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A very simple and highly efficient procedure for *N*-formylation of primary and secondary amines at room temperature under solvent-free conditions

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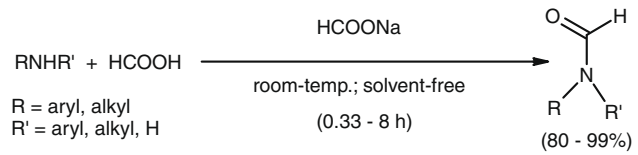
ABSTRACT

N-Formylation of primary and secondary amines has efficiently been carried out at room temperature in excellent yields by using catalytic amount of sodium formate in formic acid under solvent-free conditions. The process is remarkably simple and environmentally benign.

Formamides, an important class of amine derivatives, have widely been used in the synthesis of pharmaceutically valuable compounds such as fluroquinolones,[1] substituted aryl imidazoles,[2] 1,2-dihydroquinolines,[3] nitrogen-bridged heterocycles[4], oxazolidinones[5] and cancer chemotherapeutic agents[6]. They also constitute important precursors in the synthesis of fungicides and herbicides.[2] Furthermore, *N*-formyl compounds are Lewis bases, which are known to catalyze allylation[7] and hydrosilylation[8] of carbonyl compounds. The formyl group in combination with a *tert*-butyl ester group is useful in preparing highly functionalized peptide derivatives.[9] Recently, asymmetric allylation of aldehydes has been achieved with chiral formamides.[10] In addition, formamides are very useful reagents in Vilsmeier formylation reactions[11] as well as in the synthesis of formamidines[12] and isocyanides.[13–15] A number of formylation methods[16–29] have been reported in recent years. However, many of these methods suffer from various drawbacks such as use of expensive and toxic formylating agents and catalysts, use of organic solvents, high temperature, long reaction time and the removal of by-products. Acetic formic anhydride[30–32] still continues to be the most widely used formylating reagent, but it is sensitive to atmospheric moisture and cannot be stored due to decomposition to acetic acid and carbon monoxide.

Very recently, Das et al.[33] 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. Hence, we have been motivated to undertake the challenge to carry out *N*-formylation reaction applicable to all types of amines (aliphatic, alicyclic or aromatic primary and secondary amines) at room temperature under solvent-free conditions. In the present Letter, we wish to report a convenient and highly efficient protocol for *N*-formylation of a variety of structurally diverse primary and secondary amines at room temperature in excellent yields, involving the application of a catalytic amount of sodium formate (a cheap and readily available chemical that has been recycled and reused in this reaction) in formic acid under solvent-free conditions.[34] The process is remarkably simple, highly efficient and environmentally benign (Scheme 1).

Firstly, we carried out *N*-formylation of *p*-bromoaniline as our model reaction in order to optimize the best suited reaction conditions; it was observed (Table 1) that the reactants in the molar ratio of 1 (amine):4 (formic acid):0.2 (sodium formate) afforded the



Scheme 1.

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Table 1
N-Formylation of *p*-bromoaniline using sodium formate in formic acid at room temperature under different conditions in the absence of solvent

Entry	Conditions	Time (h)	Yield[a] (%)
1	Amine (1 mmol)/HCOOH (3 mmol)/HCOONa (0.2 mmol)	2.45	92
2	Amine (1 mmol)/HCOOH (4 mmol)/HCOONa (0.2 mmol)	4.5	99
3	Amine (1 mmol)/HCOOH (5 mmol)/HCOONa (0.2 mmol)	5	95
4	Amine (1 mmol)/HCOOH (6 mmol)/HCOONa (0.2 mmol)	11	92
5	Amine (1 mmol)/HCOOH (4 mmol)/HCOONa (0.1 mmol)	3	75
6	Amine (1 mmol)/HCOOH (excess)/HCOONa (0.2 mmol)	6	60

[a] Isolated yield.

best result with 99% isolated yield at room temperature under solvent-free conditions; sodium formate could also easily be recovered from the resulting reaction mixture and found to be reusable (checked up to fourth run).

A number of structurally diverse amines were then screened for studying the generality as well as the efficacy of this present procedure (Table 2). Most types of primary and secondary amines (aliphatic, aromatic and heterocyclic) find an easy route to their

Table 2
N-Formylation of amines using sodium formate in formic acid at room temperature under solvent-free conditions

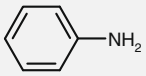
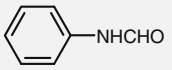
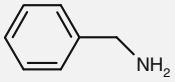
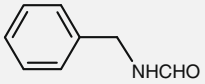
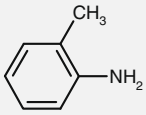
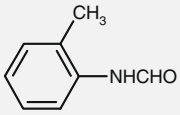
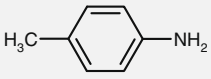
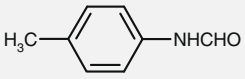
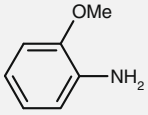
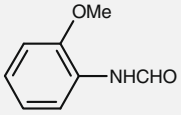
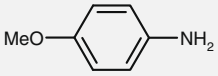
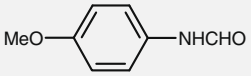
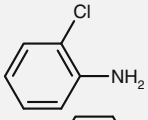
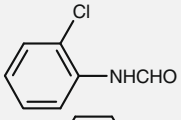
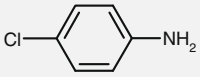
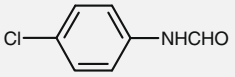
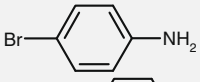
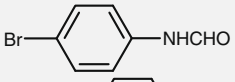
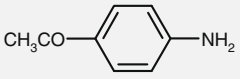
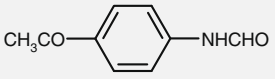
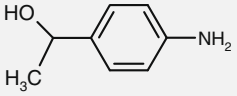
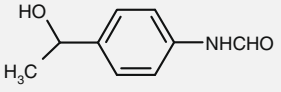
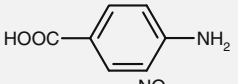
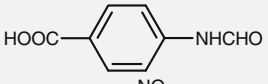
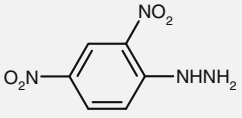
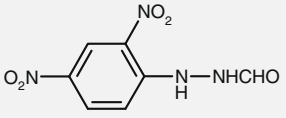
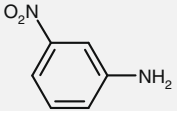
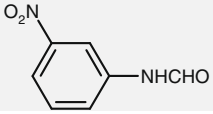
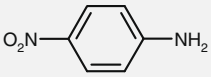
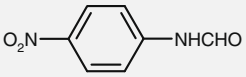
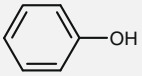
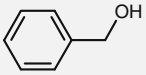
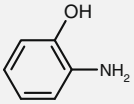
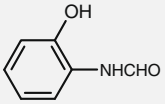
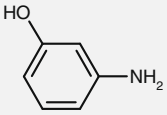
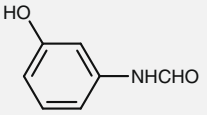
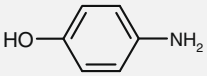
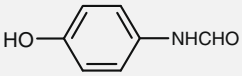
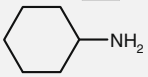
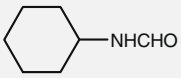
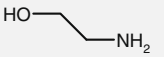
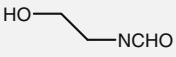
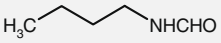
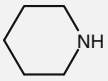
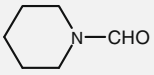
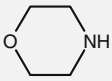
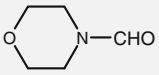
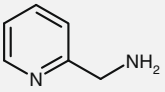
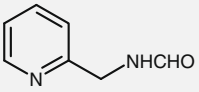
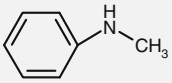
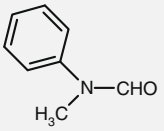
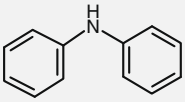
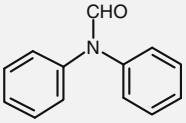
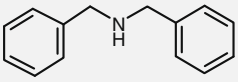
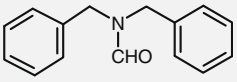
Entry	Amine	Product	Time (h)	Isolated Yield[a] (%)	Ref.[b]
1			1.0	95	29
2			2.5	85	28
3			6.0	88	35
4			7.0	90	35
5			6.0	99	36
6			3.0	99	28
7			3.0	95	29
8			2.0	98	34
9			2.75	99	29
10			1.75	98	29
11			4.5	80	26
12			4.0	95	29
13			0.33	99	37
14			2.5	99	29

Table 2 (*continued*)

Entry	Amine	Product	Time (h)	Isolated Yield[a] (%)	Ref.[b]
15			3.5	92	29
16		No reaction			
17		No reaction			
18			4.5	91	29
19			7.0	93	29
20			5.5	92	29
21			0.5	81	35
22			3.5	83	29
23			2.5	89	29
24			4.0	83	38
25			3.0	86	29
26			4.5	81	29
27			2.0	95	17
28			8.0	80	29
29			2.5	83	28

[a] Yields are of pure isolated products characterized by their physical constants, spectral (FT-IR, ^{1}H NMR and MS) and analytical data.
[b] The compound reported in the literature.

N-formyl derivatives in the presence of sodium formate in formic acid at room temperature under solvent-free conditions. The open chain aliphatic amines reacted smoothly under such reaction conditions; even benzylamine that was previously reported to provide low yield[33] (42%) furnished good yield (85%) following this reaction protocol. Anilines bearing both electron-donating and electron-withdrawing functionalities were also found to undergo the conversion in a facile manner with excellent yields. Previously, the *N*-formylation of anilines having electron-withdrawing groups was found to be difficult.[17] The present conversion is also found to be chemoselective—the presence of alcoholic or phenolic –OH group is well tolerated (Table 2). *O*-Formylation was not found to take place; thus the aminophenol (entries 18–20) and the aminoalcohols (entries 11 & 22) afforded the *N*-formyl products exclusively under the present reaction conditions. The workup of the reaction mixtures is simple and highly convenient, and the products are in many cases obtained in high purity. Furthermore, sodium formate used as a catalyst in the formylation reaction can also be recovered and reused.

In conclusion, we have developed a very simple and highly efficient solvent-free protocol for *N*-formylation of amines at room temperature using nontoxic and inexpensive sodium formate in formic acid. The advantages of this environmentally benign and safe protocol include a simple reaction setup only at room temperature, not requiring specialized equipment, high product yields, the possibility for reusing the catalyst, chemoselectivity and solvent-free conditions.

References and notes

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34. *General procedure*: To a mixture of amine (1 mmol) and formic acid (4 mmol), catalytic amount of sodium formate (0.2 mmol) was added. The mixture was stirred with a bar magnet at room temperature, and the progress of the reaction was monitored by TLC. After the reaction was complete, CH_2Cl_2 or EtOAc was added to the reaction mixture, and HCOONa was removed by filtration. The organic solvent was then washed with H_2O (2×10 mL) and a saturated solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography and/or subjected to repeated crystallizations from suitable solvent to obtain pure *N*-formyl amine. The structure of the products was confirmed by spectral (FT-IR, ^1H NMR and MS) and analytical data, as well as comparison with authentic samples obtained commercially or prepared by reported methods.
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