

# N-FORMYLATION OF ANILINES AND AMINES USING FORMIC ACID-ACETIC ANHYDRIDE OVER SILICA GEL

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**Abstract :** This study has been undertaken to investigate N-formylation in organic synthesis have been successfully carried out using formic acid, acetic anhydride over silica gel. A mixture of formic acid and acetic anhydride in situ generates acetic formic anhydride. The compounds synthesized are characterized by various physico chemical techniques viz elemental analysis, thin layer chromatography and <sup>1</sup>H NMR. These techniques suggested monomeric nature of the products.

**IndexTerms – N-Formylation, formic acid, acetic anhydride, AFA, eco-friendly, solvent-free.**

One of the challenges to research workers during the recent years has been to develop procedures that are both environmentally desirable and economically acceptable. Most of the organic solvents used in industry are toxic, costly and problematic to use. Carrying out reactions with lesser amount or no solvent would lead to clean, efficient and economical processes since the best solvent is “No Solvent at all.”

The development of procedures for the construction of the N-C bond is highly important. N-Formylation is an important step in organic synthesis, as N-Formyl compounds have been widely used for the protection of amino<sup>1</sup> and hydroxy<sup>2</sup> groups. These are also the precursors for isocyanide preparation,<sup>3-5</sup> an intermediate for mono methylated amines from primary amines,<sup>6,7</sup> or in aminations and ring transformations of benzofuran derivatives.<sup>8</sup> They have also been used in the synthesis of pharmaceutically important compounds such as fluoroquinolones,<sup>9</sup> substituted aryl imidazoles,<sup>10</sup> 1,2-dihydroquinolines,<sup>11</sup> nitrogen bridged heterocycles,<sup>12</sup> etc.

Formamides are Lewis bases, which are known to catalyze reactions such as allylation<sup>13</sup> and hydrosilylation<sup>14</sup> of carbonyl compounds. More recently, asymmetric allylation of aldehydes has been achieved with chiral formamides.<sup>15</sup> Furthermore, formamides are very useful reagents in Vilsmeier formylation reactions.<sup>16</sup> In addition, these have been used in the synthesis of formamidines.<sup>17</sup>

Numerous methods are available for N-formylation. Most common method employs the reaction of amines with carbon monoxide in presence of Rhodium or Ruthenium complexes giving N-substituted or N, N-disubstituted formamides, respectively.<sup>18</sup> Blicke and Lu<sup>19</sup> have used chloral for the formylation of amines. Waki et.al<sup>20</sup> and Chen et.al<sup>21</sup> reported formylation using activated formic acid and DCC or EDCI respectively. Yale,<sup>22</sup> Kisfatusy et.al,<sup>23</sup> Duezek et.al<sup>24</sup> and Neveux et.al<sup>4</sup> have reported activated formic esters as formylating agent.

Djuric<sup>26</sup> has used DMF, tert.butyl dimethylsilyl chloride, triethylamine and DMAP for formylation. N-Formylbenzotriazole(NFB) has very recently been reported by Katritzky et.al.<sup>27</sup> Deutsch and Niclas<sup>28</sup> performed formylation of amines and alcohols using cyanomethylformate. Staab and Polenski<sup>29</sup> used N-formylimidazole (NFI) as N-formylating agent. Shiina et.al<sup>30</sup> have used a mixture of formic acid and 4-trifluoromethylbenzoic anhydride (TMBA) in presence of catalytic amount of active Titanium (IV) salt or Ytterbium triflate in hexamethyldisilazane. Acetic formic anhydride has been used as formylating agent by Huffman,<sup>31</sup> and Strazzolini et.al.<sup>32</sup> An excellent preparation of pure acetic formic anhydride was given by Hurd and Roe<sup>25</sup> from ketene and formic acid.

Recently, Chakrabarty et.al<sup>33</sup> have used neat formic acid as N-formylating agent for carbazoles, indoles, diphenylamine and moderately weak nucleophilic anilines. Reddy et.al<sup>34</sup> reported a method for N-formylation of secondary amines and anilines using ammonium formate. A most recent method reported by Jung et.al<sup>35</sup> used aqueous 85% formic acid in toluene for formylation of amines. Despite the usefulness of these reagents, such as high yields and mild conditions, they are less practical; they are either toxic or expensive and the preparation and use of these reagents require strictly anhydrous conditions.

## Research Methodology

Keeping in view our continued interest in devising environmentally benign techniques and importance of N-formylation in organic synthesis, N-formylation have successfully been carried out using formic acid, acetic anhydride over silica gel. A mixture of formic acid and acetic anhydride (1:1) in situ generates acetic formic anhydride (AFA).<sup>33</sup>

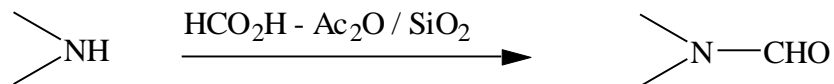
Ammonium formate when adsorbed over basic alumina was found to act as a good formylating agent for aliphatic amines, but fails for aromatic amines. Further, ammonium formate over different solid supports had been used. The results are summarized in **Table 1**. The reaction was also tried with formic acid over silica gel but yield was low. Thus reactions were carried out with formic acid-acetic anhydride over silica gel (**Table2**).

**Table 1** Results of various reagents for N-formylation of aniline

Reagent	Reaction Temp. <sup>b</sup> (°C)	Time <sup>a</sup> (Min)	Yield <sup>c</sup> (%)
HCO <sub>2</sub> NH <sub>4</sub>	60-62	10	0
HCO <sub>2</sub> NH <sub>4</sub> /Basic alumina	98-100	10	0
HCO <sub>2</sub> NH <sub>4</sub> /K <sub>2</sub> CO <sub>3</sub>	35-38	7	0
HCO <sub>2</sub> NH <sub>4</sub> /H <sub>2</sub> O	91-93	7	0
HCO <sub>2</sub> H/SiO <sub>2</sub>	48-50	4	60
HCO <sub>2</sub> H-Ac <sub>2</sub> O/SiO <sub>2</sub>	75-78	2	84

- a.* Time at which maximum yield was obtained;  
*b.* Final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during microwave experiment and was approximate temperature range;  
*c.* Yield of isolated products.



**Table2 Results of N-Formylation of anilines and amines using HCO<sub>2</sub>H-Ac<sub>2</sub>O/SiO<sub>2</sub>**

Entry	substrate	Product	Reaction temperature(°C)	Time(min.)	Yield(%)	mp/Lit. mp
1.	Aniline	Formanilide	75-78	2	84	45-49/46-48 <sup>36</sup>
2.	4-Nitroaniline	4-nitroformanilide	60-62	2	73	189-92/194-95 <sup>37</sup>
3.	3-Nitroaniline	3-Nitroformanilide	75-77	2	74	133-35/134 <sup>37</sup>
4.	2-Anisidine	<i>N</i> -Formyl-2-anisidine	95-98	4	98	80-82/83.5 <sup>37</sup>
5.	4-Anisidine	<i>N</i> -Formyl-4-anisidine	85-88	2	70	78-79/81 <sup>37</sup>
6.	3-Toluidine	Formo-3-Toluidine	75-78	2	98	276/278(bp) <sup>37</sup>
7.	4-Toluidine	Formo-4-toluidine	70-72	2	82	50-52/53 <sup>37</sup>
8.	2-Nitroaniline	2-Nitroformanilide	80-82	2	97	120-121/122 <sup>37</sup>
9.	Piperadin	<i>N</i> -Formylpiperadin	70-72	1	89	221/222(bp) <sup>37</sup>
10.	Morpholin	4-Formylmorpholin	60-62	1	95	236/236(bp) <sup>36</sup>
11.	Diethylamin	<i>N, N</i> -Diethylformamide	65-68	2	96	176/177(bp) <sup>36</sup>
12.	Benzylamin	<i>N</i> -Formylbenzylamin	80-82	2	88	60/60-61 <sup>36</sup>
13.	Diphenylamine	<i>N, N</i> -Diphenylformamide	48-51	4	97	71-74/73-74 <sup>37</sup>
14.	Anthranilic acid	<i>N</i> -Formylanthranilic acid	60-62	3	79	165-169/169 <sup>37</sup>
15.	4-Aminobenzoic-acid	<i>N</i> -Formyl-4-aminobenzoic acid	50-52	2	95	268d/268d <sup>37</sup>
16.	Hydrazine	Formic hydrazide	55-58	0.5	96	52-55/54-56 <sup>36</sup>
17.	Cyclohexylamine	<i>N</i> -Formylcyclohexyl amine	68-70	2	87	267/268-74 <sup>37</sup>

## Results and Discussion

In order to determine the possibility of existence of a specific microwave effect accelerating the reaction with respect to conventional heating, a pre-heated oil bath was used as a source of heat in comparative experiments (**Table 3**).

**Table 3** Comparison of microwave activation (MW) and thermal heating ( $\Delta$ ) in case of entries 1 and 2, power = 300W

Entry	Method	Reaction Temp. ( $^{\circ}$ C)	Time (Min)	Yield (%)
1	MW	75-78	2	84
	$\Delta$	78	2	5
	$\Delta$	78	30	72
2	MW	60-62	2	73
	$\Delta$	62	2	0
	$\Delta$	62	6hrs	0

It has been found that significantly lower yields were obtained using oil-bath heating than using MW assisted method under identical conditions of reaction time and temperature. This observation demonstrates clearly that the effect of MW irradiation is not purely thermal.

## Experimental

To a mixture of substrate (1 mmole), formic acid (2mmole), acetic anhydride (2 mmole), 2 g of silica gel was added in beaker (50 mL). The mixture is stirred properly (30 s) till free flowing powder was obtained. The reaction mixture was then irradiated in a microwave oven for an appropriate time (table 2) at 300 W (monitored by tlc). On cooling at room temperature, the product was extracted with methylenechloride (3x15mL). The combined methylene extract was washed with water and dried over sodium sulphate. The product obtained after removal of the solvent under reduced pressure was crystallized from an appropriate solvent.

The structures of the products were confirmed by  $^1$ H NMR, IR and comparison with authentic sample prepared by already reported methods.

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