The immobilized NaHSO₄·H₂O on activated charcoal: a highly efficient promoter system for N-formylation of amines with ethyl formate

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ABSTRACT
The immobilized NaHSO₄·H₂O on activated charcoal was used as a highly efficient promoter system for facile N-formylation of amines with ethyl formate. All reactions were carried out in refluxing ethyl formate (54 ºC) under mild conditions within 10-100 min to afford the product formamides in high to excellent yields (80-94%).

Keywords: Amines Activated charcoal Ethyl formate Formylation NaHSO₄·H₂O

1. Introduction

The protection of amines by the formation of formamides is one of the most important and widely used transformations in organic chemistry.¹ Formamides as important class of amine derivatives have been used widely in the synthesis of pharmaceutically valuable compounds such as fluoroquinolines,² 1-arylimidazole-5-carboxylates,³ 1-formyl-1,2-dihydroquinolines⁴ nitrogen bridged heterocycles,⁵ oxazilidones,⁶ cancer chemotherapeutic agents,⁷ fungicides,⁸ preparation of isocyanates,⁹ foramidines,¹⁰ and nitriles,¹¹ the Vilsmeier-Haake formylation reaction,¹² allylation¹³ and hydrosilylation¹⁴ of carbonyl compounds. Due to wide synthetic and biological applications of formamides, a number of methods and reagents such as Cl₃CCHO,¹⁵ CH(OE)t,¹⁶ NaOEt/CHCl₃,¹⁷ HCO₂NH₄,¹₈ HCO₂NH₄/nano Fe₃O₄/PEG-400,¹⁹ 2,2,2-trifluoroethyl formate,²⁰ phenyl formate,²¹ pentafluorophenyl formate,²² acetic formic anhydride,²³ and KF-Al₂O₃/CHCl₃,²⁴ formic acid in the presence of HCO₂Na,²⁵ NH₃OH·HCl,²⁶ I₂,²⁷ DCC,²⁸ EDCI,²⁹ ZnCl₂,³⁰ In,³¹ ZnO,³² TiO₂-P₂5 (TiO₂-SO₄²⁻),³³ nanoceria,³⁴ Zr-MCM-41,³⁵ NiFe₂O₄@SiO₂-PPA,³⁶ γ-Fe₂O₃@HAp-SO₃H,³⁷ WO₄(SO₄)²⁻,³⁸ Fe(III)-exchanged sepiolite,³⁹ 2-chloro-4,6-dimethoxy-1,3,5-triazine,⁴⁰ melamine trisulfonic acid,⁴¹ thiamine hydrochloride,⁴² TBD-based ionic liquids,⁴³ Brønsted acidic ionic liquid (RHA-
[pmim]HSO4•H2O, PEG-400, HClO4/SiO2, silica sulfuric acid, hafnium(IV) bis(perfluoroctane-sulfonylimide complex supported on fluorous silica gel, ultrasound, ultrasound/[bmim]BF4, and ultrasound/nano CeO2, ethyl formate in the presence of 2-(sulfooxy)propane-1,2,3-tricarboxylic acid/SiO2, silphos [PCl3-n(SiO2)n], and microwave/disulfonamides polymers have been reported for the formylation of various primary and secondary aromatic/aliphatic amines. In this context, some protocols did not use any catalysts/promoters, and the formylation reactions were carried out under particular conditions. Recently, N-formylation of amines has been extensively reviewed by Gerack et al. Many of these methods suffer from various drawbacks such as using expensive or toxic formylating reagents/catalysts, acidic reaction conditions, organic solvents, the excess amounts of formic acid, high reaction temperature, prolonged reaction times and removal of by-products. Therefore, there is a need to develop a better catalyst or conditions for synthesis of formamides in terms of operational simplicity and economical viability. Herein, we wish to introduce the immobilized NaHSO4•H2O on activated charcoal as an efficient promoter system for facile N-formylation of various amines in refluxing ethyl formate (54 ºC) under net conditions (Scheme 1).

2. Results and Discussion

Hydrated sodium hydrogen sulfate, NaHSO4•H2O, as a cheap and mineral weak acidic reagent, has been found to have some useful applications in organic synthesis. In this context, using NaHSO4•H2O as an efficient promoter has been successfully used by our research group for the Biginelli synthesis of 3,4-dihydropyrimidin-2(1H)-ones and facile reduction of carbonyl compounds with NaBH4. In line with the outlined strategies for N-formylation of amines, we found that this transformation in the presence of hydrated sodium hydrogen sulfate has not been investigated yet. Therefore, this subject and our research interest to prepare formamides as a key intermediate, encouraged us to investigate the influence of NaHSO4•H2O on the titled transformations.

N-formylation of amines was primarily examined by the reaction of aniline with ethyl formate as a non-acidic formylating agent in the absence and presence of NaHSO4•H2O. The results of this investigation are summarized in Table 1. Entries 1 and 2 show that the formylation of aniline in the absence of hydrated sodium hydrogen sulfate did not any take place, and the reaction with a molar ratio of aniline:NaHSO4•H2O (1:0.1) in refluxing ethyl formate (2 mL) encountered with low efficiency (40%). This result exhibited that though hydrated sodium hydrogen sulfate affected the rate of formylation reaction, however, the influence was not sufficient and therefore completion of the reaction required to an additional co-catalyst.

Nowadays, activated charcoal, because of its high degree of micro-porosity (just one gram of activated carbon has a surface area in excess of 500-1500 m2 being readily achievable) provides a high surface area and this situation makes it more desirable for academic and industrial applications. In this context, we decided to incorporate the weak acidic character of NaHSO4•H2O and micro-porosity of activated charcoal with together, and so using them as an efficient promoter system in N-formylation of aniline by ethyl formate. The incorporation of hydrated sodium hydrogen sulfate with activated charcoal was carried out by mixing some mass ratio of NaHSO4•H2O and activated charcoal in water and then evaporation of the solvent in a microwave oven to afford different composition percentage of the immobilized NaHSO4•H2O on activated charcoal. The influence of the obtained immobilized systems was then studied in N-formylation of aniline (1 mmol) with ethyl formate (2 mL) (entries 4-7). Among the examined systems, the immobilization of 0.2 g NaHSO4•H2O on 0.1 g activated charcoal
shows a dramatic acceleration leading to complete the reaction within 25 min. Therefore, the conditions mentioned in entry 7 were selected as the optimum conditions.

**Table 1.** Optimization experiments for N-formylation of aniline with ethyl formate in the presence of NaHSO₄·H₂O/activated charcoal system

<table>
<thead>
<tr>
<th>Entry</th>
<th>Charcoal (g)</th>
<th>NaHSO₄·H₂O (g)</th>
<th>Condition</th>
<th>Time (min)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>reflux</td>
<td>360</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>0.1</td>
<td>reflux</td>
<td>360</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>-</td>
<td>reflux</td>
<td>360</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.05</td>
<td>reflux</td>
<td>120</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>0.05</td>
<td>reflux</td>
<td>120</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>0.1</td>
<td>reflux</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>0.2</td>
<td>reflux</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

*aAll reactions were carried out with 1 mmol of aniline in ethyl formate (2 mL).*

Encouraged by the result, the capability of this synthetic protocol was more studied with the reaction of various aromatic primary amines containing electron-releasing or withdrawing groups with ethyl formate at the optimized reactions conditions. Table 2 shows the general trend and versatility of this synthetic method. As seen, all reactions were carried out successfully in the presence of the immobilized NaHSO₄·H₂O (0.2 g) on activated charcoal (0.1 g) within 10-55 min to afford the products formamides in high yields (80-94%). The table also shows that the effect of substitutions on aromatic rings is noteworthy. Electron-releasing groups accelerated the rate of formylation reaction and in contrast withdrawing substitutions prolonged the reaction times through the deactivation of aromatic rings. Entries 11 and 12 also show that the current protocol is only useful for N-formylation of aromatic primary amines, and in the case of 2- and 4-aminophenols, O-formylation of phenolic substitution did not any take place. This means that the chemoselective N-formylation of aromatic primary amines can be successfully carried out in the presence of phenolic substitutions. More examination also resulted that in the case of aromatic secondary and aliphatic amines such as N-methylaniline and benzylamine, this protocol was also efficient and produced the corresponding formamides in 85-91% yields (Table 2, entries 18 and 19).

**Table 2.** N-formylation of amines with ethyl formate in the presence of NaHSO₄·H₂O/activated charcoal system

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)b</th>
<th>m.p. (ºC)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₂</td>
<td>NHCHO</td>
<td>25</td>
<td>92</td>
<td>46-48</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>NH₂</td>
<td>NHCHO</td>
<td>19</td>
<td>88</td>
<td>60-62</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>CH₃NH₂</td>
<td>CH₃NHCHO</td>
<td>18</td>
<td>91</td>
<td>52-54</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>MeO-NH₂</td>
<td>MeO-NHCHO</td>
<td>12</td>
<td>90</td>
<td>81-82</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>MeO-NH₂</td>
<td>MeO-NHCHO</td>
<td>10</td>
<td>93</td>
<td>55-57</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>Cl-NH₂</td>
<td>Cl-NHCHO</td>
<td>32</td>
<td>92</td>
<td>77-80</td>
<td>48</td>
</tr>
</tbody>
</table>
The usefulness and capability of NaHSO₄·H₂O/activated charcoal system in N-formylation of amines was highlighted by a comparison of the obtained results for aniline with other reported reagents (Table 3). A case study shows that in viewpoints of availability and cheapness of the reagents, non-acidic character of formylating agent, mild reaction conditions and easy work-up procedure, the current protocol shows a more or comparable efficiency towards the other reagents. Although the exact mechanism of this synthetic method is not clear, however, we think that the weak acidic character of NaHSO₄·H₂O activates the ethyl formate for nucleophilic attack of amines. In addition, the microporosity of activated charcoal provides the excess and more efficient pores or surfaces for better interaction of amines, ethyl formate and NaHSO₄·H₂O.

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Yield (%)</th>
<th>Ref.</th>
<th>Temperature (°C)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>NH₂Cl</td>
<td>NHCHO</td>
<td>35</td>
<td>94</td>
<td>56-57</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>Cl-NH₂</td>
<td>Cl-NHCHO</td>
<td>40</td>
<td>92</td>
<td>100-102</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>Cl-NH₂</td>
<td>Cl-NHCHO</td>
<td>45</td>
<td>90</td>
<td>149-151</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td>Br-NH₂</td>
<td>Br-NHCHO</td>
<td>33</td>
<td>89</td>
<td>118-120</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>HO-NH₂</td>
<td>HO-NHCHO</td>
<td>37</td>
<td>87</td>
<td>135-137</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>NH₂OH</td>
<td>NHCHO</td>
<td>30</td>
<td>91</td>
<td>129-131</td>
<td>19</td>
</tr>
<tr>
<td>13</td>
<td>HO₂C-NH₂</td>
<td>HO₂C-NHCHO</td>
<td>55</td>
<td>90</td>
<td>256-258</td>
<td>44</td>
</tr>
<tr>
<td>14</td>
<td>O₂N-NH₂</td>
<td>O₂N-NHCHO</td>
<td>50</td>
<td>93</td>
<td>194-195</td>
<td>48</td>
</tr>
<tr>
<td>15</td>
<td>O₂N-NH₂</td>
<td>O₂N-NHCHO</td>
<td>45</td>
<td>90</td>
<td>134-135</td>
<td>65</td>
</tr>
<tr>
<td>16</td>
<td>H₂N-NH₂</td>
<td>OHCHN-NHCHO</td>
<td>30</td>
<td>80</td>
<td>210-212</td>
<td>44</td>
</tr>
<tr>
<td>17</td>
<td>NH₂NH₂</td>
<td>NHCHO</td>
<td>31</td>
<td>94</td>
<td>136-138</td>
<td>44</td>
</tr>
<tr>
<td>18</td>
<td>CH₂NH₂</td>
<td>CH₂NHCHO</td>
<td>45</td>
<td>91</td>
<td>60-62</td>
<td>48</td>
</tr>
<tr>
<td>19</td>
<td>NHMe</td>
<td>NHMe</td>
<td>100</td>
<td>85</td>
<td>123-124</td>
<td>19</td>
</tr>
</tbody>
</table>

*All reactions were carried out with 1 mmol of amines in the presence of NaHSO₄·H₂O/activated charcoal (0.2 g : 0.1 g) system in refluxing ethyl formate (2 mL). *b*Yields refer to isolated pure products.
### Table 3. Comparison of N-formylation of aniline with NaHSO₄·H₂O/activated charcoal system and other reported reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Mol%</th>
<th>Conditions</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHSO₄·H₂O/activated charcoal</td>
<td>0.014</td>
<td>C₂H₅OCHO/reflux (54 ºC)</td>
<td>25</td>
<td>92</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl₂</td>
<td></td>
<td>HCO₂H/70 ºC</td>
<td>10</td>
<td>96</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>TiO₂-P25</td>
<td>0.1 g</td>
<td>HCO₂H/r.t.</td>
<td>45</td>
<td>99</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>γ-Fe₂O₃@ Hap-SO₃H</td>
<td>0.9</td>
<td>HCO₂H/r.t.</td>
<td>20</td>
<td>97</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>SiO₂-HClO₄</td>
<td>2.5</td>
<td>HCO₂H/r.t.</td>
<td>15</td>
<td>96</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>2-(sulfooxy)propane-1,2,3-tricarboxylic acid/SiO₂</td>
<td>0.13 g</td>
<td>C₂H₅OCHO/r.t.</td>
<td>7.5 h</td>
<td>90</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>Silphos [PCl₃-n(SiO₂)n]</td>
<td>1 g</td>
<td>C₂H₅OCHO/r.t.</td>
<td>75</td>
<td>92</td>
<td>53</td>
</tr>
</tbody>
</table>

*Current protocol.

### 3. Conclusions

In summary, we have shown that NaHSO₄·H₂O/activated charcoal system can be used as an efficient promoter system for N-formylation of various amines with ethyl formate. All reactions were carried out successfully using the immobilized NaHSO₄·H₂O (0.2 g) on activated charcoal (0.1 g) per 1 mmol of amines within 10-100 min. The product formamides were obtained in 80-94% yields. The cheapness and availability of the reagents, high yields and easy work-up procedure as well as the benefits of neat reaction conditions are the advantages which make this protocol a synthetically useful addition to the present methodologies.

### Acknowledgements

The authors gratefully acknowledge the financial support of this work by the research council of Urmia University.

### Experimental

#### General

All reagents and substrates were purchased from commercial sources with the best quality and they were used without further purification. Activated charcoal was obtained from Merck Company (Art No 102186). ¹H and ¹³C NMR spectra were recorded on 300 MHz Bruker spectrometer. All chemical shifts were measured with reference to TMS (δ = 0.00 ppm). FT-IR spectra were recorded on Thermo Nicolet Nexus 670 spectrophotometer using the KBr-pellet technique. All products are known and were characterized by their ¹H, ¹³C NMR and FT-IR spectra followed by comparison with authentic data. TLC was applied for the purity determination of the substrates, products and the reaction monitoring over silica gel 60 F254 aluminum sheet.

#### Preparation of the immobilized NaHSO₄·H₂O on activated charcoal

In a round-bottomed flask, a solution of NaHSO₄·H₂O (0.2 g) in distilled water (2 mL) was prepared. Next, activated charcoal (0.1 g) was added and the mixture was stirred vigorously for 15 min at room temperature. The solvent was then evaporated by microwave irradiation (500 W) to afford the immobilized NaHSO₄·H₂O on activated charcoal (0.3 g).

#### A typical procedure for N-formylation of amines with ethyl formate in the presence of NaHSO₄·H₂O/activated charcoal system

In a round-bottomed flask (5 mL) equipped with a magnetic stirrer and condenser, a solution of aniline (1 mmol, 0.093 g) in ethyl formate (2 mL, 0.025 mol) was prepared. NaHSO₄·H₂O/activated charcoal (0.3 g) was then added and the reaction mixture was stirred under reflux conditions (54 ºC) for 25 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was passed through a short column of silica gel (200-400 mesh) and the eluted solvent was
then evaporated under reduced pressure to afford the pure $N$-phenyl formamide in 92% yield (0.111 g, Table 2, entry 1).

References


