClN_3O$: C, 42.10; H, 3.50; N, 24.56. Found: C, 42.07; H, 3.52; N, 24.53.

***N*-(3-Methyl-2-pyridinyl)formamide (2e)**

IR (KBr): 3234, 3150, 2995, 2820, 1691, 1587, 1483, 1460, 1286, 793 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.22 (s, 3H, *CH$_3$*), 7.07-8.12 (m, 3H, *pyridine-H*), 9.22 (d, 1H, *J* = 5.40 Hz, *CHO*), 10.11 (d, 1H, *J* = 5.40 Hz, *NH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 17.46, 120.63, 140.32, 146.23, 150.678, 163.95, 164.07 ppm; MS (EI): m/z 136 (M^+), 108, 107, 91, 81, 80; Anal. calcd. For $C_7H_8N_2O$: C, 61.76; H, 5.88; N, 20.58. Found: C, 61.80; H, 5.82; N, 20.60.

***N*-(2-Chloro-3-pyridinyl)formamide (2f)**

IR (KBr): 3238, 3080, 2995, 2899, 1691, 1664, 1591, 1564, 1398, 1292, 797 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 7.42-8.41 (m, 3H, *pyridine-H*), 8.51 (d, 1H, *J* = 7.70 Hz, *CHO*), 10.05 (br, 1H, *NH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 124.40, 131.75, 132.22, 141.31, 145.39, 161.82 ppm; MS (EI): m/z 158 $(M+2)^+$, 156 $(M)^+$, 128, 121, 100, 92, 65; Anal. calcd. For $C_6H_5ClN_2O$: C, 46.15; H, 3.20; N, 17.94. Found: C, 46.20; H, 3.22; N, 18.02.

***N*-(3-Hydroxy-2-pyridinyl)formamide (2g)**

IR (KBr): 3431, 3343, 3108, 2995, 2816, 1671, 1562, 1478, 1289, 893 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 5.60 (br, 2H, *NH, OH*), 6.39-7.41 (m, 3H, *pyridine-H*), 8.17 (s, 1H, *CHO*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 112.83, 119.14, 136.77, 139.93, 150.74, 164.01 ppm; MS (EI): m/z 138 $(M)^+$, 110, 97, 82, 65; Anal. calcd. For $C_6H_6N_2O_2$: C, 52.17; H, 4.34; N, 20.29. Found: C, 52.12; H, 4.36; N, 20.31.

***N*-(2-Thiazolyl)formamide (2h)**

IR (KBr): 3169, 3132, 2901, 2854, 2704, 1693, 1564, 1437, 1288, 881 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 7.26 (d, 1H, *J* = 3.55 Hz, *thiazole-H*), 7.49 (d, 1H, *J* = 3.55 Hz, *thiazole-H)*, 8.47 (s , 1H, *CHO*), 12.23 (s , 1H, *NH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 114.83, 138.58, 157.17, 160.26 ppm; MS (EI): m/z 128 (M^+), 100, 99, 73, 69, 58; Anal. calcd. For $C_4H_4N_2OS$: C, 37.50; H, 3.12; N, 21.87. Found: C, 37.55; H, 3.10; N, 21.90.

***N*-(2-Benzothiazolyl)formamide (2i)**

IR (KBr): 3171, 3057, 2892, 2850, 1694, 1560, 1443, 1272, 840 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 7.28-7.99 (m, 4H, *Ar-H*), 8.58 (s , 1H, *CHO*), 12.50 (br , 1H, *NH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 121.23, 122.28, 124.28, 126.71, 132.02, 148.87, 156.72, 161.04 ppm; MS (EI): m/z 178 (M^+), 150, 123, 108, 96, 82, 69; Anal. calcd. For $C_8H_6N_2OS$: C, 53.93; H, 3.37; N, 15.73. Found: C, 53.90; H, 3.42; N, 15.80.

***N*-(2-Benzimidazolyl)formamide (2j)**

IR (KBr): 3343, 3033, 2883, 1694, 1593, 1452, 1213, 733 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 7.09-7.46 (m, 4H, Ar-H), 8.56 (s , 1H, CHO), 11.86 (br , 2H, NH) ppm; ^{1}H NMR (500 MHz, DMSO-d_6 +D_2O): 7.11-7.46 (m, 4H, Ar-H), 8.52 (s , 1H, CHO) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 114.67, 121.66, 138.22, 146.13, 161.48 ppm; MS (EI): m/z 161 (M^+), 133, 105, 90, 78; Anal. calcd. For $C_8H_7N_3O$: C, 59.62; H, 4.34; N, 26.08. Found: C, 59.60; H, 4.39; N, 26.14.

4. Conclusion

In summary, to the best of our knowledge, this paper represents the first report on the synthesis of *N*-heteroaryl amines by employing Zr-MCM-41 nanoreactors as reusable catalyst under solvent-free conditions. The attractive features of this protocol are simple procedure, excellent yields, short reaction time, extremely mild reaction conditions and its adaptability for *N*-formylation of heteroaryl amines.

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