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Solvent-free Zinc-catalyzed Amine *N*-Formylation

Joong-Gon Kim and Doo Ok Jang[†,*]

Biotechnology Division, Hanwha Chemical R&D Center, Daejeon 305-345, Korea
[†]Department of Chemistry, Yonsei University, Wonju 220-710, Korea. [*]E-mail: dojang@yonsei.ac.kr
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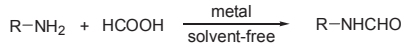
Formamides are important intermediates in the preparation of amine derivatives and have been widely used in the synthesis of pharmaceutically valuable compounds.[1] They have also been employed as reagents in Vilsmeier formylation[2] and in the allylation[3] and hydrosilylation[4] of carbonyl compounds. In addition, the formyl group is an important amine-protecting group in peptide synthesis.[5] Various reagents for the synthesis of formamides have been developed including formic acid with activating reagents such as DCC,[6] EDCI,[7] CDMT,[8] PEG-400,[9] or Lewis acids,[10] formic acid derivatives such as acetic formic anhydride,[11] 2,2,2,-trifluoroethyl formate[12] and pentafluorophenyl formate,[13] cyanomethyl formate,[14] ammonium formate,[15] and solid-supported reagents.[16] However, these agents are moisture sensitive, highly toxic, and expensive.

As part of our research effort to develop new synthetic methods using metals as catalysts,[17] we report herein a simple and convenient approach to the *N*-formylation of amines using Zn metal as a catalyst under solvent-free conditions. Catalytic reactions under solvent-free conditions have recently gained considerable attention from the viewpoint of developing eco-friendly, synthetic protocols.[18] In an earlier report,[19] we disclosed an indium-catalyzed *N*-formylation of amines that afforded formamides in high yields; however, these reactions were somewhat sluggish and required long reaction times. We envisioned that other metals might be more efficient catalysts for the *N*-formylation of amines, and thus, we screened other metals such as zinc, tin, samarium, and magnesium under solvent-free conditions (Scheme 1).

In order to determine the optimum reaction conditions, *N*-formylation of aniline with formic acid was chosen as a model reaction (Table 1). The use of 10 mol % zinc led to an 88% conversion under solvent-free conditions at 70 °C for 2 h (entry 1). Among the various metals examined for this transformation, zinc was found to be the most effective in terms of chemical yield and reaction time (entries 2-4). Activated zinc was observed to be even more effective, affording 97% of the desired product in 30 min (entry 5). With a stoichiometric amount of zinc, the reaction showed very similar efficiency to the catalytic variant of the reaction (entry 6). A decrease in the amount of formic acid produced a lower yield of the desired product (entry 7). Increasing the reaction temperature up to 100 °C had no significant effect on the yield of the product (entry 8); however, a decrease of the reaction temperature to room temperature resulted in a significantly decreased yield (entry 9). The reaction carried out in CH_3CN afforded a lower yield than when it was performed under solvent-free conditions (entry 10). The efficiency of the zinc-mediated reaction was comparable to that of the indium-promoted reaction previously reported (entry 11).[19] In comparison with ZnO, Zn is more efficient as a catalyst than ZnO for the formylation. With less than 0.5 equiv of ZnO, the formylation of amines gave poor yields while the reaction proceeded efficiently with as little as 0.1 equiv of Zn.



Scheme 1

On the basis of these preliminary results, application of this procedure to the formylation of various amines was investigated. The results are summarized in Table 2. It was observed that electronic factors play a significant role in these reactions. Anilines substituted with electron-donating groups reacted faster than did those substituted with electron-withdrawing groups and provided the desired products in higher yields. (entries 1-4). We also observed a negative influence of steric hindrance upon the yield of products (entries 5-10). Thus, with secondary amines, lower yields were obtained compared with those of primary amines (entry 1 *vs*. 6 and entry 2 *vs*. 7). The reactions with aliphatic primary and secondary amines resulted in 68 - 93% yields (entries 11-15).

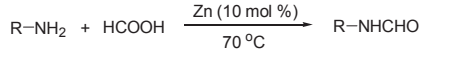
O-Formylation using the same reaction conditions was examined using phenol and benzyl alcohol as substrates. These reactions did not proceed even with a stoichiometric amount

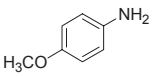
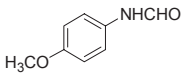
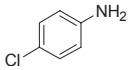
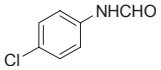
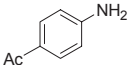
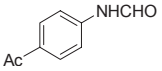
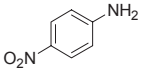
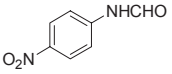
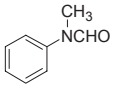
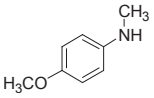
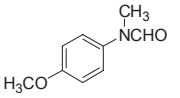
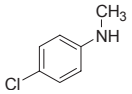
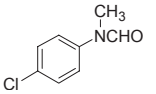
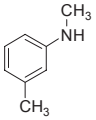
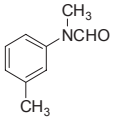
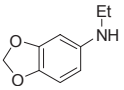
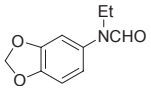
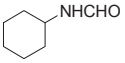
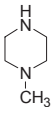
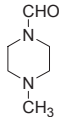
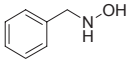
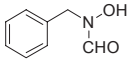
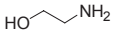
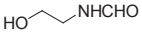
Table 1. Optimizing reaction conditions for the *N*-formylation of aniline

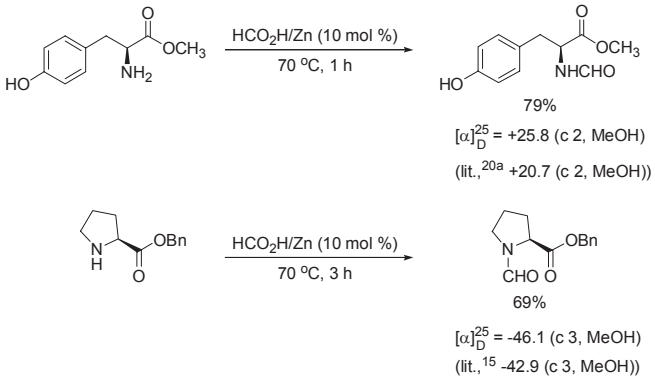
Entry	Aniline (equiv)	HCOOH (equiv)	Metal (equiv)	Time (h)	Temp (°C)	Yield (%)
1	1	3	Zn (0.1)	2	70	88
2	1	3	Sn (0.1)	24	70	71
3	1	3	Sm (0.1)	24	70	65
4	1	3	Mg (0.1)	24	70	59
5[a]	1	3	Zn (0.1)	0.5	70	97
6[a]	1	3	Zn (1.0)	0.3	70	96
7[a]	1	2	Zn (0.1)	0.5	70	91
8[a]	1	3	Zn (0.1)	0.5	100	95
9[a]	1	3	Zn (0.1)	72	rt	63
10[b]	1	3	Zn (0.1)	1	70	68
11[c]	1	3	In (0.1)	2	70	97

[a]Activated zinc metal was used. [b]In CH_3CN. [c]Taken from reference 19 for comparison.

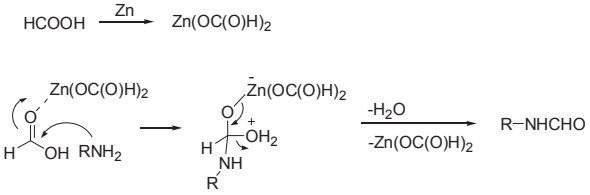
Table 2. Zinc-catalyzed *N*-formylation of various amines under solvent-free conditions



Entry	Amine	Product	Time (h)	Yield (%)
1			0.5	96
2			0.5	96
3			2	87
4			12	76
5			3	76
6			3	83
7			3	82
8			3	79
9			3	82
10	Ph_2NH	Ph_2NCHO	3	81
11	$PhCH_2NH_2$	$PhCH_2NHCHO$	0.5	93
12			1	89
13	$(^iPr)_2NH$	$(^iPr)_2NCHO$	3	71
14			3	68
15			2	73
16	Ph-OH	-	72	NR
17	$PhCH_2$-OH	-	72	NR
18			2	88
19			1	90
20			0.5	94



Scheme 2



Scheme 3

of zinc at 70 °C for a prolonged reaction time (72 h) (entries 16 and 17). The differential reactivities of amines and alcohols under these conditions allowed us to achieve a highly chemoselective formylation of amines in the presence of unprotected alcohols. Substrates containing both amino and hydroxyl groups afforded the corresponding *N*-formylated products in 88 - 94% yields, in which the hydroxyl group remained intact (entries 18-20).

We applied our new method to the synthesis of *N*-formylamino acid esters, which serve as starting materials for peptide synthesis.[20] The formylation of α-amino acid esters was readily achieved using the present method without cleavage of the methyl or benzyl ester functional groups (Scheme 2). We could not detect any sign of epimerization of the stereogenic centers of the optically pure amino acid esters by comparing the optical rotations of the products with those of the authentic samples.

A plausible mechanism for the reaction is shown in Scheme 3. Formic acid reacts with zinc metal to generate $Zn(OC(O)H)_2$,[21] which acts as a Lewis acid to coordinate the carbonyl oxygen of formic acid. Nucleophilic attack of an amine on the carbonyl carbon followed by dehydration produces the formamide.

In conclusion, we have developed an efficient and chemoselective method for the *N*-formylation of a wide variety of amines using formic acid as a formylating agent and zinc metal as a catalyst. The features of the present method include low cost, wide availability, easy handling, reagent stability and ease of operation.

Experimental Section

General procedure. A mixture of amine (2 mmol), formic acid (226 μL, 6 mmol), and activated zinc dust (pretreated with HCl, 13 mg, 0.2 mmol)[22] was stirred at 70 °C. The reaction was

monitored using TLC. After completion of the reaction, the mixture was diluted with CH_2Cl_2, and filtered through celite. The filtrate was washed with saturated $NaHCO_3$ and brine and was dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified using column chromatography on silica gel to give the corresponding formylated product.

***N*-Methyl-*N*-(*m*-tolyl)formamide:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.31 (s, 3H), 6.98 (m, 2H), 7.09 (m, 1H) 7.31 (m, 1H), 8.47 (s, 1H). Anal. Calcd for $C_9H_{17}NO_2$: C, 72.46; H, 7.43; N, 9.39; O, 10.72. Found: C, 73.23; H, 7.56; N, 9.52.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-ethylformamide:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, J = 7.2 Hz), 3.77 (q, 2H, J = 7.2 Hz), 6.01 (s, 2H), 6.61 (m, 1H), 6.67 (m, 1H), 6.81 (m, 1H), 8.24 (s, 1H). Anal. Calcd for $C_9H_{17}NO_2$: C, 62.17; H, 5.74; N, 7.25; O, 24.84. Found: C, 62.55; H, 5.67; N, 7.39.

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