Tetrahedron Letters 55 (2014) 6292–6296

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A green protocol for the N-formylation of amines using molybdate sulfuric acid as a reusable solid catalyst

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ARTICLE INFO

Article history:
Received 6 June 2014
Revised 6 September 2014
Accepted 24 September 2014
Available online 2 October 2014

Keywords:
N-formylation
Orthoformate
Amine
Molybdate sulfuric acid

ABSTRACT

A novel and efficient method for the N-formylation of amines via the reaction of orthoformates and amines is developed. The reactions are mediated by a catalytic amount of molybdate sulfuric acid as a heterogeneous solid acid.

A useful reaction in organic chemistry is the N-formylation of amines to give formamide derivatives.[1] Formamides have been used as intermediates for the synthesis of many pharmaceutical compounds such as fluoroquinolones,[2] substituted aryl imidazoles,[3] 1,2-dihydroquinolines,[4] and nitrogen-bridged heterocycles.[5] Moreover, the formyl group can be used as an amino-protecting group for the synthesis of peptides and *N*-formylamino acid esters, which can be applied as starting materials in peptide synthesis.[6]

Many strategies have been developed for the preparation of *N*-formyl amines. They can be obtained from reactions of the corresponding amines with formic acid and acetic anhydride,[7] in situ formed formic anhydride,[8] chloral followed by elimination,[9] ammonium formate,[10] and other reagents.[11] However, many of these methods suffer from drawbacks such as the use of expensive and toxic formylating agents, formation of by-products, difficult accessibility of the formylating agents, etc. Hence, new, safe, and efficient synthetic methods are of practical value for the preparation of *N*-formyl amines.

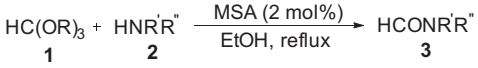
With the advance of green chemistry, heterogeneous solid acids have been used in various organic transformations as eco- and environmentally friendly catalysts. These solid acids have many benefits such as recyclability and non-toxicity, cleaner and easier work-up procedures, and reduced reaction times.[12] Molybdate sulfuric acid (MSA) is an inexpensive and easily handled solid alternative to sulfuric acid and has been used in some organic reactions.[13,14]

In continuation of our interest in using heterogeneous solid catalysts,[15–17] herein an efficient method is reported for the N-formylation of amines by the reaction of orthoformates **1** and amines **2** using molybdate sulfuric acid (MSA) as a reusable solid Brönsted acid (Scheme 1).

Initially, the solvent-free reaction between triethyl orthoformate (1.1 mmol) and aniline (1 mmol) was performed at room temperature in the absence of a catalyst as a model reaction. No N-formylation of the amine occurred, even after 24 h. Next, the model reaction was investigated in the presence of different catalysts under various conditions (Table 1).

According to Table 1, the best result was obtained by performing the model reaction using 2 mol % of molybdate sulfuric acid (MSA) in refluxing ethanol (Table 1, entry 10). The superiority of this solid acid as an analog of sulfuric acid compared with liquid sulfuric acid is attributed to the surface hydrophilic porosity, higher capacity, and large surface area of MSA.

Next, the generality of the procedure was evaluated using the reactions of various primary and secondary amines under the optimized reaction conditions. In most cases, the reactions proceeded



Scheme 1. N-Formylation of amines in the presence of molybdate sulfuric acid (MSA).

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http://dx.doi.org/10.1016/j.tetlet.2014.09.114
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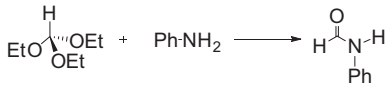
Table 1
Screening conditions for the model reaction



Entry	Catalyst (mol %)	Solvent/Temp. (°C)	Time (min)	Yield[a] (%)
1	None	none/50	240	10
2	ZnO (5)	EtOH/50	200	40
3	$ZrOCl_2$ (5)	EtOH/50	120	50
4	$MgBr_2$ (5)	EtOH/50	150	35
5	$ZnCl_2$ (5)	EtOH/50	100	50
6	H_2SO_4 (5)	EtOH/50	100	65
7	MSA (5)	EtOH/50	90	60
8	MSA (2)	EtOH/50	60	70
9	MSA (5)	EtOH/80	70	70
10	MSA (2)	EtOH/80	50	90
11	MSA (10)	EtOH/80	60	80
12	MSA (2)	H_2O/100	80	70
13	MSA (2)	CH_3CN/80	70	55
14	MSA (2)	$CHCl_3$/70	100	50
15	MSA (2)	EtOH/25	120	50
16	MSA (2)	none/80	100	70

[a] Isolated yield.

cleanly and the desired formamide derivatives were obtained in good to excellent yields (Table 2).[18–20]

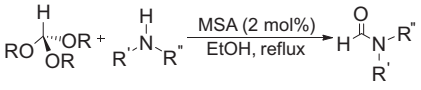
Anilines with electron-donating groups such as CH_3 and OCH_3 provided excellent yields with orthoformates, whereas lower yields were obtained when electron-poor anilines were used.

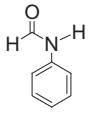
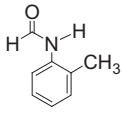
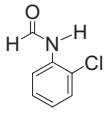
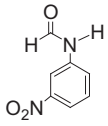
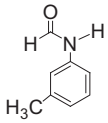
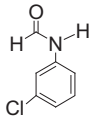
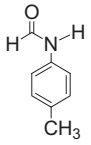
Furthermore, hindered amines such as *t*-butylamine and biphenylamine remained completely unreactive and no amide was formed, even after 12 h (Table 2, entries 26 and 27).

Although aliphatic and aromatic amines individually reacted well with orthoformate, the reaction of equal amounts of aniline and benzylamine with triethyl orthoformate in the presence of MSA gave exclusively *N*-phenyl formamide. This shows the chemoselectivity of this reaction with aromatic amines.

The products were isolated and characterized from their physical and spectral data, and were compared with authentic samples. For example, the ^{1}H NMR spectrum of *N*-(2-chlorophenyl)formamide (Table 2, entry 3) showed two singlets corresponding to the hydrogens of the formyl group (δ = 9.73) and NH (δ = 8.35). A multiplet for the aromatic protons appeared at δ = 7.19–7.55. The proton decoupled ^{13}C NMR spectrum showed seven distinct resonances that confirmed the proposed structure. The IR spectrum displayed carbonyl (1680 cm^{-1}) and NH (3250 cm^{-1}) stretching vibrations.

Table 2
MSA-catalyzed N-formylation of amines



Entry	Orthoformate	Amine	Product	Time/yield[a] (min/%)[Lit.]
1	$HCOEt_3$	$PhNH_2$		50/90[21]
2	$HCOEt_3$	2-CH_3-$C_6H_4NH_2$		50/90[22]
3	$HCOEt_3$	2-Cl-$C_6H_4NH_2$		70/75[1]
4	$HCOEt_3$	3-NO_2-$C_6H_4NH_2$		110/70[23]
5	$HCOEt_3$	3-CH_3-$C_6H_4NH_2$		50/92[1]
6	$HCOEt_3$	3-Cl-$C_6H_4NH_2$		60/70[1]
7	$HCOEt_3$	4-CH_3-$C_6H_4NH_2$		45/95[21]

(*continued on next page*)

Table 2 (*continued*)

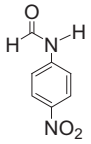
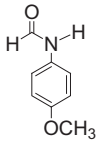
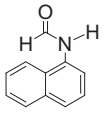
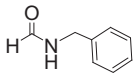
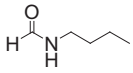
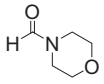
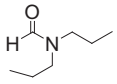
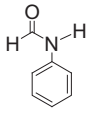
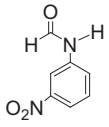
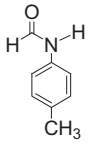
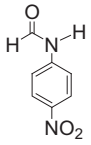
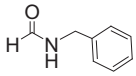
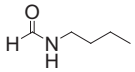
Entry	Orthoformate	Amine	Product	Time/yield[a] (min/%)[Lit.]
8	$HCOEt_3$	4-NO_2-$C_6H_4NH_2$		120/67[21]
9	$HCOEt_3$	4-CH_3O-$C_6H_4NH_2$		55/95[21]
10	$HCOEt_3$	1-NaphthNH_2		100/87[24]
11	$HCOEt_3$	$PhCH_2NH_2$		140/75[21]
12	$HCOEt_3$	*n*-$BuNH_2$		360/80[21]
13	$HCOEt_3$	$EtNH_2$		200/78[25]
14	$HCOEt_3$			300/65[21]
15	$HCOEt_3$			350/60[21]
16	$HCOEt_3$			240/73[23]
17	$HCOEt_3$	Et_2NH		300/70[1]
18	$HCOEt_3$	*n*-Pr_2NH		450/74[26]
19	$HCOEt_3$	Me_2NH		150/80[27]
20	$HCOMe_3$	$PhNH_2$		45/85[21]
21	$HCOMe_3$	3-NO_2-$C_6H_4NH_2$		95/70[23]
22	$HCOMe_3$	4-CH_3-$C_6H_4NH_2$		40/90[21]
23	$HCOMe_3$	4-NO_2-$C_6H_4NH_2$		110/70[21]
24	$HCOMe_3$	$PhCH_2NH_2$		140/70[21]

Table 2 (*continued*)

Entry	Orthoformate	Amine	Product	Time/yield[a] (min/%)[Lit.]
				
25	$HCOMe_3$	*n*-$BuNH_2$		300/80[21]
26	$HCOEt_3$	*t*-$BuNH_2$	–[b]	–[b]
27	$HCOEt_3$	Ph_2NH	–[b]	–[b]

[a] Isolated yield.
[b] No N-formylation occurred.

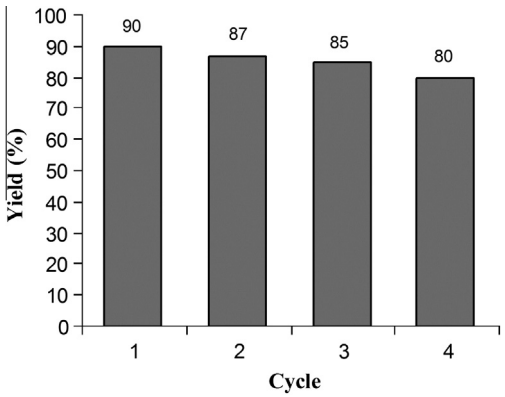
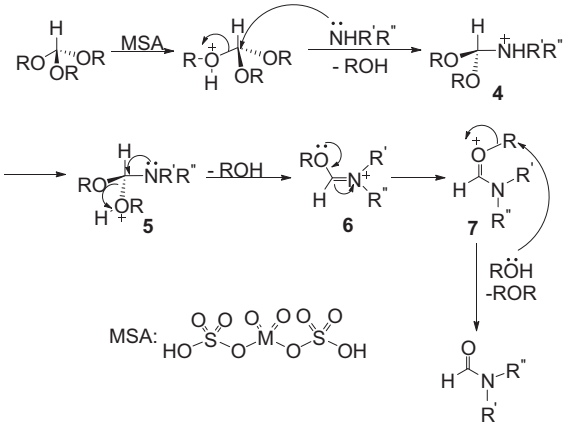


Figure 1. Recyclability of the MSA catalyst in the model reaction.



Scheme 2. Suggested mechanism for the N-formylation of amines by MSA.

To be an eco-friendly procedure, the recovery and reusability of catalysts are necessary. The recovered MSA from the model reaction was regenerated by washing with ethyl acetate and drying at 100 °C for one hour. Using the recycled catalyst four consecutive times in the model reaction gave the expected product with only a gradual decrease in the yield (Fig. 1).

Although we have not established the mechanism of our reaction in an experimental manner, a possible explanation is proposed in Scheme 2. It is reasonable to assume that intermediate **4** can result from an attack of the amine on the MSA-activated orthoformate. Compound **4** is transformed into **5**, which next loses a molecule of alcohol to produce **6** and then **7**. Finally, intermediate **7** is attacked by the alcohol to afford the final product. Based on the proposed reaction mechanism, ether is produced in the final step. To confirm this claim, the model reaction was followed by GC and the obtained results confirmed the formation of an ether in the reaction mixture (see the Supporting information).

In summary, molybdate sulfuric acid was used as a recyclable, safe, and thermally stable catalyst for the green N-formylation of amines via the reaction of amines and orthoformates in refluxing ethanol. This new reaction has many advantages such as the simple experimental procedure, use of an eco-friendly and reusable catalyst, short reaction times, and good to excellent yields.

Acknowledgment

We are grateful to Yasouj University for the financial support of this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.114.

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18. *General procedure for the N-formylation of amines*
To a mixture of orthoformate (1.1 mmol) and amine (1 mmol) in EtOH (5 mL) was added MSA (2 mol %), and the mixture was stirred under reflux for the appropriate time (Table 2). After completion of the reaction, the mixture was filtered and evaporated to afford the product. For solid products, further purification was achieved by recrystallization from Et_2O.
19. *Preparation of molybdate sulfuric acid (MSA)*[14]
Dry *n*-hexane (25 mL) was taken in a 100 mL round-bottom flask, equipped with an ice bath and an overhead stirrer Anhydrous sodium molybdate (4.118 g, 20 mmol) was added to the flask, followed by chlorosulfonic acid (0.266 mL, 40 mmol) dropwise over 30 min. This mixture was stirred for 1.5 h. The mixture was gradually poured into 25 mL of cold distilled H_2O with agitation. The bluish solid which separated out was filtered. The catalyst was washed with distilled H_2O (five times) until the filtrate showed a negative test for chloride ions, and was dried at 120 °C for 5 h. The catalyst was obtained in 90% yield as a bluish solid, which decomposed at 354 °C.
20. Selected spectral data
N-o-Tolyl formamide (Table 2, entry 2):

Pale yellow crystals; mp 60–65 °C. IR (KBr): υ_{max} = 3250, 1682, 883 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.11 (d, J = 0.8 Hz, 1H), 7.93 (m, 1H), 7.52–7.63 (m, 4H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.62, 161.64, 137.01, 133.74, 120.69, 119.86, 117.63, 19.62.

N-(2-Chlorophenyl)formamide (Table 2, entry 3)

Yellow crystals; mp 78–80 °C. IR (KBr): υ_{max} = 3250, 1680, 1542, 783 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.73 (s, 1H), 8.35 (s, 1H), 7.19–7.55 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.64, 140.94, 132.22, 130.94, 122.84, 117.71, 117.64.

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