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Formylation without catalyst and solvent at 80 °C

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ABSTRACT

A simple and efficient protocol for N-formylation of aliphatic and heterocyclic amines has been described with formic acid in the absence of catalyst and solvent.

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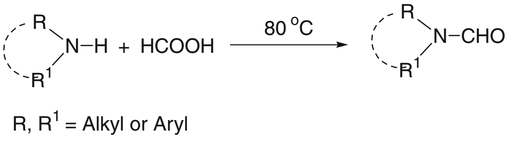
The formyl group is an extremely important amino-protecting group in peptide synthesis[1] and formamides are regarded as useful intermediates in organic synthesis and medicinal chemistry.[2] In addition, formamides are well-known reagents having a wide range of applications in organic synthesis such as allylation,[3] hydrosilylation,[4] Vilsmeier reaction[5], and for the synthesis of formamidines.[6] In the literature, various approaches are available for N-formylation using different reagents such as chloral,[7] formic acid-DCC,[8] formic acid-EDCL,[9] formic acid in toluene,[10] ammonium formate,[11] CDMT,[12] KF-alumina, and other solid-supported reagents.[13] However all these methods have some drawbacks in the light of current working practice such as application of toxic reagents, or reagents which are very expensive and less accessible, thermally unstable, or formation of side products or applicable only for aromatic amines. Very recently the formylation using $ZnCl_2$, $FeCl_3$, $AlCl_3$, and $NiCl_2$ has been reported.[14] They observed no reaction when a mixture of formic acid and aniline was heated at 100 °C for 4 h in the absence of Lewis acid. The esters of formic acid like phenyl formate and pentafluoro phenyl formate are useful reagents for direct N-formylation without requiring any catalyst.[15] No methodology has been reported so far where only formic acid is used as the sole formylating agent without any catalyst and solvent.

For general interest in the light of protection of amines, there is a need for invention of a protocol to provide greener methodology for N-formylation. As a part of our on going research to develop solvent-free reaction conditions[16] herein, we report a facile methodology for direct N-formylation under mild conditions without any catalyst and solvent (Scheme 1).

We observed that when a mixture of aniline and formic acid was heated at 80 °C in neat conditions, the N-formylated product was obtained within 25 min. The reaction was carried out at different temperatures from 60 °C to 100 °C but at temperature less than 80 °C the yields were very poor (40–50%). When the reaction was carried out at 100 °C and higher temperature a mixture of products was isolated which was very difficult to separate and characterize.

In a typical experimental procedure, a mixture of amine (1 mmol) and formic acid (1.5 mmol) was heated at 80 °C for a certain period of time as required for completion (TLC). A wide range of structurally diverse amines were subjected under this procedure to get the corresponding N-formylated products. In our experimental procedure[17], no isolable side product has been observed. All the aromatic, alicyclic, and aliphatic amines reacted well to give the N-formylated product in good to excellent yield. Several sensitive functionalities such as –OH and halogen (Cl, Br, F) were unaffected under the present reaction conditions. Electron-donating groups in aryl amines were found to be more effective in the present procedure and completed within 25 min (entry 2). The isolated yields were less for aliphatic amines (entries 13 and 14) when compared



Scheme 1.

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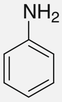
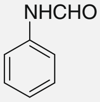
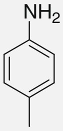
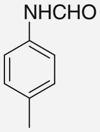
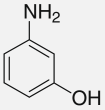
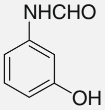
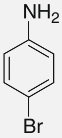
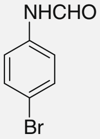
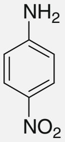
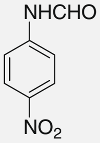
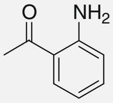
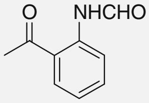
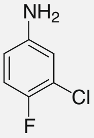
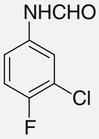
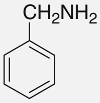
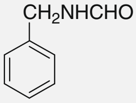
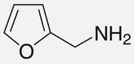
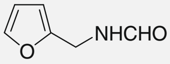
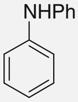
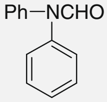
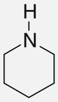
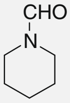
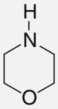
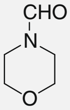
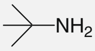
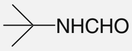
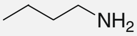
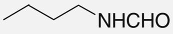
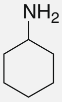
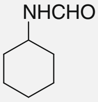
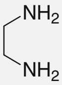
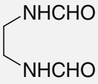
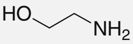
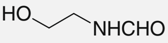
Table 1
Formylation of amines with formic acid at 80 °C

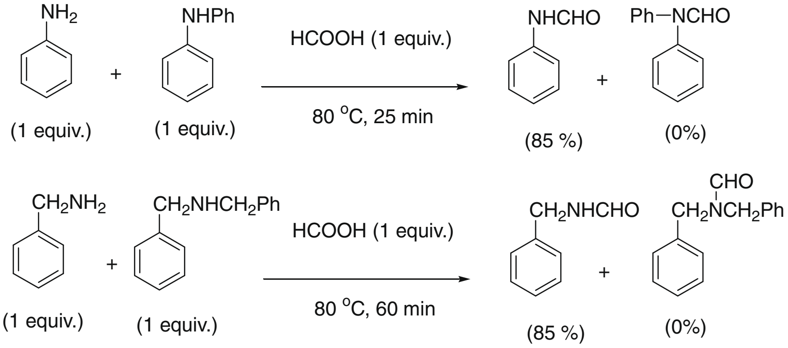
Entry	Substrate	Product	Time (min)	Yield[a] (%)	Ref.[b]
1			25	90	13c
2			25	90	13c
3			40	85	13c
4			80	75	13c
5			480	85	13c
6			80	80	13c
7			80	90	14
8			60	90	13c
9			90	80	–
10			85	60	13c
11			80	180	14
12			60	300	14

(continued on next page)

Table 1 (*continued*)

Entry	Substrate	Product	Time (min)	Yield[a] (%)	Ref.[b]
13			60	60	14
14			60	60	14
15			60	85	7
16			60[c]	85	7
17			60	80	7

[a] Isolated yield.
[b] Reported in the literature.
[c] 2-equiv w.r.t. amine.



Scheme 2.

to those for aromatic amines. The procedure is equally effective for secondary amine (entries 10, 11, and 12). Only piperidine, morpholine, and 4-nitroaniline took little higher 3, 5, and 8 h, respectively. The results are summarized in Table 1.

The difference in the reactivity of amines shows chemoselectivity of this method, as shown in Scheme 2. Thus when a mixture of primary amine and secondary amine was exposed to formic acid (1 equiv), it produced the product based on primary amine selectively.

No organic or aqueous solvents were used except for the extraction of crude product and purification.

In conclusion, we have developed a remarkably simple and highly efficient methodology for the N-formylation of amine with moderate to good yields. Operational simplicity, solvent and catalyst-free media, mild reaction conditions, environmentally friendly reaction conditions, the compatibility with various functional groups are the advantages of the present procedure. To the best of our knowledge, this is the first report of N-formylation with formic acid without any catalyst and solvent. We believe that this will present a better and more practical alternative to the existing methodologies for the N-formylation of amines.

Acknowledgments

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17. *General procedure for N-formylation of an amine*:

A mixture of diphenylamine (338 mg, 2 mmol) and formic acid (85%) (138 mg, 3 mmol) was heated at 80 °C for a certain period of time in a closed tube in an oil bath. The progress of the reaction was monitored by TLC. After completion the mixture was cooled at room temperature and 10 ml ethyl acetate was added to it. The resulting solution was washed with bicarbonate (2 × 5 ml) followed by brine (2 × 5 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to get the crude N-formylated product which was subjected to column chromatography to obtain the pure product (335 mg, 85%, white solid; mp 78–80 °C). This showed spectral and analytical data as follows (*N,N-Diphenyl-formamide, entry 10*) ^{1}H NMR (CDCl$_3$, 300 MHz): δ ppm 7.30 (br s, 10H), 8.64 (s, 1H, CHO). IR (KBr, cm^{-1}): 3049, 2896, 1672, 1581, 1490, 1404, 1321, 1259, 1122. ^{13}C NMR (CDCl$_3$, 75 MHz): δ ppm 161.8, 1441.9, 139.7, 129.8 (2C), 129.3 (2C), 127.1, 126.9, 126.2 (2C), 125.2 (2C). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.98; H, 5.61; N, 11.33. The spectral (^{1}H NMR, IR) and analytical data of another new compound is given below for ready reference.

N-Furan-2ylmethyl-formamide (entry 9):

Light yellow viscous oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ ppm 4.28 (s, 1H. one H of –CH$_2$–), 4.45 (s, 1H, one H of –CH$_2$–), 6.25 (m, 3H, furan moiety), 7.31 (m, 1H, NH), 8.12 (s, 1H, CHO). IR (KBr, cm^{-1}): 3288, 2347, 1670, 1527, 1380, 1226, 1008, 919. ^{13}C NMR (CDCl$_3$, 75 MHz): δ ppm 161.1, 150.7, 142.4, 110.5, 107.7, 35.1. Anal. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.39; H, 5.73; N, 11.21.