Short communication

Al_2O_3 Nanoparticles: An Efficient and Recyclable Nanocatalyst for the Rapid Synthesis of *N*-Heteroaryl Formamides under Solvent-Free Conditions

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Abstract

A series of *N*-heteroaryl formamides were efficiently synthesized from heteroarylamines and formic acid using Al_2O_3 nanoparticles as a heterogeneous catalyst under solvent-free conditions. The smaller size of Al_2O_3 nanoparticles with a higher surface to volume ratio has a promising catalytic activity, resulting in a short reaction times and high reaction yields under mild reaction conditions. The catalyst could be recycled and reused four times without a noticeable decrease in its activity.

Keywords: Formamide, Heteroaryl amine, Formic acid, Solvent-free, Al_2O_3

1. Introduction

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

In recent years, a number of methods have been reported for *N*-formylation of amines using 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] In addition, various catalysts, such as $ZnCl_2$, $FeCl_3$, $AlCl_3$, $NiCl_2$ and $[Cp^*IrI_2]_2$ have been reported for the formylation of aliphatic and aromatic amines.[22] Although most of these processes offer distinct advantages, most of them suffer from certain drawbacks such as use of expensive and toxic formylation reagents and catalysts, large excess of formic acid, long reaction times, harsh reaction conditions, and the use of a large quantity of volatile organic solvents. Moreover, the success of all methods is limited to aromatic and aliphatic amines. Therefore, in continuation of our efforts to develop environmentally benign protocols,[23] we used Al_2O_3 nanoparticles[24] as nanocatalyst for preparation of *N*-heteroaryl formamides under solvent-free conditions.

2. Results and Discussion

The reaction of 2-aminopyrimidine and formic acid, catalyzed by Al_2O_3 nanoparticles under solvent-free conditions, was considered as a standard model reaction. First, we have screened a number of different catalysts in the model reaction. The presence of various Lewis acids as catalyst in the reaction under solvent-free conditions resulted in low reaction yields even after prolonged reac-

Table 1. Screening of various catalysts in the model reaction.

Entry	Catalyst	Time (min)	Yield (%)
1	$ZnCl_2$	120	65
2	$ZnSO_4$	70	80
3	$CuCl_2$	60	55
4	$SnCl_2$	75	45
5	$CuSO_4$	60	40
6	$CO(NO_3)_2$	90	35
7	$FeCl_3$	50	80
8	Nano-Al_2O_3	30	91
9	$AlCl_3$	180	78

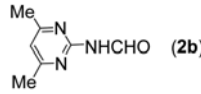
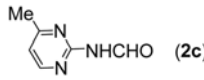
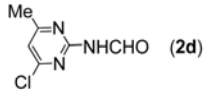
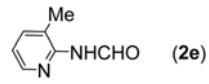
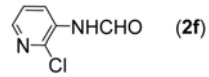
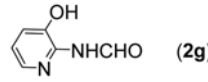
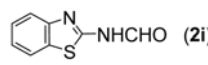
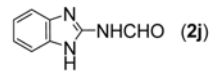
tion times (Table 1). However, the same reaction under solvent-free conditions, using Al_2O_3 nanoparticles, gave an excellent reaction yield in a short reaction time (Table 1, entry 8).

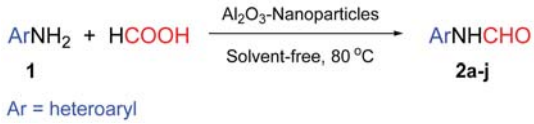
We have also studied the influence of molar ratio of formic acid to heteroarylamine on the reaction yield. The results revealed that 2 mol of formic acid relative to 1 mol of amine improve the reaction yield. Moreover, different reaction temperatures were tested in the model reaction of 2-aminopyrimidine and formic acid, using 10 mol% of catalyst under solvent-free conditions. Our investigations demonstrated that 80 °C is an optimal reaction temperature in terms of reaction time and obtained yields. Furthermore, we also screened different catalyst concentrations (2, 5, 7, 10 and 15 mol%) in the model reaction and found out that the reaction in the presence of 10 mol% of catalyst appeared to be optimal one, giving the best reaction yield. Further increase in the catalyst concentration to 15

Table 2: The influence of the amount of Al_2O_3 nanoparticles on 2-(formylamino)pyrimidine yield.

Entry	Catalyst loading (mol %)	Temperature (° C)	Time (min)	Yield (%)
1	2	80	30	70
2	5	80	30	81
3	7	80	30	85
4	10	80	30	91
5	15	80	30	91

Table 3. Synthesis of *N*-heteroaryl formamides catalyzed by Al_2O_3 nanoparticles.

Entry	Product (2)	Time (min)	Yield (%)	M.p. (°C)[ref]
1	 (**2a**)	30	91	146–148[22]
2	 (**2b**)	50	88	120–122
3	 (**2c**)	30	89	155–156
4	 (**2d**)	40	85	298–300
5	 (**2e**)	10	90	135–136
6	 (**2f**)	10	85	128–129
7	 (**2g**)	20	86	148–149
8	 (**2h**)	35	89	160–162[25]
9	 (**2i**)	40	92	248–250
10	 (**2j**)	35	82	160–161



Scheme 1. Al_2O_3 nanoparticle-catalyzed *N*-formylation of heteroarylamines with formic acid.

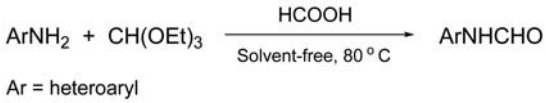
mol% did not improve the yield of the product (Table 2). However, we assumed that Al_2O_3 nanoparticles activate the formic acid by efficient binding of the oxygen atom of formic acid on the vacant orbital of aluminum atom.

The generality of this reaction was examined by the reaction of several heteroaryl amines (**1**) with formic acid, using Al_2O_3 nanoparticles (10 mol %) as a nanocatalyst, under the optimized conditions (Scheme 1 and Table 3).

As shown in Table 3, in most cases the desired products were obtained with good to excellent yields. Moreover, the use of other heteroaryl amines such as 2-aminopyridine, 2-amino-4-methylpyridine, 2-amino-6-methylpyridine and 3-aminopyridine gave unknown products under similar reaction conditions and the desired product could not be isolated.

Products **2a–j** were characterized on the basis of spectroscopic information. For example, in the ^{1}H NMR spectrum of compound **2j** aromatic hydrogens gave signals for 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 signals at about δ 8.56 and 11.86 ppm, respectively. Upon addition of D_2O to the sample, the broad signal at δ 11.86 ppm disappeared.

We also investigated the reusability of the catalyst. After each run the catalyst was removed by centrifugation, washed with ethyl acetate and re-used. It was found that the recycled catalyst could be used for four consecutive reactions without significant decrease in the reaction yield (Table 4). Furthermore, the reaction of the heteroaryl amines with triethylorthoformate in the presence of formic acid as catalyst was also investigated and showed low yields of the corresponding *N*-heteroaryl formamides under the same reaction conditions (Scheme 2).



Scheme 2. Preparation of *N*-heteroaryl formamides with triethylorthoformate.

Table 4: Recyclability of the nanocatalyst in the synthesis of *N*-heteroaryl formamides.

No. of Cycles	Fresh	Run 1	Run 2	Run 3
Yield	91	91	90	89
Time (min)	30	30	30	30

3. Experimental Section

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-300 Avance spectrometers using DMSO-d_6 as solvent. Chemical shifts (δ) are reported in parts per million and are 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 CHNO–Rapid Heraeus elemental analyzer (Wellesley, MA).

3. 1. General Procedure for the Synthesis of *N*-heteroaryl formamides (2a-j)

To a mixture of heteroarylamine (1 mmol) and formic acid (2 mmol), Al_2O_3 nanoparticle powder (10 mol %) was added. The reaction mixture was magnetically stirred on a preheated oil bath at 80 °C for the appropriate time as indicated in Table 2. After completion of the reaction, as indicated by TLC (silica gel, n-hexane/ethyl acetate, 50/50), the reaction mixture was cooled to room temperature and ethyl acetate (5 mL) was added. Nanoparticles were 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 (n-hexane/ethyl acetate, 50/50) to afford the pure products.

***N*-(pyrimidin-2-yl)formamide (2a)**[22] IR (KBr): 3137, 3103, 2929, 2789, 1697, 1586, 1416, 1280, 853 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.20 (t, 1H, *J* = 4.85 Hz, *pyrimidine-H5*), 8.61 (d, 2H, *J* = 4.85 Hz, *pyrimidine-H4,6*), 9.39 (d, 1H, *J* = 9.55 Hz, *CHO*), 10.97 (d, 1H, *J* = 9.55 Hz, *NH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 117.92, 158.49, 159.48, 163.97 ppm; MS (EI): m/z 123 (M^+), 95, 68, 53, 41; Anal. calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.06; N, 34.14. Found: C, 48.82; H, 3.99; N, 34.17.

***N*-(4,6-dimethylpyrimidin-2-yl)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, *2xCH$_3$*), 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-methylpyrimidin-2-yl)formamide (2c)** IR (KBr): 3143, 3090, 2991, 2818, 1693, 1599, 1570, 1518, 1404, 1373, 1308, 1219, 841 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 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): δ 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-methylpyrimidin-2-yl)formamide (2d)** IR (KBr): 3287, 3070, 2884, 2738, 1686, 1598, 1351, 1085, 846 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 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): δ 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-methylpyridin-2-yl)formamide (2e)** IR (KBr): 3234, 3150, 2995, 2820, 1691, 1587, 1483, 1460, 1286, 793 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 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): δ 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-chloropyridin-2-yl)formamide (2f)** IR (KBr): 3238, 3080, 2995, 2899, 1691, 1664, 1591, 1564, 1398, 1292, 797 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 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): δ 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-hydroxypyridin-2-yl)formamide (2g)** IR (KBr): 3431, 3343, 3108, 2995, 2816, 1671, 1562, 1478, 1289, 893 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 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): δ 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*-(thiazol-2-yl)formamide (2h)**[25] IR (KBr): 3169, 3132, 2901, 2854, 2704, 1693, 1564, 1437, 1288, 881 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 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): δ 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*-(benzothiazol-2-yl)formamide (2i)** IR (KBr): 3171, 3057, 2892, 2850, 1694, 1560, 1443, 1272, 840 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 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): δ 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*-(benzimidazol-2-yl)formamide (2j)** IR (KBr): 3343, 3033, 1694, 1592, 1452, 1213 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.09–7.46 (m, 4H, *Ar-H*), 8.56 (s, 1H, *CHO*), 11.86 (br, 2H, *NH*) ppm; ^1H NMR (500 MHz, DMSO-d_6 +D_2O): δ 7.11–7.46 (m, 4H, *Ar-H*), 8.52 (s, 1H, *CHO*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 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. Conclusions

We have successfully employed Al_2O_3 nanoparticles as catalyst in the synthesis of *N*-heteroaryl formamides under solvent-free conditions. The attractive advantages of this protocol are simple procedure, mild reaction conditions, short reaction times, high yields, the reusability of the catalyst, and extension of the method to the *N*-formylation of heteroarylamines.

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6. References

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Povzetek

V prispevku je opisana učinkovita priprava *N*-heteroaril formamidov iz heteroarilaminov in metanojske kisline z uporabo Al_2O_3 nanodelcev kot heterogenega katalizatorja ter brez uporabe topila. Majhni Al_2O_3 nanodelci z veliko specifično površino imajo v reakciji velik katalitski učinek, saj reakcije potekajo hitro pri milih pogojih z visokimi zkoristki. Katalizator lahko tudi recikliramo, saj po štirikratni uporabi še ni zazanavnega zmanjšanja njegove katalitske aktivnosti.