JOC*Note*

ZnO as a New Catalyst for *N*-Formylation of Amines under Solvent-Free Conditions

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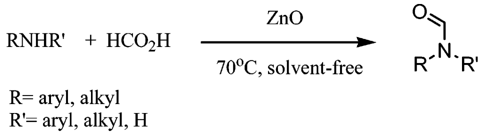

The treatment of amines with formic acid in the presence of ZnO under solvent-free conditions brings about highly and efficient *N*-formylation to give the corresponding formamides in excellent yields. The *N*-formylation reaction not only involves mild conditions, simple operation, and high yields but also high chemoselectivity.

Formamides are a class of important intermediates in organic synthesis. They have been widely used in the synthesis of pharmaceutically important compounds such as fluoroquinolines,[1] substituted aryl imidazoles,[2] 1,2-dihydroquinolines,[3] nitrogen-bridged heterocycles,[4] etc. Formamides are Lewis bases, which are known to catalyze reactions such as allylation[5] and hydrosilylation[6] of carbonyl compounds. More recently, asymmetric allylation of aldehydes has been achieved with chiral formamides.[7] Furthermore, formamides are very useful reagents in Vilsmeier formylation reactions.[8] In addition, and they have been used in the synthesis of formamidines[9] and isocyanides. More over, the formyl group is a useful amino-protecting group in peptide synthesis[10] and *N*-formylamino acid esters can, for example, serve as starting materials for peptide synthesis.[11]

A number of formylation methods have been reported in recent years. Acetic formic anhydride[12,13] continues to be the most widely used formylating reagent, but it is sensitive to atmospheric moisture and cannot be stored due to decomposition to acetic acid and carbon monoxide. Many other useful formylation reagents have been reported such as chloral,[14] activated formic acid using DCC,[15] or EDCI,[16] activated formic acid esters,[17−20] $KF-Al_2O_3$,[21] ammonium formates,[22] CDMT,[23] solid-supported reagents,[24] and other reagents. Heating with ethyl or phenyl formate seems a good procedure, but the method requires very long times and high-temperature for completion.[25] However, there are several factors in some cases limiting their applications, for example, thermal instability, formation of byproducts, difficult accessibility to the preparation of the formylating agents.

TABLE 1. Formylation of Aniline under Different Reaction Conditions

entry	conditions	solvent	time (h)/ T (°C)	yield[a] (%)
1	aniline (1 mmol)/HCO_2H (excess)/ZnO (1 mmol)	none	48/70	trace
2	aniline (1 mmol)/HCO_2H (5 mmol)/ZnO (1 mmol)	none	3/70	50
3	aniline (1 mmol)/HCO_2H (3 mmol)/ZnO (1 mmol)	none	3/70	90
4	aniline (1 mmol)/HCO_2H (1 mmol)/ZnO (1 mmol)	none	3/70	5
5	aniline (1 mmol)/HCO_2H (3 mmol)/ZnO (0.5 mmol)	none	0.16/70	99
6	aniline (1 mmol)/HCO_2H (3 mmol)/ZnO (0.25 mmol)	none	2/70	20
7	aniline (1 mmol)/HCO_2H (3 mmol)/ZnO (0. 5 mmol)	none	0.16/25	70
8	aniline (1 mmol)/HCO_2H (3 mmol)/ZnO (0.5 mmol)	DMF	48/70	0
9	aniline (1 mmol)/HCO_2H (3 mmol)/ZnO (0.5 mmol)	CH_2Cl_2	48/70	0
10	aniline (1 mmol)/HCO_2H (3 mmol)/ZnO (0.5 mmol)	CH_3CN	48/70	0
11	aniline (1 mmol)/ HCO_2H (3 mmol)	none	48/70	50
12	aniline (1 mmol)/CH_3CO_2H (3 mmol)/ZnO (0.5 mmol)	none	48/70	0

[a] Isolated yields.

In recent years, the use of inorganic solid oxides as catalysts, reagents, and reaction media has received considerable attention

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TABLE 2. ZnO-Catalyzed *N*-Formylation of Amines

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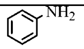
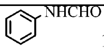
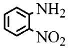
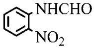
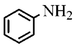
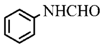
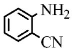
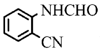
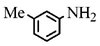
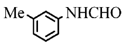
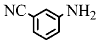
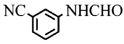
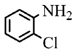
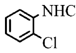
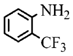
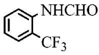
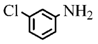
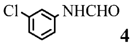
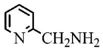
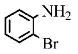
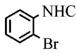
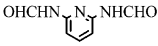
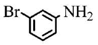
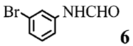
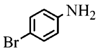
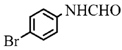
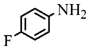
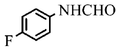
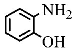
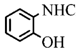
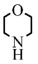
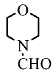
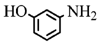
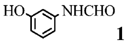
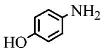
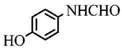
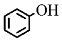
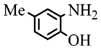
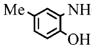
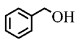
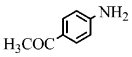
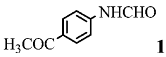
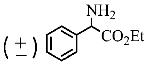
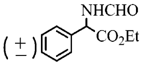
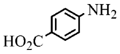
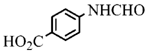
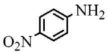
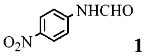
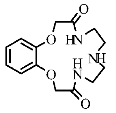
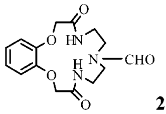
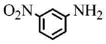
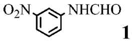
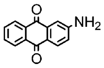
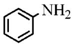
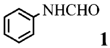
1		 **1**	10	99	18		 **17**	120	85
2			40	99[b]	19		 **18**	300	85
3		 **2**	20	92	20		 **19**	60	95
4		 **3**	60	90	21		 **20**	180	87
5		 **4**	25	93	22		 **21**	60	85
6		 **5**	60	90	23		 **22**	120	73
7		 **6**	30	94	24	PhNHPh	PhN(CHO)Ph **23**	120	75
8		 **7**	20	98	25	$(CH_3)_2CHNHCH(CH_3)_2$	$(CH_3)_2CHN(CHO)CH(CH_3)_2$ **24**	180	65
9		 **8**	20	98	26	$CH_3CH_2CH_2CH_2NH_2$	$CH_3CH_2CH_2CH_2NHCHO$ **25**	40	90
10		 **9**	30	95	27		 **26**	180	65
11		 **10**	60	90		$HOCH_2CH_2NH_2$	$HOCH_2CH_2NHCHO$ **27**	40	85
12		 **11**	50	93	28		no reaction		
13		 **12**	15	94	29		no reaction		
14		 **13**	10	97	30		 **28**	60	73
15		 **14**	60	93	31				
16		 **15**	720	77	32		 **29**	80	60
17		 **16**	60	87	33		no reaction		
					34	 , PhNHPh	 **1**	120	99

[a] Yields are the isolated compounds. [b] Reaction was recorded on 100 mmol scale.

because of their high level of chemo selectivity and environmental compatibility as well as simplicity of operation and their use of availability at low cost. Thus, a number of heterogeneous reactions using inorganic oxides such as SiO_2, Al_2O_3, clay, zeolite, etc. have already been reported.[26]

In particular, zinc oxide (ZnO) as such is an important material with wide range of applications. This particular catalyst with high specific surface area make it a potential candidate especially for a wide range of applications.[27] We now report a practical formylation procedure using formic acid in the presence of ZnO as a new catalyst. The reaction of amines with formic acid first appeared in 1955.[28] Fieser reported that *N*-methylaniline reacted with formic acid to give *N*-methylformanilide. Recently, Choi and co-workers[29] have reexamined this method using aqueous 85% formic acid. However, this method needed to use a large amount of solvent with a Dean-Stark trap under reflux conditions and involve longer reaction times. We have

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[26] Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. *Synlett* **2002,** 1526.

[27] (a) Hosseini Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2004**, *69*, 6953. (b) Sharghi, H.; Hosseini Sarvari, M. *Synthesis* **2002**, *8*, 1057. (c) Hosseini Sarvari, M. *Synthesis* **2005**, *5*, 787. (d) Hosseini Sarvari, M. Sharghi, H. *Tetrahedron* **2005**, *61*, 10903. (e) Kim, Y. J.; Varma, R. S.; *Tetrahedron Lett.* **2004**, *45*, 7205.

[28] Fieser, L. F.; Jones, J. E. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 590.

[29] Jung, S. H.; Ahn, J. H.; Park, S. K., Choi, J.-K. *Bull. Korean Chem. Soc.* **2002**, *23*, 149.

extended this method as a general procedure which accommodates practicality and functionality. The method can also be carried out under solvent-free conditions, impressing that the catalyst (ZnO) is reusable.

As shown in Table 1, the reaction of aniline as a model compound with formic acid was examined under various reaction conditions. The use of excess formic acid provided only a trace amount of the desired product (entry 1). When the amount of formic acid was reduced the yields were dramatically increased (entries 2 and 3). The effect of solvents was also studied. No product was detected in any solvents (entries 8−10). The best results were obtained with 3 mmol of formic acid in solvent-free conditions using 0.5 mmol of ZnO as catalyst (entry 5). On the basis of these preliminary results, the application of this procedure to various amines was investigated. The results are summarized in Table 2.

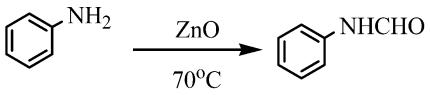
Aromatic and aliphatic primary and secondary amines can react with formic acid. For a variety of amines, e.g., hindered amines (entries 24, 25), heterocyclic amines (entries 22, 23, 27, and 32), and a diamine (entry 23), the reaction shows good results without any significant influence of their structures on the product yields. Reactions of aromatic amines bearing both electron-donating and -withdrawing groups proceed smoothly to give the corresponding *N*-formyl compound in quantitative yields (entries 1−21). The conversion of aniline into *N*-formylaniline on a 100 mmol scale (entry 2) proceeds just as well as the reaction on a 1 mmol scale. In comparison with other previously methods, 4-nitroaniline (entry 16) was formylated in 77% isolated yield using the present protocol but according to the method reported by Choi and co-workers[29] but did not afford the same reaction. Primary amines are easily formylated to provide formamide in short reaction time and high yields. However, secondary amines need longer reaction times, and the corresponding formamides are afforded in 60−75% yields.

It is interesting to note that *N*-formylamino acid esters could be obtained in good yields using the procedure outlined in this report (entry 31). It is notable that the amino acid ester used is not an optically active substrate. Also, entry 32 can survive in the present method indicating the mildness of reactions, whereas 2-amino antraquinone (entry 33) remains inert under the conditions.

O-Formylation of alcohol or phenol derivatives under these reaction conditions was not successful. No reaction was observed with phenol and alkyl alcohol (entries 29 and 30). It was found that this reaction is chemoselective. This justifies that only *N*-formylated product was formed with molecules containing both the hydroxyl and amino groups (entries 10−13 and 28).

According to Table 2, the reaction of secondary amines with formic acid is slow in comparison to those primary amines. Indeed, a mixture of primary and secondary amines furnishes only the expected formanilide **1** on reaction with 1 mmol of formic acid (entry 34).

TABLE 3. Reuse of ZnO



no. of uses	yield (%)	Recovery of ZnO
1	90	96
2	86	90
3	84	90

Furthermore, catalytic activity of the recovered catalyst (ZnO) was examined. As shown in Table 3, the yields of *N*-formylaniline after two and three reuses of the catalyst were almost the same as that in the first use. In every case, almost >90% of the ZnO was easily recovered from reaction mixture by simple washing with dichloromethane.

In conclusion, we have developed a novel and highly efficient solvent-free protocol for *N*-formylation of amines using nontoxic, inexpensive, and biocompatible ZnO powder. The advantages of this environmentally benign and safe protocol include a simple reaction setup, not requiring specialized equipment, very mild reaction conditions, high product yields, short reaction times, the possibility for reusing the catalyst, chemoselectivity, and solvent-free conditions.

Experimental Section

General Procedure. To a mixture of HCO_2H (3 mmol, 0.11 mL) and ZnO (0.5 mmol, 0.04 g) was added an amine (1 mmol), and then the reaction mixture was heated in an oil bath at 70 °C and stirred with a magnetic stirrer. The progress of the reaction was monitored by TLC. After the reaction was complete, CH_2Cl_2 or EtOAc was added to the reaction mixture, and ZnO was removed by filtration. The organic solvent was then washed with H_2O (2×10 mL) and a saturated solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. After removal of the solvent, the pure product was obtained. This was further purified by recrystallization with suitable solvent (ether or $CHCl_3$). The structure of the products was confirmed by ^1H NMR, IR, and comparison with authentic samples obtained commercially or prepared by reported methods.

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Supporting Information Available: Complete experimental procedure and relevant spectra (^{13}C and ^1H NMR spectra) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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