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Clean and Green Approach for N-formylation of Amines using Formic acid under neat reaction condition

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ABSTRACT

Efficient and clean procedure for N-formylation of amines has been carried out under neat reaction condition. Environmentally friendly process furnishing moderate to excellent yields of product and simple work-up giving pure products are attractive features of the reaction.

Key words: Amines, formic acid, N-formylation.

INTRODUCTION

In recent years much effort has been carried out on formylations of amines. N-formyl compounds have been widely used in organic synthesis as protecting group of amines [1]. They are also used for synthesis of pharmaceutically important heterocycles [2-5]. Formamides are the Lewis bases, which are known to catalyze reactions such as allylations [6] and hydrosilylations [7] of carbonyl compounds. In additions to this they have been useful amino-protecting groups in peptide synthesis [8].

Literature survey reveals that number of formylation methods is reported in the literature. Acetic formic anhydride [1, 9] chloral [10], DCC [11], or EDCI [12], activated formic acid esters [13-16], KF-Al₂O₃ [17], ammonium formate [18], solid supported reagent [19] and other reagents. However, many of these methods suffer from different drawbacks such as the applications of expensive and toxic formylation agents and catalyst. Long reaction time, harsh reaction conditions, low yields of the products, tedious workup and purification of the products.

With increasing the environmental concerns and regulatory constraints faced in the chemical and pharmaceutical industries, development of environmentally benign organic reactions have become has a crucial and demanding research area in modern organic chemical research [20].

There fore more and more chemists are avoided use of solvent, solid support, microwave. Therefore, we report now excellent yields in various N-formylation of amines from mixture of pure reactants without the necessity for use of solvents for removal of catalysts or tedious work up. This endeavour succeeded in solid state reactions or as melt reactions with direct crystallization at the reaction temperature.

MATERIALS AND METHODS

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. ¹H NMR spectra were recorded in DMSO-*d*₆ on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

Experimental Procedure:

Formic acid was added to aniline and then reaction mixture was heated under stirring for 60°C. Progress of the reaction was monitored by TLC. After completion of reaction, reaction mixture was quenched over ice and extracted with ethyl acetate and washed with NaHCO₃. The organic layer dried over Na₂SO₄ and concentrated to yield pure product.

Spectroscopic data of selected compounds:

1. N-(*p*-tolyl)- formamide:

IR(KBr): 3225, 2940, 1667, 1610, 1543, 1450, 1397, 1300 cm.⁻¹ ¹H NMR (DMSO*d*₆): δ 2.32 (s, 3H, CH₃), δ 7.09-7.60 (m, 4H, Ar-H), δ 8.15 (s, 1H, -NH), δ 8.09 (s, 1H, -CHO) δ ppm; M.S. (m/z): 135[M⁺]; Anal. Calcd for C₈H₉NO: C, 71.09; H, 6.71; N, 10.36%. Found: C, 70.92; H, 6.63; N, 10.25%

2. N-(4-methoxyphenyl)- formamide:

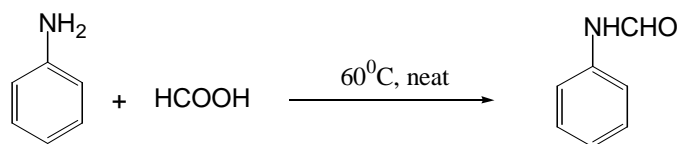
IR(KBr): 3218, 2945, 1640, 1525, 1456, 1350 cm.⁻¹ ¹H NMR (DMSO*d*₆): δ 3.85 (s, 3H, OCH₃), δ 7.21-7.56 (m, 4H, Ar-H), δ 8.18 (s, 1H, -NH), δ 7.98 (s, 1H, -CHO) δ ppm; M.S. (m/z): 151[M⁺]; Anal. Calcd for C₈H₉NO₂: C, 63.56; H, 6.00; N, 9.27%. Found: C, 63.48; H, 5.93; N, 9.15%

2. N-(4-chlorophenyl)- formamide:

IR(KBr): 3235, 2938, 1656, 1575, 1458, 1320, 767 cm.⁻¹ ¹H NMR (DMSO*d*₆): δ 7.10-7.40 (m, 4H, Ar-H), δ 8.12 (s, 1H, -NH), δ 8.04 (s, 1H, -CHO) δ ppm; M.S. (m/z): 155[M⁺]; Anal. Calcd for C₇H₆ClNO: C, 54.04; H, 3.89; N, 9.00%. Found: C, 53.98; H, 3.73; N, 8.92%

2. N-(4-bromophenyl)- formamide:

IR(KBr): 3238, 2935, 1650, 1568, 1430, 1358, 756 cm.⁻¹ ¹H NMR (DMSO*d*₆): δ 7.10-7.56 (m, 4H, Ar-H), δ 8.10 (s, 1H, -NH), δ 8.02 (s, 1H, -CHO) δ ppm; M.S. (m/z): 198[M⁺]; Anal. Calcd for C₇H₆BrNO: C, 42.03; H, 3.02; N, 7.00%. Found: C, 41.98; H, 2.95; N, 6.92%



Scheme 1

Table 1: N-formylation of amine under different reaction conditions

Entry	Condition	Solvent	Time (h)/T (°C)	Yield (%)
1	Aniline (1mmol)	HCO ₂ H	2/60	traces
2	Aniline (1 mmol)/ HCO ₂ H (2mmol)	None	2/60	40
3	Aniline (1 mmol)/ HCO ₂ H (3mmol)	None	1/60	60
4	Aniline (1 mmol)/ HCO ₂ H (4mmol)	None	0.5/60	98
5	Aniline (1mmol)/HCO ₂ H (2mmol)	Water	6/80	76

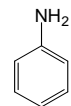
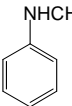
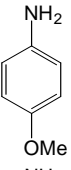
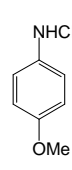
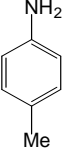
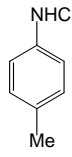
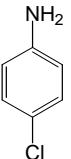
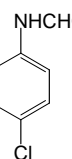
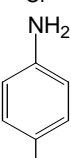
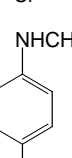
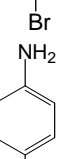
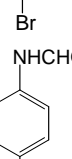
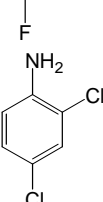
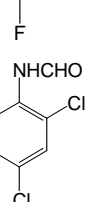
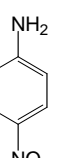
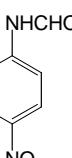
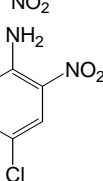
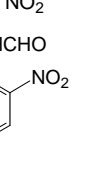
As a part of our on going program on the development of novel methods in organic synthesis under mild conditions [21]. We describe a new efficient and practical route for the N-formylation of amine using different amines and formic acid under neat reaction condition at 60 °C (**Scheme 1**).

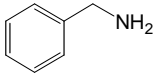
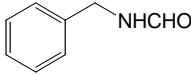
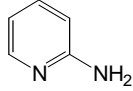
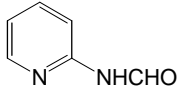
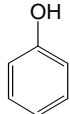
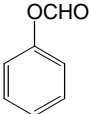
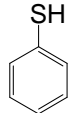
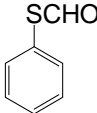
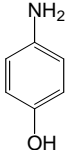
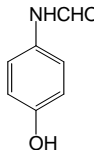
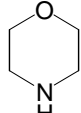
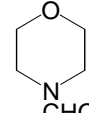
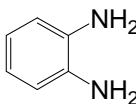
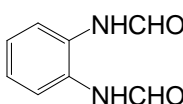
As shown in Table 1, the mixture of aniline and formic acid was examined under various reaction conditions. The use of formic acid (Table 1, Entry 1) as solvent provides only traces amount of desired product. When the amount of formic acid was reduced the yields were dramatically increased. The use of water as solvent also studied, moderate yield was obtained (Table 1, Entry 5). The best results were observed with 1:4 ratio of aniline: formic acid respectively (Table 1, Entry 4). On the basis of preliminary results the applications of this procedure to various amines was investigated.

It is important to note that amines possessing electron-donating groups furnished excellent yields of the corresponding product in short reaction times (Table 2, Entries 1-5) whereas amines with electron-withdrawing substituents resulted in comparatively moderate yield and required longer reaction time (Table 2, Entries 6-9). Heterocyclic amines and diamines were transformed in to the corresponding N-formylation in good yields under the same condition; which is problematic under acidic conditions (Table 2, Entry 11, 16). Aliphatic and secondary cyclic amines are also giving moderate yields of the product (Table 2, Entries 10, 15).

O-formylation of phenol and thiol under these conditions was not successful (Table 2, Entry 12, 13). No reaction was observed with phenol and thiol. It conforms that this reactions is chemoselective. This conforms that the only N-formylation product was formed to molecules containing both hydroxyl and amino groups (Table 2, Entry 14).

Table 2: N-formylations various amines and aromatic compounds using formic acids in water and neat reaction condition.

Entry	Amines	Products	Time (min)	Yield (%)
1			30	98
2			25	96
3			35	95
4			45	93
5			60	94
6			60	85
7			90	80
8			120	75
9			180	50

10			45	85
11			120	82
12			240	No reaction
13			240	No reaction
14			45	86
15			60	70
16			55	60

CONCLUSION

In conclusion, we have developed a novel and highly efficient neat reaction protocol for N-formylation of amine. The advantages of the present protocol need not require any special conditions and equipment. Moderate to excellent yields, environmentally benign, short reactions time and chemoselectivity are important features of the present protocol.

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