



Facile N-formylation of amines using Lewis acids as novel catalysts

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ABSTRACT

Alky, aryl, and heteroaryl amines were found to react efficiently with formic acid under Lewis acid catalysis giving N-formyl derivatives in high yields. A study of ZnCl₂-catalyzed N-formylation of a variety of amines using formic acid as formylating agent is described.

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Formylation of amines is an important reaction in synthetic organic chemistry. Formamides have wide applications as intermediates in the preparation of pharmaceuticals¹ such as fluoroquinolones and as important reagents for Vilsmeier formylation.² They are also in use as Lewis base catalysts in organic transformations such as allylation,³ hydrosilylation⁴ of carbonyl compounds. In addition, the formyl group is one of the important amino-protecting groups in peptides synthesis⁵ and the N-formyl derivatives are useful precursors in the preparation of N-methyl compounds.⁶

In recent years, a number of methods have been reported on N-formylation of amines. Some of the useful formylation reagents are chloral,⁷ formic acid-DCC,⁸ formic acid-EDCI,⁹ formic acid esters,¹⁰ KF-alumina,¹¹ and other solid-supported reagents,¹² ammonium formate,¹³ CDMT.¹⁴ Many of the N-formylation methods have disadvantages such as expensive reagents, formation of side products, thermal instability, and difficult accessibility to reagents. Thus, a mild, convenient, and high yield procedure using inexpensive catalyst would be valuable.

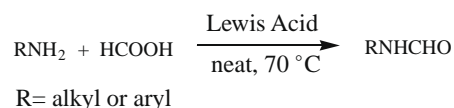
In continuation of our interest in the development of new synthetic methods using Lewis acids as catalysts,¹⁵ we report herein a convenient and novel approach for activation of formic acid as an N-formylation agent using Lewis acid as catalyst under solvent-free condition (Scheme 1).

In our study, no reaction was observed when a mixture of aniline and formic acid was heated at 100 °C for 4 h. However, addition of a catalytic amount of Lewis acid to this mixture has rapidly induced N-formylation producing formanilide in high yields. In this reaction, we have obtained formanilide in very high yields (>90%), when ZnCl₂, SnCl₂, LaCl₃, and La(OTf)₃ were used as

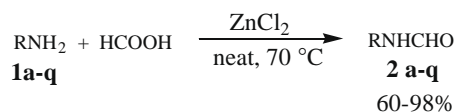
catalysts. This reaction has proceeded well with other Lewis acids also such as FeCl₃, AlCl₃, and NiCl₂ giving yields in the range of 80–90%, but no reaction was observed in the presence of ZnF₂ and AlF₃.

Among all the catalysts studied in this reaction, the best results were obtained with ZnCl₂, which is not only inexpensive but also environment friendly. This has encouraged us to further investigate the N-formylation of a variety of alkyl, aryl, and heteroarylamines **1a–q** with formic acid under similar conditions using ZnCl₂ as a catalyst¹⁶ (Scheme 2). The results are shown in Table 1.

In this study, the arylamines having electron-donating groups were found to be more active to N-formylation as their reactions were completed in less than 1.5 h. Primary amines, secondary amines, and arylamines substituted with electron-withdrawing groups, that is, **1g**, **1h**, and **1i** were, however, sluggish requiring 3–12 h for completion of the reaction. The plausible mechanism for N-formylation of amines under Lewis acid catalysis is shown in Scheme 3.



Scheme 1. Lewis acid-catalyzed N-formylation of amines with formic acid.

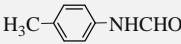
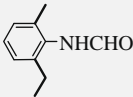
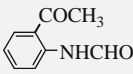
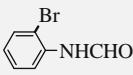
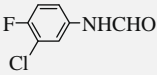
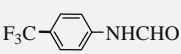
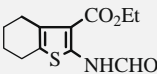
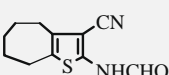
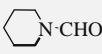
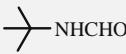
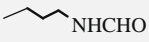


Scheme 2. ZnCl₂-catalyzed N-formylation of amines with formic acid.

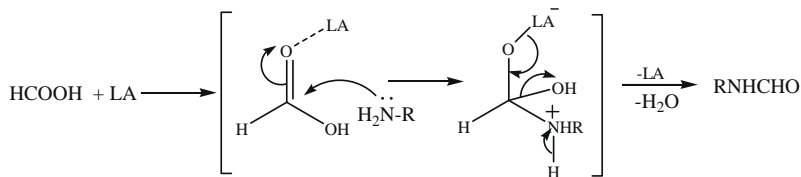
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Table 1
ZnCb-catalyzed N-formylation of amines with formic acid

Entry	Formamide 2	Time (min)	Yield ^a (%)
a		10	96
b		30	98
c		60	80
d		90	85
e		90	80
f		80	92
g		720	90
h		720	90
i		900	92
J		30	96
k		200	95
l		240	92
m		90	90
n		240	80
o		360	60
p		45	60
q		60	60

^a Isolated yields. All products gave satisfactory ¹H NMR, IR and mass spectral data.



Scheme 3. Mechanism of Lewis acid-catalyzed N-formylation of amines with formic acid.

When compared to formic acid, higher carboxylic acids are more resistant to amidation. In our study, the reactions of acetic acid and propionic acid with anilines in the presence of ZnCl_2 have produced the corresponding amides in moderate yields (55% and 50%, respectively) upon heating at 70 °C for 12 h and the long chain carboxylic acids such as decanoic acid and levulinic acid remained unreactive with aniline upon heating at 100 °C for 24 h.

The esters of formic acid such as phenyl formate and pentafluorophenyl formate were useful reagents for direct N-formylation without requiring any catalyst.¹⁰ However, these reagents are expensive and not readily available. Unlike these aryl formates, ethyl formate is highly sluggish and recently, $\text{TiCl}_3(\text{OTf})$ ¹⁷ and silica-bonded *N*-propylsulfamic acid¹⁸ were reported to be effective catalysts for N-formylation using ethyl formate. When compared to these procedures, the present protocol is more advantageous as the reagents are inexpensive and easily available. This method is simple and applicable to a variety of amines.

In conclusion, we have developed a novel and efficient method for N-formylation of an amine using formic acid as a formylating agent and ZnCl_2 as a catalyst. This Letter describes first the observation of Lewis acid-catalyzed N-formylation of amines using formic acid and it offers a simple, economical, environment friendly method for N-formylation of amines.

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References and notes

- (a) Kobayashi, K.; Nagato, S.; Kawakita, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1995**, 575; (b) Chen, B.-C.; Bendarz, M. S.; Zhao, R.; Sundeen, J. E.; Chen, P.; Shen, Z.; Skoumbourdis, A. P.; Barrish, J. C. *Tetrahedron Lett.* **2000**, 41, 5453; (c) Jackson, A.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1319.
- Downie, I. M.; Earle, M. J.; Heaney, H.; Shubaihar, K. F. *Tetrahedron* **1993**, 49, 4015.
- Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, 56, 6620.
- Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.
- Hartinez, J.; Laur, J. *Synthesis* **1982**, 979.
- (a) Kraus, N. A. *Synthesis* **1973**, 361; (b) Kizuka, H.; Elmaleh, D. R. *Nucl. Med. Biol.* **1993**, 20, 239.
- Blicke, F. F.; Lu, C.-J. *J. Am. Chem. Soc.* **1952**, 74, 3933.
- Waki, J.; Meinhofer, J. *J. Org. Chem.* **1977**, 42, 2019.
- Chen, F. M. F.; Benoiton, N. L. *Synthesis* **1979**, 709.
- (a) Yale, H. L. *J. Org. Chem.* **1971**, 36, 3238; (b) Kisfaludy, L.; Laszlo, O. *Synthesis* **1987**, 510; (c) Duezek, W.; Deutsch, J.; Vieth, S.; Niclas, H. *J. Synthesis* **1996**, 37.
- Mihara, M.; Ishino, Y.; Minakara, S.; Komatsu, M. *Synthesis* **2003**, 2317.
- Das, B.; Krishnaiah, M.; Balasubramanyam, P.; Veeranjanyulu, B.; Nandan kumar, D. *Tetrahedron Lett.* **2008**, 49, 2225.
- Reddy, P. G.; Kumar, G. D. K.; Bhaskaran, S. *Tetrahedron* **2000**, 41, 9149.
- Luca, L. D.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* **2004**, 2570.
- (a) Shanthan Rao, P.; Venkataratnam, R. V. *Tetrahedron Lett.* **1991**, 32, 5821; (b) Sridhar, M.; Ramanaiah, B. C.; Narsaiah, Ch.; Mahesh, B.; Kumaraswamy, M.; Kishore Kumar, M.; Vishnu Murthy, A.; Shanthan Rao, P. *Tetrahedron Lett.* **2009**, 50, 3897.
- General procedure for N-formylation of an amine*: 2-Amino-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carbonitrile (0.5 g, 2.6 mmol) and anhydrous ZnCl_2 (35 mg, 0.26 mmol) were taken in a 50 ml round bottomed flask fitted with a calcium chloride guard tube. To the mixture, formic acid (0.3 ml, 7.8 mmol) was added drop-wise with constant stirring for 10 min. This mixture was heated at 70 °C for 1 h and the progress of the reaction was monitored by TLC. When the reaction was completed, the mixture was cooled to room temperature and diluted with ethyl acetate (40 ml). The organic layer was washed with water (2 × 10 ml), brine (2 × 10 ml) and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (silica gel–100–200 mesh, ethyl acetate/hexane 1:10) to obtain the corresponding *N*-formyl derivative, **21** (0.53 g, 92%, mp 194–196 °C), which gave satisfactory spectral data as follows: ^1H NMR (CDCl_3 , 300 MHz): δ ppm 1.45 (m, 3H), 1.7 (m, 5H), 1.9 (m, 2H), 8.45 (s, 1H), 9.2 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ ppm 23.1, 28.6, 29.1, 31.2, 31.6, 67.4, 115.2, 128.8, 135.4, 148.8, 160.4; I.R. (KBr , ν cm^{-1}): 3397, 2210, 1679, 1565, 1450, 1113, 1026, 957; HRMS(ESI) for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{OS}$ ($\text{M}-\text{H}^+$) = 219.059 (observed), 219.060 (calculated).
- Firouzabadi, H.; Iranpoor, N.; Farahi, S. *J. Mol. Catal. A: Chem.* **2008**, 289, 61.
- Niknam, K.; Saberi, D. *Tetrahedron Lett.* **2009**, 50, 5210.