

Melamine trisulfonic acid-catalyzed N-formylation of amines under solvent-free conditions

Xiao Juan Yang · Yong Sen Zhang

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Abstract A highly convenient method for N-formylation of amines via treatment by formic acid in the presence of melamine trisulfonic acid as a catalyst has been developed. This method showed improvements over previous reports in terms of yield, reaction time and chemoselectivity.

Keywords N-formylation · Melamine trisulfonic acid · Formamides · Solvent-free

Introduction

The formyl group is an important amino protecting group in peptide synthesis [1]. Formamides are important intermediates in organic synthesis that have been used in the synthesis of biological active compounds, for example, fluoroquinolones [2], substituted imidazoles [3], 1,2-dihydroquinolines [4], and nitrogen-bridged heterocycles [5]. They are also widely used as precursors for the preparation of isocyanates [6], formamidines [7], and nitriles [8]. The most common methods for the synthesis of formamides are the reaction of amines with formic acid, in the presence of a catalyst, such as TiO₂-P25 [9], TiO₂-SO₄²⁻ [10], nano-MgO [11], Amberlite IR-120 [12], I₂ [13], VB₁ [14], In [15], sulfonic acid supported on hydroxyapatite-encapsulated- γ -Fe₂O₃ nanocrystallites [16], ZnCl₂ [17], NiO₂ [18], polyethylene glycol [19], and ZnO₂ [20]. These methods are suitable for certain synthetic conditions; however, many of these procedures are associated with one or more disadvantages such as expensive reagents, longer reaction times, tedious work-up

X. J. Yang (✉)
College of Chemistry and Chemical Engineering, Xinxiang University, Xinxiang 453003,
Henan, China
e-mail: yangxiaojuan2005@126.com

Y. S. Zhang
The Third Affiliated Hospital, Xinxiang Medical University, Xinxiang 45300, Henan, China

procedure, low selectivity, and large amounts of catalysts which would eventually result in the generation of large amounts of toxic waste.

Recently, melamine trisulfonic acid (MTSA) has emerged as a promising solid acid catalyst for acid-catalyzed reactions, such as synthesis of β -acetamido ketones [21], oxathioacetalization of aldehydes [22], nitrosation of secondary amines, and oxidation of urazoles [23]. This catalyst is safe, easy to handle, and environmentally benign, and presents fewer disposal problems. MTSA as a solid acid catalyst is prepared from the reaction of melamine with neat chlorosulfonic acid at room temperature (Scheme 1).

In this paper, we present a novel, mild, and efficient method for the *N*-formylation of amines using amines and formic acid in the presence of MTSA as a catalyst (Scheme 2).

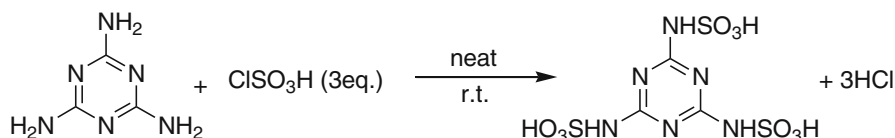
Results and discussion

Initially, when the reaction of aniline (1 mmol) and formic acid (2 mmol) with a catalytic amount of MTSA (0.03 mmol) was heated at 60 °C under solvent-free conditions as a simple model substrate, the reaction proceeded rapidly to give the corresponding *N*-phenylformamide in high yield after a relatively short reaction time.

To clarify the generality of this reaction, several amine derivatives were treated with formic acid under solvent-free conditions to afford the corresponding formamides **3**. The results are shown in Table 1. All known compounds were characterized by comparison of their physical and spectroscopic data with authentic samples. We found that anilines containing electron-donating substituents such as $-\text{CH}_3$, $-\text{OCH}_3$, and $-\text{OH}$ (entries 2–6) and electron-withdrawing groups such as $-\text{NO}_2$ and halides (entries 7–11) did not affect the reaction time and yields. Aliphatic and secondary cyclic amines are also giving moderate yields of the product (entries 13–18).

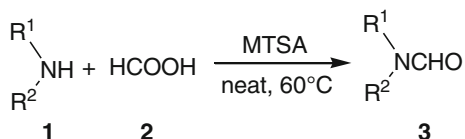
The general reaction mechanism involves nucleophilic attack of amines on the protonation of the carbonyl group of formic acid, which leads to the formation of intermediates **4**, which is transformed into the desired formylated product, water, and proton, which further catalyzes the reaction (Scheme 3).

To illustrate the efficiency of the proposed method, Table 2 compares some of our results with some of those reported in the literature for relevant reagents, which demonstrates its significant superiority. Compared with some of the reported methods in Table 2, the present method has a short reaction time, good yield, and



Scheme 1 Synthesis of MTSA

Scheme 2 N-formylation of amines using amines and formic acid in the presence of MTSA



solvent-free conditions. In addition, MTSA is a stable, cost effective, recyclable, and noncorrosive catalyst with high efficiency.

Conclusion

We have developed a simple, mild, and environmentally benign method for N-formylation of amines with formic acid catalyzed by MTSA at 60 °C. This method offers the advantage of shorter reaction times, high chemoselectivity, and easy workup. We believe that this methodology could be an important addition to the existing methodologies.

Experimental

NMR spectra were determined on Bruker AV-400 instrument at room temperature using tetramethylsilane as internal standard. Coupling constants (*J*) were measured in Hz; infrared (IR) spectra were determined on FTS-40 infrared spectrometer. Mass spectra were taken on a Macro mass spectrometer (Waters) by electrospray method. Commercially available reagents were used throughout without further purification unless otherwise stated.







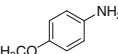

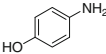





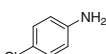

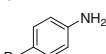

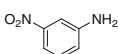

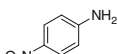















Preparation of MTSA catalyst

A 250-mL suction flask charged with 5 mL chlorosulfonic acid (75.2 mmol) was equipped with a gas inlet tube for conducting HCl gas over an adsorbing solution. Melamine (3.16 g, 25.07 mmol) was added in small portions over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately (Scheme 1). After completion of the addition of melamine, the mixture was shaken for 30 min; meanwhile, the residual HCl was removed by suction. MTSA (7.7 g, 85 %) was obtained as a white solid.

General procedure for the preparation of **3**

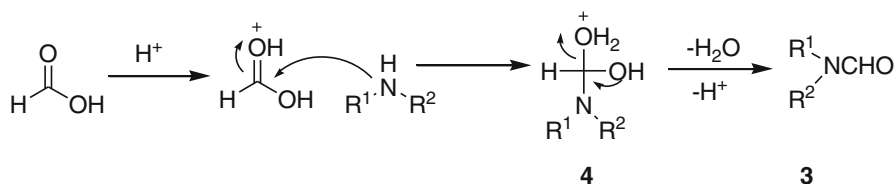
A mixture of amines (1 mmol), formic acid (2 mmol), and MTSA (0.03 mmol) was prepared and stirred at 60 °C for appropriate time (Table 1). After completion of the reaction (TLC), the mixture was diluted with CH₂Cl₂ (20 mL), washed with H₂O (10 mL), and then dried over anhydrous MgSO₄. After filtration and evaporation of the solvent, the residue was purified by column chromatography on silica gel to give the formylated product. All the compounds are known and their physical properties

Table 1 Synthesis of formamides catalyzed by MTSA

Entry	Amines	Products	Time (min)	Yield (%) ^b
1		 3a	60	98
2		 3b	45	96
3		 3c	45	94
4		 3d	60	97
5		 3e	40	96
6		 3f	40	93
7		 3g	75	92
8		 3h	60	93
9		 3i	75	94
10		 3j	90	90
11		 3k	90	89
12		 3l	90	91
13		 3m	90	91
14		 3n	75	93
15		 3o	90	90
16		 3p	90	89
17		 3q	75	90
18		 3r	75	89

Reaction conditions: amines (1 mmol), formic acid (2 mmol), MTSA (0.03 mmol), neat, 60 °C

^a Isolated yield



Scheme 3 The general reaction mechanism

Table 2 Comparison of different catalysts for formation of *N*-phenylformamide

Entry	Catalyst (mol%)	Equivalent ratio amine:formic acid	Temperature (°C)	Time (min)	Yield (%) ^a	References
1	I ₂ (5)	1:2	70	120	94	[13]
2	In (10)	1:3	70	120	97	[15]
3	Nano-MgO (25)	1:1.5	MW	1	98	[11]
4	ZnCl ₂ (100)	1:3	70	60	96	[17]
5	MTSA (3)	1:2	60	60	98	This study

^a Isolated yield

are the same as the reported values. ¹H NMR, IR, and mass spectral data of all the products match the reported data.

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References

- J. Hartinez, J. Laur, *Synthesis* **1982**, 979 (1982)
- A. Jackson, O. Meth-Cohn, *J. Chem. Soc. Chem. Commun.* **1995**, 1319 (1995)
- B.C. Chen, M.S. Bednarz, R. Zhao, J.E. Sundeen, P. Chen, Z. Shen, A.P. Skoumbourdis, J.C. Barrish, *Tetrahedron Lett.* **41**, 5453 (2000)
- K. Kobayashi, S. Nagato, M. Kawakita, O. Morikawa, H. Konishi, *Chem. Lett.* **24**, 575 (1995)
- A. Kakehi, S. Ito, S. Hayashi, T. Fujii, *Bull. Chem. Soc. Jpn.* **68**, 3573 (1995)
- Y. Han, L. Cai, *Tetrahedron Lett.* **38**, 5423 (1997)
- K.F. Mahmoud, S.P. Newtown, US Patent 5,155,267 (1992)
- A. Dieter, K. Gerhard, US Patent 4,419,297 (1983)
- B. Krishnakumar, M. Swaminathan, *J. Mol. Catal. A* **334**, 98 (2011)
- S. Ashoka, G.T. Chandrappa, M.A. Pasha, *Catal. Lett.* **138**, 82 (2010)
- M.R.M. Bhojgowd, A. Nizam, M.A. Pasha, *Chin. J. Catal.* **31**, 518 (2010)
- J.-G. Kim, D.O. Jang, *Synlett* **2010**, 2093 (2010)
- M. Lei, L. Ma, L.H. Hu, *Tetrahedron Lett.* **51**, 4186 (2010)
- J.-G. Kim, D.O. Jang, *Synlett* **2010**, 1231 (2010)
- J. Deng, L.-P. Mo, F.-Y. Zhao, L.-L. Hou, L. Yang, Z.-H. Zhang, *Appl. Catal. A* **377**, 64 (2010)
- A.C. Shekhar, A.R. Kumar, G. Sathiaiah, V.L. Paul, M. Sridhar, P.S. Rao, *Tetrahedron Lett.* **50**, 7099 (2009)
- H. Thakuria, B.M. Borah, G. Das, *J. Mol. Catal. A* **274**, 1 (2007)
- B. Das, M. Krishnaiah, P. Balasubramanyam, B. Veeranjanyulu, D.N. Kumar, *Tetrahedron Lett.* **49**, 2225 (2008)
- M. Hosseini-Sarvari, H. Sharghi, *J. Org. Chem.* **71**, 6652 (2006)

20. H.-Z. Li, H.-Y. Li, K.-F. Yu, L.-W. Xiao, *Chin. J. Org. Chem.* **23**, 883 (2003)
21. A. Zare, *E-J. Chem.* **9**, 2322 (2012)
22. F. Shirini, J. Albadi, *Bull. Korean Chem. Soc.* **31**, 1119 (2010)
23. G. Chehardoli, M. Zolfigol, T. Faal-Rastegar, S. Mallakpour, A. Ghorbani-Choghamarani, *J. Chem. Sci.* **121**, 441 (2009)