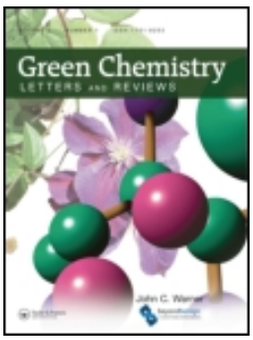

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RESEARCH LETTER

An efficient, catalyst- and solvent-free *N*-formylation of aromatic and aliphatic amines

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A simple, efficient, and cost-effective procedure for the synthesis of formamides under catalyst- and solvent-free conditions at 60°C using formic acid/ethyl formate as a formylating agent has been developed. The protocol is applicable to a wide variety of aromatic and aliphatic amines providing moderate to excellent yield of desired products.

Keywords: *N*-formylation; amines; solvent-free; catalyst-free

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Introduction

Formamide synthesis is one of the important areas in organic chemistry as they contribute to be the key intermediate in synthesis of various pharmaceutical compounds like fluoroquinolines (*1*), nitrogen bridged heterocycles (*2*), oxazolidinones (*3*), cancer chemotherapeutic agents (*4*), and other pharmaceutical compounds (*5,6*). Formamides are also useful reagents for Vilsmeier formylation (*7*) and are used as polar solvents in various organic reactions. They are well known to catalyze base catalysis reactions like allylation (*8*) and hydrosilyation of carbonyl compounds (*9*). Additionally, formamides also act as an amino-protecting group during peptide synthesis and as precursors in preparations of *N*-methyl compounds (*10*). Various methods have been developed for formylation of amines in recent years (*11–23*). However, many of these methods suffer from drawbacks such as use of expensive and toxic formylating agents or employing expensive catalyst, formation of side products, use of excessive amount of formylating reagent/substrate ratio, etc.

Das et al. (*18*) reported a useful method for *N*-formylation of anilines at room temperature using formic acid in polyethylene glycol-400 (PEG-400); but the method seems to be limited only to aromatic primary amines and PEG-400 acts as a solvent in the reaction which makes the workup more tedious. Recently, Brahmachari et al. (*24*) reported a simple and efficient procedure for *N*-formylation of primary and secondary amines at room temperature under solvent-free conditions using sodium formate in catalytic amount. However, during our study on formylation reaction, we found that the *N*-formylation of amines using formic acid or ethyl formate proceeded without aid of any catalyst. Hence, in the present paper, we report solventless *N*-formylation of amines without employing catalyst with good to excellent yields of the desired product, thus making the process more economically feasible and environmentally benign (Scheme 1).

Results and discussion

Initially, reaction of aniline with formic acid was chosen as model reaction. During optimization of reaction parameters, we observed that aniline reacted smoothly with formic acid at room temperature providing desired product in good yield (94%) within short period of time (Table 1, entry 1). However, in order to make the protocol more general for formylation of sterically hindered amines, the reaction was optimized with respect to temperature and molar ratio. The temperature was raised up to 60°C and was observed to be quite sufficient to carry out the reaction with optimum yield of desired product (Table 1, entry 2). It was observed that there is no need to use more excess of formic acid, as 1.2:1 molar ratio of formic acid to amine was sufficient to yield the desired product (Table 1, entry 3). However, for ethyl formate:amine, optimized molar ratio was 3:1 (Table 1, entry 5). In previous reports (*18,21*) solvents were used for conducting the reaction. However, during solvent study we observed that the

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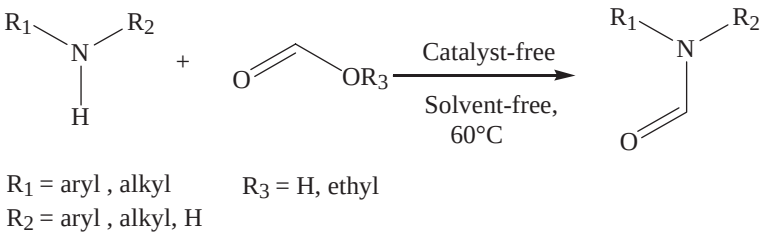

Scheme 1. Formylation of amines.

reaction proceeds near to completion in absence of solvent while it yields trace amount of desired products in presence of solvent without catalyst (Table 1, entry 6).

In order to test the generality and efficiency of the developed protocol, the optimized reaction conditions were then applied for formylation of various aromatic and aliphatic amines using formic acid and ethyl formate as formylating agent (Table 2, entries 1–21). Various substituted anilines were converted to corresponding *N*-formyl amides in good to excellent yields. Aniline having electron donating groups like Me, OMe provided an excellent yield of 96–97% with formic acid whereas 83–89% yield was obtained when ethyl formate was used as a formylating agent (Table 2, entries 2–3). The halogen (F, Cl, Br, I) containing anilines provided good yields ranging from 84% to 93% of corresponding products except for *N*-(2-Chloro-phenyl)-formamide with ethyl formate which endows 42% of considerable yield (Table 2, entry 5b). The electron withdrawing groups like NO_2, $COCH_3$, COOH, and CF_3 were found to react smoothly under the optimized reaction conditions demonstrating good yields of desired products (Table 2, entries 8–11). The reaction also worked well with sterically hindered 2-amino benzophenone as a substrate (Table 2, entry 12). When heterocyclic amines like 2-amino pyridine were employed, the reaction was too sluggish providing moderate yield of product in 24–48 h (Table 2, entry 13). It was observed that the reaction would require considerable time to yield the expected products when ethyl formate was used as a formylating agent.

As reported by Das et al. (*18*), when PEG-400 was used for formylation of amines, benzyl amine provided poor yield whereas aliphatic amines like *n*-hexylamine did not undergo any conversion and hence protocol was limited for aniline derivatives itself. However the present protocol is more advantageous, as it facilitates formylation of both aliphatic and aromatic amines under catalyst- and solvent-free conditions. Benzyl amine was found to react smoothly with formic acid and ethyl formate providing 91–93% yield of *N*-benzyl formamide, respectively (Table 2, entry 14). Straight chain aliphatic amine like *n*-hexylamine was studied for formylation protocol and was found quite effective with 68–94% yield of required product (Table 2, entry 15). Aliphatic and aromatic secondary amines like dibutylamine and di-phenylamine furnish formylated products with good yields (Table 2, entries 16–17). Alicyclic amines like cylcohexylamine, piperidine, morpholine, and piperazine were formylated with 87–98% yield (Table 2, entries 18–21). Interestingly, piperazine was selectively formylated under these optimized conditions. Thus, the protocol proved to be general for formylation of various different aromatic, aliphatic, and heteroaromatic amines providing good to excellent yield of the formylated products reflecting a broad field of application of the present methodology.

The general reaction mechanism involves nucleophilic attack of amines on the electrophilic carbon of formic acid or ethyl formate, which leads to the formation of intermediates, these on further loss of water or ethanol, respectively, furnishes the desired

Table 1. Optimization of reaction parameters for *N*-formylation of amines.

Entry	Reaction conditions	Time	Yield[a] (%)
1	Aniline (1 mmol)/formic acid (3 mmol)/neat/rt	20 min	94
2	Aniline (1 mmol)/formic acid (1.2 mmol)/neat/60°C	5 min	93
3	Aniline (1 mmol)/formic acid (1.2 mmol)/neat/rt	20 min	91
4	Aniline (1 mmol)/ethyl formate (1.2 mmol)/neat/60°C	6 h	51
5	Aniline (1 mmol)/ethyl formate (3 mmol)/neat/60°C	6 h	94
6	Aniline (1 mmol)/ethyl formate (3 mmol)/di-isopropyl ether/60°C	6 h	Traces

[a]Yield based on GC analysis.

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Table 2. *N*-formylation of amines using formic acid/ethyl formate under catalyst- and solvent-free conditions.[a]

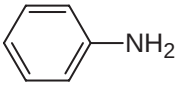
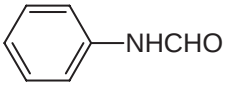
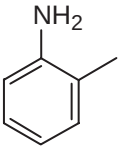
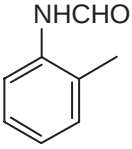
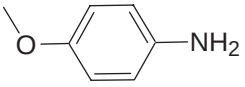
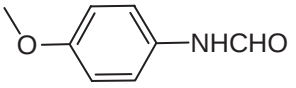
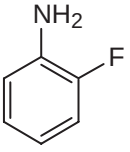
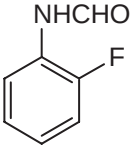
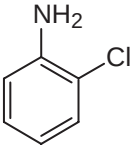
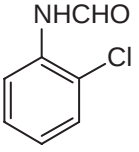
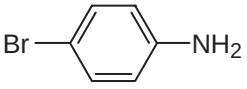
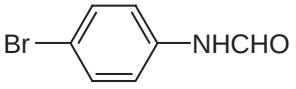
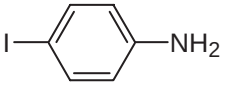
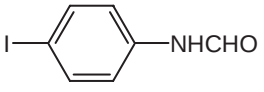
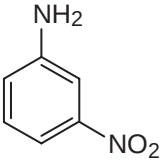
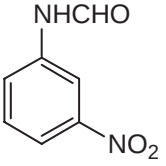
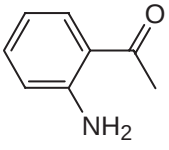
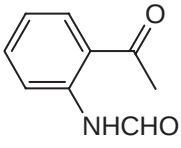
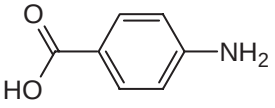
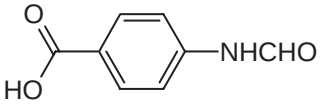
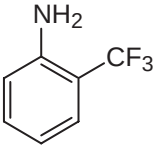
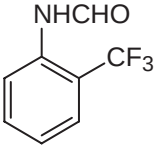
Entry	Amines	Method[b]	Time	Product	Yield[c] (%)	Ref.
1		a b	5 min 6 h		93 89	(*23*)
2		a b	15 min 18 h		97 89	(*26*)
3		a b	20 min 90 min		96 83	(*23*)
4		a b	40 min 6 h		92 84	(*27*)
5		a b	15 min 24 h		92 42	(*23*)
6		a b	1.3 h 18 h		93 91	(*23*)
7		a b	3 h 24 h		91 90	(*28*)
8		a b	20 min 5 h		82 80	(*23*)
9		a b	2.5 h 48 h		78 40	(*18*)
10		a b	30 min 6 h		90 88	(*18,23*)
11		a b	2 h 48 h		76 50	(*23*)

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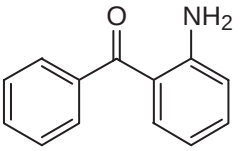
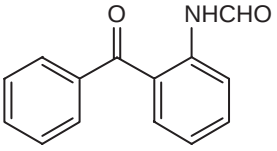
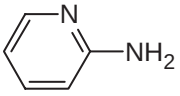
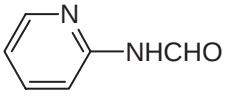
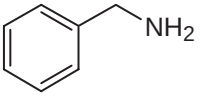
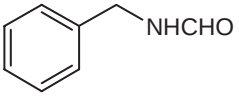
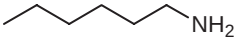
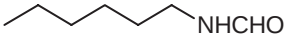
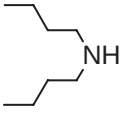
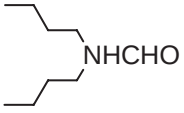
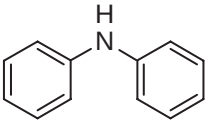
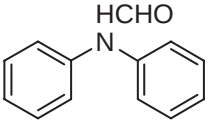
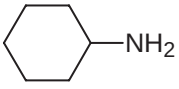
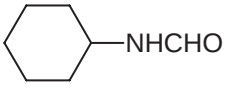
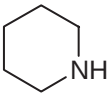
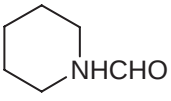
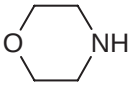
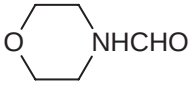
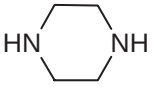
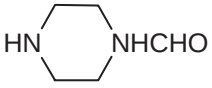
Table 2 (*Continued*)

Entry	Amines	Method[b]	Time	Product	Yield[c] (%)	Ref.
12		a b	1 h 7 h		94 92	(*18*)
13		a b	24 h 48 h		68 55	(*29,30*)
14		a b	15 min 4 h		91 93	(*21,22*)
15		a b	45 min 24 h		68 94	(*21*)
16		a b	12 h 24 h		98 92	(*25*)
17		a b	24 h 48h		88 43	(*23*)
18		a b	30 min 18 h		91 96	(*21*)
19		a b	18 h 24 h		87 94	(*21,22*)
20		a b	3 h 24 h		98 97	(*21,22*)
21		a b	16 h 24 h		90 89	(*25*)

[a]Reaction conditions: aniline (1 mmol), formic acid (1.2 mmol)/ethyl formate (3 mmol), temperature (60°C).
[b]Formylating reagent: formic acid (a), ethyl formate (b).
[c]Yield based on GC analysis.

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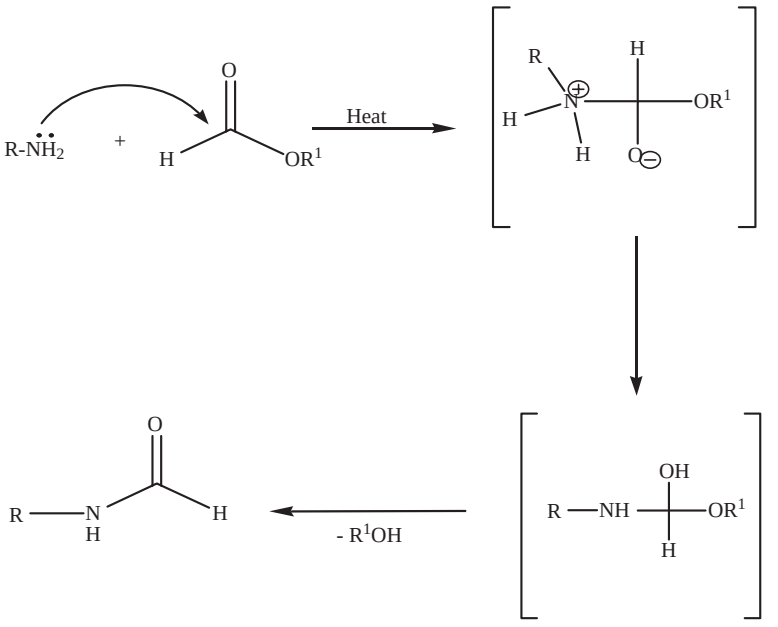

Figure 1. Proposed mechanism for *N*-formylation of amines using formic acid/ethyl formate.

formylated product. Formic acid being acidic and reactive in nature as compared to ethyl formate provides higher yields of formylated products within lower reaction time (see Figure 1).

Experimental

General

All chemicals were purchased from Sigma-Aldrich and S.D. Fine Chemicals Ltd. with their highest purity available. The chemicals were used without any further purification. The products are well characterized by using analytical techniques like GC-MS (Shimadzu QP 2010), MS-MS (Varian Inc, 410 Prostar 500 MS), and FT-IR (Perkin Elmer) analyses.

Experimental procedure

In a typical experimental procedure, aniline (1 mmol) and formic acid (1.2 mmol) or ethyl formate (3 mmol) were carefully added to a sealed glass vial without any additional solvent or catalyst and were magnetically stirred at 60°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted by using DCM or EtOAc. The obtained organic mixture was then washed with water (2×10 ml) and a saturated solution of $NaHCO_3$ and was then dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the residue obtained was then subjected to recrystallization with a suitable solvent or was isolated through column chromatography to obtain pure *N*-formylated products. All the products were well known and were compared with authentic samples and were characterized by GC-MS (Shimadzu QP 2010), MS-MS (Varian Inc, 410 Prostar 500 MS), and FT-IR (Perkin Elmer).

Conclusion

In conclusion, we have developed a very simple and highly efficient methodology for the synthesis of various aliphatic and aromatic formamides under catalyst- and solvent-free conditions. The notable advantages offered by this method are simple operation, good yield of products, and cost effectiveness thus making the process economically feasible.

Acknowledgements

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Spectral data of formamides (Table 2 entries 1–21)

(1) *N-Phenyl-formamide (Table 2, entry 1)*
MS (70 eV, EI): m/z (%): 121 (100) (M^+), 93 (95), 66 (75), 51 (15).

(2) *N-o-Tolyl-formamide (Table 2, entry 2)*
MS (70 eV, EI): m/z (%): 135 (55) (M^+), 118 (15), 106 (100), 77 (30), 51 (15).

(3) *N-(4-Methoxy-phenyl)-formamide (Table 2, entry 3)*
MS (70 eV, EI): m/z (%): 151 (90) (M^+),108 (100), 122 (20), 95 (15), 80 (50), 65 (15), 53 (25).

(4) *N-(2-Fluoro-phenyl)-formamide (Table 2, entry 4)*
MS (70 eV, EI): m/z (%): 139 (75) (M^+), 111 (100), 83 (40), 64 (30), 57 (20).

(5) *N-(2-Chloro-phenyl)-formamide (Table 2, entry 5)*
MS (70 eV, EI): m/z (%): 155 (30) (M^+), 127 (60), 120 (100), 100 (120), 92 (35), 73 (15), 65 (40).

(6) *N-(4-Bromo-phenyl)-formamide (Table 2, entry 6)*
MS (70 eV, EI): m/z (%): 201 (60) (M^+), 199 (65), 173 (55), 171 (55), 92 (80), 65 (100), 50 (15).

(7) *N-(4-Iodo-phenyl)-formamide (Table 2, entry 7)*
MS (70 eV, EI): m/z (%): 247 (100) (M^+),219 (25), 92 (60), 65 (80), 50 (15).

(8) *N-(3-Nitro-phenyl)-formamide (Table 2, entry 8)*
MS (70 eV, EI): m/z (%): 166 (60) (M^+), 138 (20), 108 (15), 92 (60), 80 (20), 65 (100), 52 (15).

(9) *N-(2-Acetyl-phenyl)-formamide (Table 2, entry 9)*
MS (70 eV, EI): m/z (%): 163 (25) (M^+), 148 (15), 135 (65), 120 (100), 92 (50), 65 (40), 43 (35).

(10) *4-Formylamino-benzoic acid (Table 2, entry 10)*
MS (70 eV, EI): m/z (%): 165 (15) (M^+), 106 (100), 79 (25)

(11) *N-(2-Trifluoromethyl-phenyl)-formamide (Table 2, entry 11)* MS (70 eV, EI): m/z (%): 189 (60) (M^+), 161 (30), 141 (75), 114 (100), 63 (15).

(12) *N-(2-Benzoyl-phenyl)-formamide (Table 2, entry 12)* MS–MS (ESI^+) *m/z* calcd for (M^{+1}): 226.24; found (M + 1): 226.10

(13) *N-Pyridin-2-yl-formamide (Table 2, entry 13)*
MS (70 eV, EI): m/z (%): 120 (30) (M^+), 94 (100), 78 (15), 67 (95), 51 (15).

(14) *N-Benzyl-formamide (Table 2, entry 14)*
MS (70 eV, EI): m/z (%): 135 (100) (M^+), 106 (40), 91 (50), 79 (45), 65 (20), 51 (25).

(15) *N-Hexyl-formamide (Table 2, entry 15)*
MS (70 eV, EI): m/z (%): 129 (10) (M^+), 114 (10), 100 (30), 86 (15), 72 (25), 58 (100), 46 (45).

(16) *N,N-Dibutyl-formamide (Table 2, entry 16)*
MS (70 eV, EI): m/z (%): 157 (10) (M^+), 128 (10), 114 (60), 72 (100), 58 (15), 44 (25).

(17) *N,N-Diphenyl-formamide (Table 2, entry 17)*
MS (70 eV, EI): m/z (%): 197 (100) (M^+), 168 (80), 169 (60), 167 (50), 104 (25), 94 (20), 77 (35), 66 (50), 51 (35).

(18) *N-Cyclohexyl-formamide (Table 2, entry 18)*
MS (70 eV, EI): m/z (%): 127 (10) (M^+), 98 (10), 84 (55), 82 (15), 67 (25), 56 (40), 46 (100).

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(19) *Piperidine-1-carbaldehyde (Table 2, entry 19)*
MS (70 eV, EI): m/z (%): 114 (10) (M^+), 113 (100), 112 (30), 98 (35), 84 (50), 70 (20), 56 (70), 42 (55).

(20) *Morpholine-4-carbaldehyde (Table 2, entry 20)*
MS (70 eV, EI): m/z (%): 115 (95) (M^+), 100 (70), 86 (50), 72 (25), 57 (90), 56 (95), 42 (100).

(21) *Piperazine-1-carbaldehyde (Table 2, entry 21)*
MS (70 eV, EI): m/z (%): 114 (10) (M^+), 99 (10), 85 (25), 72 (25), 56 (100), 42 (35).

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