SECTION II

N-FORMYLATION OF AMINES WITHOUT CATALYST & SOLVENT
I.2.1 INTRODUCTION

The amide linkage is one of the most important functional groups in contemporary chemistry. It is essential to sustain life, making up the peptide bonds in proteins and enzymes. It is found in numerous natural products and also one of the most prolific moieties in modern pharmaceutical molecules. Formamides, an important class of amine derivatives, have widely been used in the synthesis of pharmaceutically valuable compounds such as fluroquinolones, substituted aryl imidazoles, 1,2-dihydroquinolines, nitrogen-bridged heterocycles oxazolidinones and cancer chemotherapeutic agents. They also constitute important precursors in the synthesis of fungicides and herbicides. Furthermore, N-formyl compounds are Lewis bases, which are known to catalyze allylation and hydrosilylation of carbonyl compounds. The formyl group in combination with a tert-butyl ester group is useful in preparing highly functionalized peptide derivatives. The general scheme for N-Formylation is given below (Scheme 1).

Different methods are available in literature for synthesis of N-Formylated product. Before going to our work a short review has been discussed here before our work.
I.2.2 N- FORMYLATION OF AMINES: A BRIEF REVIEW

Currently, the most popular industrial methods of amide synthesis rely on activation of a carboxylic acid and subsequent coupling of the activated species with an amine. Although huge development has been made to fine-tuning these coupling reagents for more efficient amide synthesis. However, the formylation procedure, which seems to be practically unknown, was discovered by Hofmann\textsuperscript{11} in 1872. He found that ethylenediamine reacted energetically with chloral to produce chloroform and another liquid product which he assumed was N,N'-diformylethylenediamine since, by hydrolysis, it was converted into ethylenediamine and formic acid. He stated that treatment of ethylamine with chloral converted it into ethylformamide, and he also mentioned that formamide can be obtained by this process but that in this instance the process is not an advantageous one.

F. F. Blike and Chi-Jung Lu\textsuperscript{12} found that formylation with the aid of chloral is an excellent general procedure for the formylation of a strong organic base. A rapid reaction takes place at a low temperature, chloroform is the only by-product and the formyl derivative usually obtained in good yield.

Later on, Stevan W. Djuric\textsuperscript{13} reported a new method for the N-formylation of secondary amines using organosilicon chemistry (Scheme 2).

\[
\begin{align*}
R_2\text{NH} &\xrightarrow{t-\text{BuMe}_2\text{SiCl}} \text{DMF,Et}_3\text{N}, 4\text{-DMAP,} \\
&\quad \text{40}^{\circ}\text{C}, 10\text{h} \\
R_2\text{NCHO} &\quad \text{R = Aryl}
\end{align*}
\]

\textbf{Scheme 2}

The formylation reaction could be considered to proceed through one of these two mechanisms (a) via a silylamine, or (b) via a "Vilsmeier" type intermediate (Fig 1).
via Silylamine

\[ \text{R}_2\text{NH} \rightarrow \text{R}_2\text{NSi-t-BuMe}_2 \xrightarrow{\text{DMF}} \text{R}_2\text{NCHO} \]

"Vilsmeier" type intermediate

\[ \text{R}_2\text{NH} \xrightarrow{\Delta} \text{R}_2\text{N} = \xrightarrow{\text{H}_2\text{O}} \text{R}_2\text{NCHO} \]

\[ \text{via} \]

\[ \begin{array}{c}
\text{Me}_2\text{N} \\
\text{OSi-t-BuMe}_2 \\
\text{R}_2\text{N}
\end{array} \]

Fig 1

Berry et al\textsuperscript{14} reported an improved methodology for the N-formylation of secondary amines using chlorotrimethylsilane and imidazole in N,N-dimethyl formamide (Scheme 3). Few examples are described in Table 1.

\[ \text{R}^1\text{NH} \xrightarrow{\text{Me}_3\text{SiCl (3eq). Imidazole (3eqv). Me}_2\text{NCHO (6eqv.). rt}} \text{R}^1\text{N=CHO} \]

\[ \text{R}^1, \text{R}^2 = \text{Aryl} \]

Scheme 3
Table 1: N-formylation of amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time(h)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure" /></td>
<td>12</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure" /></td>
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<td>3</td>
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<td>72</td>
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<tr>
<td>4</td>
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<td>18</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure" /></td>
<td>48</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure" /></td>
<td>48</td>
<td>94</td>
</tr>
</tbody>
</table>

* Isolated yield.

In 2000, S. Baskaran et al\textsuperscript{15} introduced a new methodology for the \(N\)-formylation of secondary amines and anilines using ammonium formate as a formylating agent. They showed that ammonium formate as relatively less expensive and efficient \(N\)-formylating agent for Secondary amines and anilines (Scheme 4).

Later on S. Baskaran and his group\textsuperscript{16} reported a direct and mild route to formanilides from aromatic nitro compounds bearing different functional groups under Catalytic transfer hydrogenation (CTH) conditions by using ammonium formate/Pd-C system. They made the interesting observation that ammonium formate in an aprotic solvent like acetonitrile can function as a formylating agent apart from being a source of hydrogen (Scheme 5).
A highly facile and chemoselective method for the reductive \textit{N}-formylation of aryl azides under catalytic transfer hydrogenation conditions by using this same ammonium formate/Pd-C system has been reported by S. Baskaran \textit{et al} \textsuperscript{17} (Scheme 6).

Joong-Kwon Choi and his group \textsuperscript{18} reported a practical and convenient procedure for the \textit{N}-formylation of amines using formic acid. They have developed a practical and convenient procedure for \textit{N}-formylation using aqueous 85\% formic acid using toluene as solvent (Scheme 7). Different amines were subjected to afford the formylated product in good to excellent yield as shown in the Table 2.
Table 2: Formylation of different amines using formic acid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Time(h)</th>
<th>Yield(%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{NH}_2 )</td>
<td>( \text{NHCHO} )</td>
<td>9</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>( \text{N} )</td>
<td>( \text{CHO} )</td>
<td>6</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>( \text{O}_2\text{N} ) ( \text{NH}_2 )</td>
<td>No reaction</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>( \text{N} ) ( \text{H} ) ( \text{N} ) ( \text{H} ) ( \text{N} )</td>
<td>( \text{N} ) ( \text{CHO} )</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>( \text{N} )</td>
<td>( \text{CHO} )</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>( \text{N} ) ( \text{OH} )</td>
<td>( \text{CHO} )</td>
<td>4</td>
<td>96</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield.

M. Mihara et al\textsuperscript{19} demonstrated that KF–Al\(_2\)O\(_3\) is a useful solid-supported reagent for generation of dichlorocarbene from chloroform in the N-formylation reaction of secondary amines. The application of KF–Al\(_2\)O\(_3\) for N-formylation of several secondary amines provides a new method for the synthesis of formamide derivatives, which features selectivity, mild reaction conditions and simple procedures (Scheme 8).

\[
\text{PhNHMe} + \text{CHCl}_3 \xrightarrow{\text{KF-Al}_2\text{O}_3} \text{CH}_3\text{CN, rt} \quad \text{PhNCHO}
\]

Scheme 8

S. Kotha and his group\textsuperscript{20} reported an environmentally benign process for the synthesis of N-formyl amino acid esters using ammonium formate as an efficient formylating agent (Scheme 9).
L. De Luca et al.\textsuperscript{21} introduced a simple and mild method for the N-formylation of amines and \(\alpha\)-amino esters under the reaction with 2-chloro-4,6-dimethoxy[1,3,5]triazine and formic acid. The reaction can be accelerated under microwave irradiation and undergoes without racemization in the case of optically active \(\alpha\)-amino esters (Scheme 10).

**Scheme 10**

The comparison has been described in Table 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Method</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pyrrolidine</td>
<td>A</td>
<td>35(^\circ)C, 4h</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>MW, 3 min</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Heptylamine</td>
<td>A</td>
<td>35(^\circ)C, 8h</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>MW, 3 min</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexylamine</td>
<td>A</td>
<td>35(^\circ)C, 13h</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>MW, 6 min</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Benzylamine</td>
<td>A</td>
<td>35(^\circ)C, 5h</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>MW, 6 min</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>4-Methoxyaniline</td>
<td>B</td>
<td>MW, 6 min</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>(S)-Alanine methyl ester</td>
<td>A</td>
<td>35(^\circ)C, 10h</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>MW, 6 min</td>
<td>99</td>
</tr>
</tbody>
</table>
B. Desai and his co-worker\textsuperscript{22} demonstrated that formate or formic acid immobilised on a solid support (polymer matrix or inorganic solid) can function as a formylating agent to produce formamides starting from primary and secondary amines (\textbf{Scheme 11}).

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_11}
\end{center}

N. Iranpoor \textit{et al} \textsuperscript{23} introduced Silphos $[\text{PCl}_{3-n} (\text{SiO}_2)_n]$ a heterogeneous phosphine reagent for formylation and acetylation of alcohols and amines with ethyl formate and acetate. This procedure provides a method to separate the product by a simple filtration (\textbf{Scheme 12}).

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_12}
\end{center}

A. K. Bose \textit{et al}\textsuperscript{24} reported a Microwave-induced organic reaction enhancement (MORE) technique (open vessel; controlled microwave energy to stay below the boiling point of the reaction mixture) for the N-formylation of aliphatic and aromatic amines and amino heterocycles with aq formic acid (80\%) on a multiple gram scale in a few minutes (\textbf{Scheme 13}).

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_13}
\end{center}
Hosseini-Sarvari and Sharghi\textsuperscript{25} published their highly efficient reaction using ZnO as a catalyst under solvent-free conditions at 70°C, achieving some excellent yields in short reaction times (Scheme 14). They also demonstrated the reusability of the ZnO catalyst, incurring only a small decrease in yield of amide after the third use.

\begin{center}
\begin{align*}
\text{HN} & + \text{HCO}_2\text{H} \xrightarrow{\text{ZnO}} \text{N} \rightarrow \text{CO} \\
\text{R} & = \text{alkyl, aryl} \\
\text{R}' & = \text{alkyl, aryl, H}
\end{align*}
\end{center}

Scheme 14

B. Das \textit{et al}\textsuperscript{26} reported the N-Formylation of anilines at room temperature by treatment with formic acid in polyethylene glycol (PEG-400). No additional solvent and catalyst were required (Scheme 15).

\begin{center}
\begin{align*}
\text{Ar} & \rightarrow \text{NH}_2 \xrightarrow{\text{HCOOH}} \text{Ar} \rightarrow \text{NHCHO} \\
\text{PEG 400, rt, 4-6 h} & \quad 79-93\%
\end{align*}
\end{center}

Scheme 15

K. Niknam and D. Saberi\textsuperscript{27} employed silica-bonded N-propyl sulfamic acid (SBNPSA) as a new catalyst for the formylation of alcohols and amines with ethyl formate under mild and heterogeneous conditions at room temperature with good to excellent yields (Scheme 16).

\begin{center}
\begin{align*}
\text{RX} & + \text{H} \rightarrow \text{O} \xrightarrow{\text{SBNPSA}} \text{R} \rightarrow \text{O} \\
\text{X} & = \text{O, NH} \\
\text{R} & = \text{primary, secondary, tertiary alkyl}
\end{align*}
\end{center}

Scheme 16

Use of ionic liquid as a catalyst for N-formylation of amines has been described by Akbari and his co-worker\textsuperscript{28} reported the use of guanidine derived. The recovered ionic liquid can be recycled for four runs without loss of activity (Scheme 17). A selected example of formylation using this procedure has been illustrated in Table 4.
Part I

Section II

![Scheme 17]

**Scheme 17**

**Table 4: N-formylation of amines.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time(min)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₂</td>
<td>NHCHO</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>NH₂</td>
<td>NHCHO</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>MeO NH₂</td>
<td>MeO NHCHO</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>NH₂</td>
<td>NHCHO</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>NH₂</td>
<td>NHCHO</td>
<td>8</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>NH</td>
<td>N-CHO</td>
<td>5</td>
<td>94</td>
</tr>
</tbody>
</table>

P. S. Rao and his co-worker reported a range of Lewis acid catalysts like dichloride complexes of zinc, tin, lanthanum, iron, aluminium and nickel for N-formylation reaction. Best results were obtained using ZnCl₂ as a catalyst under the solvent-free condition at 70°C (**Scheme 18**).

![Scheme 18](image)

**Scheme 18**

Very recently G. Brahmachari et al. reported a solvent-free protocol for N-formylation of amines at room temperature using nontoxic and inexpensive sodium formate in formic acid (**Scheme 19**).

![Scheme 19](image)

**Scheme 19**
After publishing our work, Kim and Jang\textsuperscript{31} have reported the use of indium metal as a catalyst for the N-formylation of amines with formic acid, under solvent-free conditions at 70\degree C. They found the reaction to be efficiently catalysed by 10 mol\% of the indium metal, which they presume reacts with the formic acid to form In(O\textsubscript{2}CH\textsubscript{3})\textsubscript{3} and acts as a Lewis acid in the reaction (Scheme 20).

\[
\text{R} \text{NH}_\text{2} + \text{HCOOH} \xrightarrow{\text{In (10mol \%) \atop 70\degree C}} \text{R} \text{NHCHO}
\]

**Scheme 20**

Later on B. Kaboudin and M. Khodamorady\textsuperscript{32} have developed a process for the N-formylation of amines in water. The process involves the treatment of amines with triethyl orthoformate in water under reflux conditions without any additives (Scheme 21). A brief result has been displayed in Table 5.

\[
\text{R} \text{NH}_\text{2} + \text{HC(OEt)}_3 \xrightarrow{\text{H}_\text{2}O \atop \text{A= Reflux \atop \text{B= MW}}} \text{R} \text{NCHO}
\]

**Scheme 21**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textperiodcentered Substrate</th>
<th>Method</th>
<th>Time(h)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>A</td>
<td>24</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>2</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>2-EtC\textsubscript{6}H\textsubscript{4}</td>
<td>A</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>3-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>B</td>
<td>3</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>3-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>A</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>B</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>A</td>
<td>24</td>
<td>51</td>
</tr>
</tbody>
</table>

**Table 5:** Formylation in water.

Very recently, H. Sakurai and his co-worker\textsuperscript{33} have observed a new methodology for the N-formylation of amines catalyzed by Nano-gold under aerobic oxidation conditions with MeOH or Formalin (Scheme 22).
Molecular iodine acts as a catalyst under solvent-free conditions for N-formylation of amines as reported by D. O. Jang et al.\textsuperscript{34} The reaction was applicable for chemoselective N-formylation of amino groups and \( \alpha \)-amino acid esters without epimerization (Scheme 23).

\[
\text{Ph—NH}_2 \overset{I_2}{\rightarrow} \text{Ph—NHCHO}
\]

\textbf{Scheme 23}

Very recently, B. Krishnakumar and M. Swaminathan\textsuperscript{35} have developed a strategy for N-formylation of an amine with formic acid using TiO\(_2\)-P25 or TiO\(_2\)-SO\(_4^{2-}\). The Sulfated titania is more efficient and reusable than TiO\(_2\)-P25 for this reaction at room temperature (Scheme 24).

\textbf{Scheme 24}

T. Cochet \textit{et al}\textsuperscript{36} have introduced a convenient and chemoselective formylation of amines using \( N \)-formylsaccharin as formylating agent (Scheme 25).

\[
\text{R}_1^1 \text{R}_2^2 \overset{1. \text{THF, rt, 15 min}}{\rightarrow} \text{R}_1^1 \text{R}_2^2 \overset{2. \text{NaHCO}_3 \text{(aq)}}{\rightarrow} \text{R}_1^1 \text{R}_2^2 \text{CHO}
\]

\textbf{Scheme 25}
Lokesh A. Shastri and his co-worker\textsuperscript{37} have reported a rapid and easy route for the N-formylation of secondary amines using chloroform and sodium ethoxide via dichlorocarbene by the Riemer–Tiemann reaction with excellent yield (Scheme 26).

\[
\begin{align*}
R'\text{NH} & \xrightarrow{\text{NaOEt (21\%)} \atop \text{CHCl}_3, 50^\circ\text{C, 1h}}} R'\text{NCHO} \\
R' &= \text{CH}_3, \text{C}_2\text{H}_5, \text{isopropyl}
\end{align*}
\]

Scheme 26

A variety of structurally diverse amines were subjected for formylation which are summarized in Table 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H\textsubscript{3}C\text{NH}H\textsubscript{3}C</td>
<td>H\textsubscript{3}C\text{NCHO}H\textsubscript{3}C</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>H\textsubscript{3}CH\text{2C}\text{NH}H\textsubscript{3}CH\text{2C}</td>
<td>H\textsubscript{3}CH\text{2C}\text{NCHO}H\textsubscript{3}CH\text{2C}</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>92</td>
</tr>
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<td>65</td>
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<tr>
<td>5</td>
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<td></td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>95</td>
</tr>
</tbody>
</table>

Very recently in 2011, Robert H. E. Hudson \textit{et al.}\textsuperscript{38} have developed a simple protocol for the N-formylation of amino acid esters and primary amines by utilizing imidazole at 60\textdegree C using DMF as solvent (Scheme 27).
I.2.3 CONCLUSION

From this short review it is obvious that the N-Formylation of amine is an important topic of research in modern organic synthesis and many groups from the different part of the glove have given their best effort to improve the formylation reaction. All the reported methods employed the conventional procedure using different catalytic systems and solvent. For general concern and in the light of protection of amines, there is require for invention of a protocol to provide more greener methodology for N-formylation without using any catalyst and solvent. The next few paragraphs will describe our methodology to rich this goal.
I.2.4 OUR PROCEDURE

As described in the last section (Part I, Section I) our ongoing research to develop a greener methodology. Herein, we report a facile methodology for direct N-formylation under mild conditions without any catalyst and solvent (Scheme 28).

\[
\begin{array}{c}
\text{R-N-H} + \text{HCOOH} \xrightarrow{80^\circ C} \text{R-N-CHO} \\
\text{R, R}^1 = \text{Alkyl or Aryl}
\end{array}
\]

Scheme 28

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 temperature 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 were isolated which were very difficult to separate and characterize.

Our protocol is very simple and 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). The reaction is very clean and a series of N-formylated products has been isolated from the corresponding amines. All the structurally diverse amines like the aromatic, alicyclic and aliphatic underwent formylation to give the N-formylated product in good to excellent yield in equal mode under this procedure. No isolable side product has been observed in our experimental procedure. No organic or aqueous solvents were used except for the extraction of crude product and purification. Several sensitive functionalities such as –OH (Table 7, entry 3), halogen (Cl, Br, F) (Table 7, entry 4, 7) 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, 14) when compared to aromatic amines. The procedure is equally effective for secondary amine (entries 10, 11, 12).
Only piperidine, morpholine and 4-nitroaniline, took little higher 3, 5 and 8 hours respectively. The results are summarized in (Table 7).

**Table 7:** N-Formylation of amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ref.&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="NH2.png" alt="Structure" /></td>
<td><img src="NHCHO.png" alt="Structure" /></td>
<td>25</td>
<td>90</td>
<td>13c</td>
</tr>
<tr>
<td>2</td>
<td><img src="NH2.png" alt="Structure" /></td>
<td><img src="NHCHO.png" alt="Structure" /></td>
<td>25</td>
<td>90</td>
<td>13c</td>
</tr>
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<td>13c</td>
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<sup>a</sup>: isolated yield, <sup>b</sup>: reported in literature
Table 7 Contd........

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<th>Entry</th>
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<th>Ref. &lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
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<td>80</td>
<td>7</td>
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</tbody>
</table>

<sup>a</sup>: isolated yield, <sup>b</sup>: reported in literature, <sup>c</sup>: 2-equivalent w.r.t. amine
When an external mixture of primary and secondary amines was subjected to formylation, the difference in the reactivity shows chemoselectivity of this method (Scheme 29). Thus, when a mixture of aniline and diphenyl amine was exposed to formic acid (1 equiv.) the N-formylated product of aniline was isolated as the sole product. The chemoselectivity has also been experimented using a mixture of benzyl amine and dibenzyl amine. We are pleased to report that no formylated product has been found in case of dibenzyl amines.

\[
\text{Scheme 29}
\]

I.2.5 CONCLUSION

From the above results and discussion it is obvious that we can conclude that our developed methodology is a remarkably simple and highly efficient. Operational simplicity, solvent and catalyst-free media, mild reaction conditions, environmentally friendly reaction conditions, the compatibility with various functional groups are the main advantages of the procedure. It should be mentioned that to the best of our knowledge, our observation 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.
I.2.6 EXPERIMENTAL

**General:** $^1$H and $^{13}$C NMR spectra were recorded in DMSO and CDCl$_3$ solution at ambient temperature on a spectrometer operating at 300, 400, 500 MHz for $^1$H and 75, 100, 125 MHz for $^{13}$C. Chemical shift were recorded as $\delta$ values in parts per million (ppm), and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants $J$ were given in Hz. IR spectra were recorded on a FT-IR spectrometer. IR spectra of solid products were recorded in KBr and thin plates for liquid products. TLC was done on silica gel coated glass slide (Merck, Silica gel G for TLC). Silica gel (60-120 mesh, SRL, India) and Petroleum ether (bp. 60-80 °C) was used for column chromatography. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Merck, SRL, Spectrochem and Process Chemicals. All the amines were distilled before use.

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

A mixture of amine (2 mmol) and formic acid (85%) (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 (2×5ml) followed by brine (2×5ml) 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.
Spectral data, mp and analytical data of N-formylated products presented in order of their entries in Table 8

N-Phenylformamide (entry 1)26:

White solid; mp. 47-49 °C;
IR (KBr): 819, 1204, 1338,1514, cm−1;
$^1$H NMR (500 MHz, CDCl$_3$): δ 7.10-7.19 (m, 5H), 8.30 (s, 1H), 9.17 (bs, 1H);
$^{13}$C NMR (125 MHz, CDCl$_3$): δ 118.83 (2C), 124.7 (2C), 137.12, 159.94, 163.24.

N-p-Tolylformamide (entry 2)26:

White solid; mp. 51-53 °C;
IR (KBr): 1214, 1358, 1534 cm−1;
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.29 (s, 3H), 6.90-7.46 (m, 4H), 8.30 (s, 1H), 9.19 (bs, 1H);
$^{13}$C NMR (125 MHz, CDCl$_3$): δ 21.2, 119.5 (2C), 130.6 (2C), 135.5, 159.8, 163.6.

N-(3-hydroxyphenyl)formamide (entry 3)26:

White solid; mp.127 °C;
IR (KBr): 1254, 1378, 1523, 3260, cm−1;
% Part I

---

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 6.01-7.16 (m, 4H), 8.19 (s, 1H), 8.68 (d, $J = 11$Hz, 1H), 9.49 (s, 1H), 9.97 (s, 1H), 10.02 (bs, 1H);
$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 104.6, 108.3, 110.9, 129.6, 138.7, 159.8, 162.7;

N-(4-Bromophenyl)formamide (entry 4)$^{26}$:

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {NHCHO} ..
  \node at (0.5,0) {Br} ..
\end{tikzpicture}
\end{center}

White solid; mp. 117-121\textdegree C;
IR (KBr): 1220, 1367.1563 cm$^{-1}$;
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.93-6.99 (m, 2H), 7.39-7.45 (m, 2H), 8.15 (brs, 1H), 8.23 (s, 1H), 8.46 (d, $J = 11.3$ Hz, 1H), 9.21 (brs, 1H);
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 120.9, 121.1 (2C), 132.7 (2C), 158.4, 163.3.

N-(4-Nitrophenyl)formamide (entry 5)$^{26}$:

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {NHCHO} ..
  \node at (0.5,0) {NO$_2$} ..
\end{tikzpicture}
\end{center}

Yellow solid; mp. 196-200 \textdegree C;
IR (KBr): 1320, 1567.1663 cm$^{-1}$;
$^1$H NMR (250MHz, CDCl$_3$): $\delta$ 7.57 (d, $J = 8.72$ Hz, 2H), 7.97 (d, $J = 8.75$ Hz, 2H), 8.31 (s, 1H), 10.43 (brs, 1H);
$^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ 112.1 (2C), 117.1 (2C), 151.7, 159.8, 162.3.
N-(2-Acetylphenyl)formamide (entry 6)\textsuperscript{26}:

\[
\begin{array}{c}
\text{O} \\
\text{NHCHO}
\end{array}
\]

White solid; mp.79-80\textdegree C;
IR (KBr): 1220, 1367.1668, cm\textsuperscript{-1};
\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta 2.53 (s, 3H), 7.75 (d, \textit{J} = 2.47 Hz, 2H), 7.94 (d, \textit{J} = 1.82 Hz, 2H), 8.22 (brs, 1H), 8.44 (s, 1H);
\textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}): \delta 16.0, 112.1, 117.1, 130.4 (2C), 132.9, 159.8, 162.3, 197.5.

N-(3-Chloro-4-fluorophenyl)formamide (entry 7)\textsuperscript{29}:

\[
\begin{array}{c}
\text{NHCHO} \\
\text{Cl} \\
\text{F}
\end{array}
\]

Colourless liquid;
IR (KBr): 1260, 1457.1664, cm\textsuperscript{-1};
\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta 6.93-6.99 (m, 1H), 7.39-7.45 (m, 2H), 8.15 (brs, 1H), 8.23 (s, 1H), 8.46 (d, \textit{J} =11.3 Hz, 1H), 9.06 (brs, 1H);
\textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}): \delta 116.3, 116.6, 120.9, 121.1, 132.7, 158.4, 163.3;

N-benzylformamide (entry 8)\textsuperscript{26}:

\[
\begin{array}{c}
\text{NHCHO} \\
\text{Cl}
\end{array}
\]

White solid; mp.60-61\textdegree C;
IR (KBr): 1420, 1567, 1658, cm\textsuperscript{-1};
\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta 4.61(s, 2H), 6.99-7.58 (m, 5H), 8.54 (s, 1H), 9.02 (s, 1H);
\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \delta 42.8, 117.5 (2C),131.0 (2C), 137.0, 161.7, 164.9.
N-(Furan-2-ylmethyl)formamide (entry 9):

![N-(Furan-2-ylmethyl)formamide](image)

Light yellow viscous oil;
IR (KBr): 1226, 1380, 1527 cm\(^{-1}\);
\(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 4.28 (s, 1H), 4.45 (s, 1H), 6.25 (m, 3H), 7.31 (m, 1H), 8.12 (s, 1H);
\(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 35.1, 107.7, 110.5, 142.4, 150.7, 161.1.

N,N-Diphenylformamide (entry 10):  

![N,N-Diphenylformamide](image)

White solid; mp. 78–80 °C;
IR (KBr): 1259, 1490, 1581 cm\(^{-1}\);
\(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 7.07-7.32 (m, 10H), 8.64 (s, 1H);
\(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 125.2 (2C), 126.2, 126.9, 127.1 (2C), 129.3 (2C), 129.8 (2C), 139.7, 141.9, 161.8;

Piperidine-1-carbaldehyde (entry 11):  

![Piperidine-1-carbaldehyde](image)

Colorless liquid,
IR (KBr): 1659, 2860, 2939 cm\(^{-1}\);
\(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 1.50–1.71(m, 6H), 3.30 (t, \(J = 8\) Hz, 2H), 3.46 (t, \(J = 7.6\) Hz, 2H), 8.00 (s, 1H);
\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 24.59, 24.99, 26.48, 40.53, 46.75, 160.58;
Morpholine-4-carbaldehyde (entry 12)\textsuperscript{29}: 

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CHO}
\end{array}
\]

Colorless liquid
IR (KBr): 1663, 2857, 2991 cm\textsuperscript{-1};
\(^1\)H NMR (400MHz, DMSO-\textit{d}_6): \(\delta\ 3.36\ (t,\ J = 8\ Hz,\ 4H), \ 3.50\ (t,\ J = 7.6\ Hz,\ 2H), \ 3.56\ (t,\ \ 2H), \ 8.02\ (s,\ 1H);
\(^{13}\)C NMR (100 MHz,DMSO-\textit{d}_6): \(\delta\ 40.20, 45.86, 66.87, 67.08, 161.23;\)

\textbf{N-\textit{tert}-Butylformamide (entry 13)}\textsuperscript{29}: 

\[
\begin{array}{c}
\text{NHCHO}
\end{array}
\]

Colorless liquid
IR (KBr): 1668, 2957, 3191 cm\textsuperscript{-1};
\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\ 1.30\ (s,\ 9H), \ 6.84\ (brs,1H), \ 8.68\ (s,\ 1H);
\(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\ 30.5\ (3C), \ 45.9, \ 162.6;\)

\textbf{N-Butylformamide (entry 14)}\textsuperscript{29}: 

\[
\begin{array}{c}
\text{NHCHO}
\end{array}
\]

Colorless liquid
IR (KBr): 1672, 2867, 3091 cm\textsuperscript{-1};
\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\ 0.93\ (t,\ J =7.05Hz,\ 3H), \ 1.25-1.57(m,\ 4H), \ 3.18-3.34\ (m,\ 2H), \ 5.77\ (brs,\ 1H), \ 8.54\ (s,\ 1H);
\(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\ 13.5, \ 19.9, \ 31.5, \ 37.9, 161.2.\)
N-Cyclohexylformamide (entry 15)$^{12}$:

\[
\text{NHCHO}
\]

Colorless liquid

IR (KBr): 1662, 2877, 3001 cm$^{-1}$;

$^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.50–1.71 (m, 6H), 1.98 (t, $J$ =7.52, 4H), 3.54 (s, 1H), 8.30 (s, 1H), 9.17 (bs, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 24.59 (2C), 26.48, 40.53(2C), 46.75,163.58;

N,N'-Diformyl (entry 16)$^{12}$:

\[
\text{NHCHO}_2
\]

White solid; mp.110-111$^0$C;

IR (KBr): 1260, 1357.1678, cm$^{-1}$;

$^1$H NMR (300MHz, CDCl$_3$): $\delta$ 3.21-4.30 (m, 4H), 8.17 (s, 2H), 9.20 (s, 2H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 43.1 (2C), 163.2 (2C).

N-(2-Hydroxyethyl)formamide (entry 17)$^{12}$:

\[
\text{HO} \quad \text{NHCHO}
\]

Colorless liquid

IR (KBr): 1662, 2877, 3291 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.21-4.30 (m, 4H), 4.70 (brs, 1H), 6.54 (brs, 1H), 6.81(brs, 1H), 8.07 (s, 1H), 8.18(s, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 40.9, 61.8, 161.8.
SOME IMPORTANT $^1$H & $^{13}$C NMR SPECTRA
REFERENCES

Formylation without catalyst and solvent at 80 °C

Matiur Rahman, Dhiman Kundu, Alakananda Hajra *, Adinath Majee *

Department of Chemistry, Visva-Bharati University, Santiniketan 731 235, India

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 and formamides are regarded as useful intermediates in organic synthesis and medicinal chemistry. In addition, formamides are well-known reagents having a wide range of applications in organic synthesis such as allylation, hydroxylation, Wilsmeier reaction, and for the synthesis of formamidines. In the literature, various approaches are available for N-formylation using different reagents such as chloral, formic acid-EDC, formic acid-EDCL, formic acid in toluene, ammonium formate, CDIM, KF-alumina, and other solid-supported reagents. 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 ZnCl₂, FeCl₃, AlCl₃, and NiCl₂ has been reported. 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 pentafluorophenyl formate are useful reagents for direct N-formylation without requiring any catalyst.

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 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, no isolable side product has been observed. All the aromatic, aliphatic, 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 to aromatic amines.
Table 1
Formylation of amines with formic acid at 80 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Ref.</th>
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<tbody>
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<td>1</td>
<td>NH₂</td>
<td>NHCHO</td>
<td>25</td>
<td>90</td>
<td>13c</td>
</tr>
<tr>
<td>2</td>
<td>NH₂</td>
<td>NHCHO</td>
<td>25</td>
<td>90</td>
<td>13c</td>
</tr>
<tr>
<td>3</td>
<td>NH₂OH</td>
<td>NHCHO</td>
<td>40</td>
<td>85</td>
<td>13c</td>
</tr>
<tr>
<td>4</td>
<td>NH₃Br</td>
<td>NHCHO</td>
<td>80</td>
<td>75</td>
<td>13c</td>
</tr>
<tr>
<td>5</td>
<td>NH₂NO₂</td>
<td>NHCHO</td>
<td>480</td>
<td>85</td>
<td>13c</td>
</tr>
<tr>
<td>6</td>
<td>O NH₂</td>
<td>O NHCHO</td>
<td>80</td>
<td>80</td>
<td>13c</td>
</tr>
<tr>
<td>7</td>
<td>NH₂Cl</td>
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<td>80</td>
<td>90</td>
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</tr>
<tr>
<td>8</td>
<td>CH₂NH₂</td>
<td>CH₂NHCHO</td>
<td>60</td>
<td>90</td>
<td>13c</td>
</tr>
<tr>
<td>9</td>
<td>NHPH₂</td>
<td>NHCHO</td>
<td>90</td>
<td>80</td>
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<td>11</td>
<td>N</td>
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<td>80</td>
<td>180</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>N</td>
<td>NCHO</td>
<td>60</td>
<td>300</td>
<td>14</td>
</tr>
</tbody>
</table>

(continued on next page)
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 cinchoneselectivity 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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References and notes


17. General procedure for N-formylation of an amine:
A mixture of diphenylamine (138 mg, 3 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 water (2 × 5 ml) and dried over sodium sulphate. 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 (NDI-dimethylformamide, entry 10): 1H NMR (CDCl3, 300 MHz); δ ppm 7.30 (br s, 5H, H), 8.64 (s, 1H, CHO); IR (KBr, cm−1): 3040, 2896, 1672, 1581, 1490, 1404, 1321, 1259, 1122. 13C NMR (CDCl3, 75 MHz); δ ppm 161.8, 1441.8, 138.7, 129.8 (2C), 128.3 (2C), 127.1, 126.8, 126.2 (2C), 123.2 (2C). Anal. Calcd for C21H16NO: C, 79.16; H, 5.02; N, 7.10. Found: C, 78.98; H, 5.61; N, 11.33. The spectral (1H NMR, IR) and analytical data of another new compound is given below for ready reference.

1,4-Diphenyl-1’-formylformamide (entry 9):
Light yellow viscous oil. 1H NMR (CDCl3, 300 MHz); δ ppm 4.28 (s, 1H, one H of -CH2-), 4.45 (s, 1H, one H of -CH2-), 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, 1002, 919. 13C NMR (CDCl3, 75 MHz); δ ppm 161.1, 150.7, 142.4, 136.5, 107.7, 35.1. Anal. Calcd for C16H10NO2: C, 75.59; H, 5.64; N, 11.19. Found: C, 75.39; H, 5.73; N, 11.21.
Corrigendum to "Formylation without catalyst and solvent at 80 °C" [Tetrahedron Lett. 51 (2010) 2896]

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The time and yield details for entries 9–12 in Table 1 were incorrect when this paper was published. Please find the corrected version of Table 1 below.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Ref.</th>
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<td></td>
<td></td>
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| Entry | Substrate | Product | Time (min) | Yield (%) | Ref.  
|-------|-----------|---------|------------|-----------|------
| 8     | CH₂NH₂    | CH₂NHCHO| 60         | 90        | 13c  
| 9     | NH₂      | NHCHO   | 80         | 90        | —    
| 10    | NHPh     | Ph-NHCHO| 60         | 85        | 13c  
| 11    | NH₂      | CHO     | 180        | 80        | 14   
| 12    | NH₂      | NH₂     | 300        | 60        | 14   
| 13    | NH₂      | NH₂     | 60         | 60        | 14   
| 14    | NH₂      | NH₂     | 60         | 60        | 14   
| 15    | NH₂      | NHCHO   | 00         | 80        | 7    
| 16    | NH₂      | NHCHO   | 60'        | 85        | 7    
| 17    | HO-NH₂   | NHCHO   | 60         | 80        | 7    

---

* Isolated yield.
** Reported in the literature.
*** 2-equiv w.r.t. amine.