Bull. Korean Chem. Soc. **2012**, Vol. 33, No. 7

http://dx.doi.org/10.5012/bkcs.2012.33.7.2251

An Efficient Method for *N*-Formylation of Amines Using Natural HEU Zeolite at Room Temperature Under Solvent-Free Conditions

Siavash Bahari, Babak Mohammadi-Aghdam,[*] S. Mohammad Sajadi,[†] and Fereshteh Zeidali[‡]

Department of Chemistry, Ahar Branch, Islamic Azad University, Ahar, Iran
[*]E-mail: b-mohammadi-a@iau-ahar.ac.ir; b.mohamadi@yahoo.com
[†]Department of Petrolium Geoscience, Faculty of Sciences, University of Soran, PO Box 624, Soran,
Kurdistan Regional Government, Iraq
[‡]Ilam petrochemical Complex, Ilam, Iran

Received March 3, 2012, Accepted April 2, 2012

A rapid and practical green route for *N*-formylation of primary and secondary amines with formic acid at room temperature under the solvent-free conditions using HEU zeolite as a heterogeneous, reusable and highly efficient catalyst is described. The process is remarkably simple and environmentally benign. Excellent chemoselectivity was observed for the conversion of primary amines in the presence of secondary amines.

Key Words : *N*-Formylation, Amines, Solvent-free, Natural HEU zeolite, Formic acid

Introduction

Formamides are important intermediates in the preparation of amine derivatives and have been widely used in the synthesis of pharmaceutically valuable compounds.[1,2] Formamides serve as very useful reagents in Vilsmeier formylation and in the synthesis of formamidines and isocyanides.[3] Moreover, formamides are Lewis bases, which are used as catalysts in reactions such as allylation, synthesis of acid chlorides from carboxylic acids, and hydrosilylation of carbonyl compounds.[4] In addition, the formyl group is an important amine-protecting group in peptide synthesis.[5]

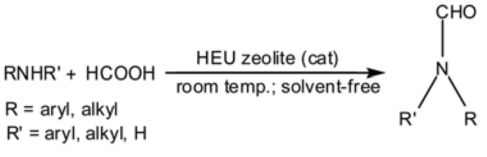
Several methods have been reported in the literature for the *N*-formylation of amines. Acetic formic anhydride[6] is a well known formylating reagent, but is sensitive to moisture and cannot be stored due to decomposition to acetic acid and carbon monoxide. Formylation using chloral,[7] activated formic acid in the presence of DCC[8] or EDCI,[9] activated formic esters,[10] ammonium formate in acetonitrile,[11] 2,2,2-trifluoroethyl formate,[12] ZnO[13] and polyethylene glycol[14] have been used for this purpose.

However, there are several factors in some of these methods which limited their applications. In many of these methods, the applicable reagents are toxic, expensive or out of accessible. Also, most of the other *N*-formylation methods have disadvantages such as long reaction times, formation of side products and thermal instability. Recently, Das *et al.*[14] reported a useful method for *N*-formylation of anilines at room temperature by using formic acid in polyethylene glycol (PEG-400); however, the success of this method is limited only to aromatic primary amines, and the method does not avoid the use of organic solvent. Recently the formylation using $ZnCl_2$, $FeCl_3$, $AlCl_3$, and $NiCl_2$ has been reported.[15]

They observed no reaction when a mixture of formic acid and aniline was heated at 100 °C for 4 h in the absence of Lewis acid. Aqueous formic acid (85%) has previously been reported as a formylating agent under conventional heating. However, this method needs a Dean-Stark trap under reflux conditions in toluene and involves long reaction times.[16] Also, the formylation of anilines having electron-withdrawing groups was found to be difficult.[16] Very recently, Heydari and co-workers reported *N*-formylation of amines using sulfonic acid supported hydroxyapatite encapsulated γ-Fe_2O_3.[17] Despite the usefulness of this method, such as high yields and mild conditions, there are difficulties in the preparation of catalyst and availability of reagents. Furthermore HCl evolution occurs during the preparation of catalyst. Therefore, the pursuit of more convenient and practical synthetic methods for these compounds still remains an active research area.

The use of heterogeneous catalysts in different areas of organic synthesis has now reached significant levels, not only because it enables environmentally benign synthesis, but also due to the good yields, accompanied by excellent selectivities, that can frequently be achieved.[18] Zeolites are uniform microporous crystalline materials and have been investigated extensively and applied as solid catalysts in the field of petrochemistry.[19] Zeolites are also known to catalyze various synthetic organic transformations much more effectively and selectively than the Lewis acid catalysts.[20]

Herein we report the *N*-formylation of amines using formic acid in the presence of a catalytic amount of zeolite HEU[20b] at room temperature under solventless conditions in



Scheme 1. Reaction of *N*-formylation of amines using formic acid in the presence of zeolite HEU.

high yields, which can be reused without any loss of activity (Scheme 1).

Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. Products were characterized by spectroscopy data (IR, NMR spectra), and melting points. The NMR spectra were recorded in DMSO and $CDCl_3$. ^1H NMR spectra were recorded on a Bruker Avance DRX 400 MHz instrument. Iranian HEU zeolite from the Semnan province, Iran was used in this work.[20b]

General Experimental Procedure for *N*-Formylation of Amines. To a solution of amine (1.0 mmol) and aq. formic acid (1.2 mmol) was added HEU zeolite (0.05 g) and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (see Table 1). After completion of the reaction, ethyl acetate was added and the HEU zeolite was removed by filtration. After removal of the solvent, the pure product was obtained.

Spectroscopic Data of Selected Products.

***N*-Phenyl formamide (Table 1, entry 1):** ^1H NMR (400 MHz, $CDCl_3$) δ 7.12-7.61 (m, 5H, Ar-H), 8.19 (s, 1H, *cis*), 8.66 (d, 1H, J = 11.3, *trans*), 8.79 (brs, 1H, *cis*), 9.38 (brs, 1H, *trans*).

***N*-(4-Methylphenyl) formamide (Table 1, entry 3):** ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 7.07-7.61 (m, 4H), 8.11 (s, 1H), 8.14 (s, 1H).

***N*-(4-Methoxyphenyl) formamide (Table 1, entry 4):** ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 7.20-7.58 (m, 4H), 7.99 (s, 1H), 8.16 (s, 1H).

***N*-(4-Bromophenyl) formamide (Table 1, entry 7):** ^1H NMR (400 MHz, $CDCl_3$) δ 7.12-7.58 (m, 4H), 8.06 (s, 1H), 8.12 (s, 1H).

***N*-(4-Chlorophenyl) formamide (Table 1, entry 9):** ^1H NMR (400 MHz, $CDCl_3$) δ 7.11-7.42 (m, 4H), 8.06 (s, 1H), 8.13 (s, 1H).

4-Morpholine carbaldehydede (Table 1, entry 16): ^1H NMR (400 MHz, $CDCl_3$) δ 3.34-3.78 (m, 8H), 8.05 (s, 1H).

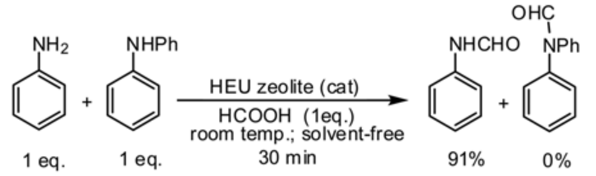
***N*-Formylpiperidine (Table 1, entry 17):** B.p. 92-95 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.81-1.86 (m, 4H), 3.50 (t, 2H), 3.52 (t, 2H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.65, 25.89, 41.66, 46.89, 162.52.

***N*-Methyl-*N*-formylaniline (Table 1, entry 18):** ^1H NMR (400 MHz, DMSO-d_6) δ 3.23 (s, 3H), 7.25-7.47 (m, 5H), 8.55 (s, 1H).

***N*,*N*-Diphenyl formamide (Table 1, entry 19):** ^1H NMR (400 MHz, DMSO-d_6) δ 7.17 (d, 2H, J = 7.5 Hz), 7.26-7.33 (m, 4H), 7.37-7.41 (m, 4H), 8.70 (s, 1H).

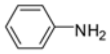
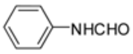
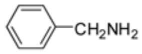
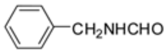
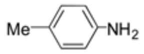
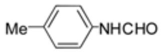
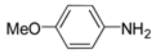
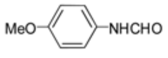
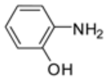
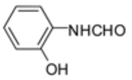
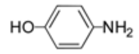
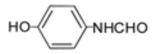
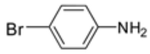
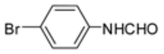
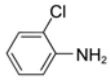
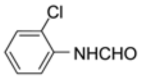
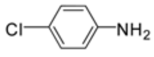
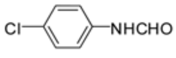
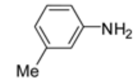
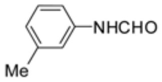
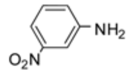
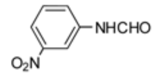
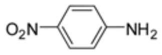
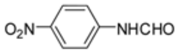
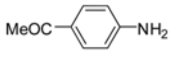
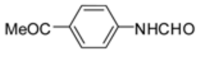
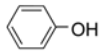
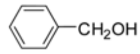
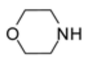
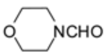
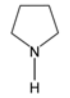
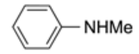
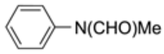
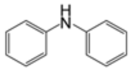
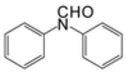
Results and Discussion

A variety of primary and secondary amines (aromatic, aliphatic and heterocyclic) was treated with formic acid in the presence of HEU zeolite as the catalyst to give the corresponding *N*-formyl amines in good to excellent yields (Table 1). Anilines bearing both electron-donating and



Scheme 2. *N*-Formylation of primary amines in the presence of secondary amines.

Table 1. *N*-Formylation of amines using HEU zeolite in formic acid at room temperature under solvent-free conditions[a]

Entry	Amine	Product	Time (min)	Yield[b] (%)	Ref.[c]
1			30	91, 88[d]	22, 27
2			35	93	22, 27
3			30	90	22, 27
4			25	91	22
5			35	87	22
6			40	86	22, 27
7			20	88	22, 27
8			30	93	22
9			20	88	22
10			25	93	13
11			25	90	22
12			30	89	22, 27
13			30	88	13, 22
14		No reaction	–	–	–
15		No reaction	–	–	–
16			35	73	22, 27
17			50	76	This work
18			50	82	22
19			70	74	22, 27
20	$HOCH_2CH_2NH_2$	$HOCH_2CH_2NHCHO$	40	75	22
21	$H_3C(CH_2)_3NH_2$	$H_3C(CH_2)_3NHCHO$	35	78	22

[a]Reaction conditions: amine (1.0 mmol), formic acid (1.2 mmol) and HEU Zeolite (0.05 g). [b]Yield refers to the pure isolated product. [c]Reported in the literature. [d]Yield after the fifth cycle.

Table 2. Comparison HEU zeolite with reported catalysts in the *N*-formylation of benzylamine

Entry	Formylating method	Solvent	Temperature	Time	Yield (%)	Ref.
1	HCOOH, Sodium formate	Solvent-free	Room temperature	2.5 h	85	22
2	HCOOH, Anhydrous $ZnCl_2$	Solvent-free	70 °C	90 min	90	15
3	Methylformate	PhMe	Room temperature	2 h	94	23
4	Ammonium formate	CH_3CN	Reflux	6 h	88	11
5	HCOOH, PEG	Solvent-free	Room temperature	6 h	42	14
6	HCOOH, H_2O_2, Copper salt	MeOH	Room temperature	75 min	80	24
7	HCOOH, Amberlite IR-120	Solvent-free	Microwave, 320 W	95 min	92	25
8	$HC(OEt)_3$	H_2O	Microwave, 90 °C	2 h	78	26
9	HCOOH	Solvent-free	80 °C	60 min	90	27
10	γ-Fe_2O_3@ HAp-SO_3H	Solvent-free	Room temperature	40 min	92	17
11	HCOOH, HEU zeolite	Solvent-free	Room temperature	35 min	93	[a]
12	HCOOH, HEU zeolite	CH_3CN	Room temperature	55 min	82	[a]
13	HCOOH, HEU zeolite	EtOH	Room temperature	55 min	80	[a]

[a] This work.

electron-withdrawing functionalities were also found to undergo the conversion in a facile manner with excellent yields. In our experimental procedure, no isolable side product has been observed. Several sensitive functionalities such as -OH and halogen (Cl, Br) were unaffected under the present reaction conditions. The open chain aliphatic amines reacted smoothly under such reaction conditions; even benzylamine that was previously reported to provide low yield[21] (42%) furnished good yield (93%) following this reaction protocol (Table 1, entry 2). Previously, the *N*-formylation of 4-nitroaniline was found to be difficult.[16] It is well known that the amino group in 4-nitroaniline is of very low basicity and hence not easily acylated. In contrast with previously reported methods, the method can be applied to conversion of poorly reactive 4-nitroaniline (Table 1, entry 12).

In comparison with the primary amines, secondary amines need longer reaction times (Table 1). Thus excellent chemoselectivity was observed for the conversion of primary amines in the presence of secondary amines, as shown in Scheme 2.

O-Formylation of phenols did not take place. It was found that this reaction *is* chemoselective, and only *N*-formylation product was formed with molecules containing both the hydroxyl and the amino group. Thus, the aminophenols furnished only the *N*-formylation products under the present reaction conditions (entries 5, 6 and 20).

To show the merits of HEU zeolite in comparison with other reported catalysts, we summarized some of results for *N*-formylation of benzylamine in Table 2, which shows that HEU zeolite is an equally or more efficient catalyst with respect to reaction time and yield than previously reported ones. Also, the reaction performed in MeCN and ethanol was less effective than those performed under solvent-free conditions (Table 2, entry 12 and 13).

HEU was used in a recycle experiment; after each cycle the catalyst was filtered off and reused in the next cycle without any post-treatment. The catalyst shows good activity even after five cycles (Table 1, entry 1).

Conclusion

In conclusion, we have developed a novel and highly efficient solvent-free protocol for *N*-formylation of amines using nontoxic, inexpensive, and natural HEU zeolite. Operational simplicity, short reaction times, the possibility for reusing the catalyst, chemoselectivity, solvent-free media, very mild reaction conditions, environmentally friendly reaction conditions, the compatibility with various functional groups are the advantages of the present procedure. No methodology has been reported so far where only formic acid is used as the sole formylating agent without any solvent in the presence of natural catalyst.

Acknowledgments. We are thankful to the Ahar Branch, Islamic Azad University, for the partial support of this research.

References

1. Kobayashi, K.; Nagato, S.; Kawakita, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1995**, 575.
2. Chen, B. C.; Bednarz, M. S.; Zhao, R.; Sundeen, J. E.; Chen, P.; Shen, Z.; Skoumbourdis, A. P.; Barrish, J. C. *Tetrahedron Lett.* **2000**, *41*, 5453.
3. Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015.
4. (a) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *56*, 6620. (b) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.
5. Martrniez, J.; Laur, J. *Synthesis* **1982**, 979.
6. Strazzolini, P.; Giumanini, A. G.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081.
7. Blicke, F. F.; Lu, C. J. *J. Am. Chem. Soc.* **1952**, *74*, 3933.
8. Waki, J.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 2019.
9. Chen, F. M. F.; Benoiton, N. L. *Synthesis* **1979**, 709.
10. (a) Yale, H. L. *J. Org. Chem.* **1971**, *36*, 3238. (b) Kisfaludy, L.; Laszlo, O. *Synthesis* **1987**, 510. (c) Neveux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. I* **1991**, 1197. (d) Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H.-J. *Synthesis* **1996**, 37.
11. Reddy, P. G.; Kumar, G. D. K.; Baskaran, S. *Tetrahedron Lett.* **2000**, *41*, 9149.
12. Hill, D. R.; Hasiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S. J.

Org. Lett. **2002**, *4*, 111.

13. Hosseni-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652.
14. Biswanath, D.; Meddeboina, K.; Balasubramanayam. P.; Boyapati, V. D.; Nandan, K. D. *Tetrahedron Lett*. **2008**, *49*, 2225.
15. Chandra Shekhar, A.; Ravi Kumar, A.; Sathaiah, G.; Luke Paul, V.; Sridhar, M.; Rao, S. *Tetrahedron Lett.* **2009**, *50*, 7099.
16. Jung, S. H.; Ahn, J. H.; Park, S. K.; Choi, J.-K. *Bull. Korean Chem. Soc*. **2002**, *23*, 149.
17. Mamani, L.; Sheykhan, M.; Heydari, A.; Faraji, M.; Yamini, Y. *Appl. Catal. A* **2010**, *377*, 64.
18. (a) Mohammadi, B.; Hosseini Jamkarani, S. M.; Kamali, T. A.; Nasrollahzadeh, M.; Mohajeri, A. *Turk. J. Chem*. **2010**, *34*, 613. (b) Nasrollahzadeh, M.; Bayat, Y.; Habibi, D.; Moshaee, S. *Tetrahedron Lett.* **2009**, *50*, 4435. (c) Habibi, D.; Nasrollahzadeh, M. *Synth. Commun*. **2010**, *40*, 3159. (d) Modarresi-Alam, A. R.; Nasrollahzadeh, M.; Khamooshi, F. *Arkivoc* **2007**, *xvi*, 234. (e) Modarresi-Alam, A. R.; Khamooshi, F.; Nasrollahzadeh, M.; Amirazizi, H. A. *Tetrahedron* **2007**, *63*, 8723. (f) Modarresi-Alam, A. R.; Nasrollahzadeh, M.; Khamooshi, F. *Scientia Iranica* **2008**, *15*, 452. (g) Habibi, D.; Nasrollahzadeh, M. *Monatsh fur Chem*. **2011**, DOI 10.1007/s00706-011-0670-8. (h) Habibi, D.; Nasrollahzadeh, M.; Bayat, Y. *Synth. Commun*. **2011**, *41*, 2135.
19. (a) Breck, D. W. *Zeolite Molecular Sieves*; Wiley: New York, 1974. (b) Dyer, A. *An Introduction to Zeolite Molecular Sieves*; Chichester, 1988.
20. (a) Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. *Tetrahedron* **2009**, *66*, 3866. (b) Tajbakhsh, M.; Mohajerani, B.; Heravi, M. M.; Ahmadi, A. N. *J. Mol. Catal. A: Chem*. **2005**, *236*, 216. (c) Habibi, D.; Nasrollahzadeh, M.; Kamali, T. A. *Green Chem.* **2011**, *13*, 3499.
21. Das, B.; Krishnaiah, M.; Balasubramanayam, P.; Veeranjaneyulu, B.; Kumar, D. N. *Tetrahedron Lett*. **2008**, *49*, 2225.
22. Brahmachari, G.; Laskar, S. *Tetrahedron Lett.* **2010**, *51*, 2319.
23. Deutsch, J.; Eckelt, R.; Köckritz, A.; Martin, A. *Tetrahedron* **2009**, *65*, 10365.
24. Tumma, H.; Nagaraju, N.; Reddy, K. V. *J. Mol. Catal. A: Chem*. **2009**, *310*, 121.
25. Muthukur Bhojegowd, M. R.; Nizam, A.; Pasha, M. A. *Chin. J. Catal*. **2010**, *31*, 518.
26. Kaboudin, B.; Khodamorady, M. *Synlett* **2010**, 2905.
27. Rahman, M.; Kundu, D.; Hajra, A.; Majee, A. *Tetrahedron Lett.* **2010**, *51*, 2896.