SYNTHESIS AND CHARACTERIZATION OF FORMAMIDINE DERIVATIVES FROM IMIDATE VIA DIFFERENT CATALYSTS

A. Yahyazadeh[a]*, M. Hadisi Nea[a] and S. Majnooni[a]

Keywords: formamidine, imidate, sulfonic acid, aluminium chloride, anilinium chloride, silica sulfuric acid.

In this research, synthesis of (1E)-N’-((Z)-2-amino-1,2-dicyanovinyl)-N-(4-ethoxyphenyl)formamidine from imidate was investigated in the presence of different catalysts such as sulfonic acid (-SO\(_3\)H), P-Toluene sulfonic acid (PTSA), aluminium chloride (AlCl\(_3\)), ceric ammonium nitrate (CAN), anilinium chloride (C\(_6\)H\(_5\)NH\(_3\)\(^+\)Cl\(^-\)), Montmorillonite (K10), silica sulfuric acid (SiO\(_2\)-OSO\(_3\)H), silica-supported perchloric acid (HClO\(_4\)-SiO\(_2\)). Silica sulfuric acid exhibited high catalytic activity for this reaction and afforded excellent yields within a lesser time. Other formamidine derivatives were prepared from the reaction of imidate with amines in the presence of silica sulfuric acid under argon at room temperature.

Introduction

Amidines have long been regarded as valuable intermediates in the synthesis of heterocyclic compounds. Characteristic structural features of many natural substances would be very helpful for medicinal chemists because amidines are found in many bioactive natural products and identified as important pharmacophores. They possessing anti-degenerative, anti-cancer, anti-platelet, and antimicrobial activities. Amidine derivatives also act as serine protease inhibitors. Very important compounds were prepared from amidines such as imidazole rings, purins, quinazolines. Conventional strategies for amidine synthesis include the addition of metal amides or amines to nitriles, the addition of amines to imido ester intermediates, and the condensation of amides with amines in the presence of halogenating reagents. In this research, we have synthesized amidine derivatives from imidate in the presence of different catalysts.

Experimental

All chemicals and reagents were prepared from Sigma/Aldrich and Merck Chemical Companies. All solvents purified and dried using established procedures. Solvents were removed using rotary evaporator under reduced pressure. The \(^1\)H NMR spectra were recorded on Bruker XL (400 MHZ) instruments (with \(\beta\)-values given in Hz) and IR spectra on a Shimadzu IR-470 spectrophotometer. The melting points were measured on an Electro thermal digital melting point apparatus and are uncorrected.

In this research, synthesis of (1E)-N’-((Z)-2-amino-1,2-dicyanovinyl)-N-(4-ethoxyphenyl)formamidine from imidate was investigated in the presence of different catalysts such as sulfonic acid (-SO\(_3\)H), P-Toluene sulfonic acid (PTSA), aluminium chloride (AlCl\(_3\)), ceric ammonium nitrate (CAN), anilinium chloride (C\(_6\)H\(_5\)NH\(_3\)\(^+\)Cl\(^-\)), Montmorillonite (K10), silica sulfuric acid (SiO\(_2\)-OSO\(_3\)H), silica-supported perchloric acid (HClO\(_4\)-SiO\(_2\)). Silica sulfuric acid exhibited high catalytic activity for this reaction and afforded excellent yields within a lesser time. Other formamidine derivatives were prepared from the reaction of imidate with amines in the presence of silica sulfuric acid under argon at room temperature.
**Synthesis and characterization of formamidine derivatives**

Section A - Research Paper


(1Z)-N-(4-methoxybenzyl)-N’-((Z)-2-amino-1,2-dicyanovinyl)-formamidine, 2b

Green solid, (87%) m.p: 150-152 °C; IR (KBr): 3480 (NH), 3360 (N-H), 2950 (C-H), 2200 (C=N), 1630 (N-H bend), 1600 (C=C), 1550 s (C=N), 1360 (CH3 bend), 1260 (C-N), 1250 (C-O), 840 (C-H bend) cm⁻¹; ¹H NMR (CDCl3): 7.97 (s, 1H), 7.71 (s, 1H), 7.26 (q, J = 5Hz, 2H), 6.99 (s, 1H), 6.96 (d, J = 10Hz, H), 6.06 (s, 2H, H), 4.48 (d, J = 5Hz, 2H), 3.81 (s, 3H) ppm.

(1Z)-N-(2-methoxybenzyl)-N’-((Z)-2-amino-1,2-dicyanovinyl)-formamidine, 2c

Cream solid, (86%) m.p: 148-150 °C; IR (KBr): 3400 (NH), 3300(NH), 3150(C-H aromatic), 2950(C-H aliphatic), 2200(C= N), 1640(N-H bend), 1465(CH3 bend), 850(C-H bend) cm⁻¹; ¹H NMR (DMSO): 7.97(d, 1H), 7.71(d, J= 4.04 HZ, 1H), 7.27(q, J=5HZ, 2H), 7 (m, J=5 HZ, 1H), 6.91(m, J=10Hz, 1H), 6.06 (s, 2H), 4.47(d, J= 5Hz 2H), 3.81 ( s, 3H) ppm.

(1Z)-N’-((Z)-2-amino-1,2-dicyanovinyl)-N-(2-methoxyphenyl)-formamidine 2d

Green solid, (90%) m.p: 138-140 °C; IR (KBr): 3380 (NH), 3330(NH), 3150(C-H aromatic), 2950(C-H aliphatic), 2200(C-N), 1640(N-H bend), 1600(C=C), 1520 (C=N), 1460(CH3 bend), 1280 (C-O), 860(C-H bend) cm⁻¹; ¹H NMR (CDCl3): 8.30 (s, 1H), 7.71 (s, 1H), 7.28 (d, J=1.2 Hz, 1H), 7.10 (m, J= 3.24 Hz, 1H), 7.01 (m, J = 7 Hz, 2H), 4.48 (s, 2H, H), 3.93 (s, 3H) ppm.

(1Z)-N’-((Z)-2-amino-1,2-dicyanovinyl)-N-(3,4-dimethoxyphenyl)formamidine 2e

Light green solid, (94%) m.p: 142-144 °C; IR (KBr): 3450 (NH), 3325 s (NH), 3100(C-H aromatic) 2950 (C-H aliphatic), 2210(C=N), 1630 (N-H bend), 1570 (C-C), 1510 (C=N), 1375 (CH3 bend), 1260 (C-N), 1240 (C-O), 830 (C-H bend) cm⁻¹; ¹H NMR (DMSO): 9.85 (s, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.28 (m, 2H), 6.89 (d, J = 8.5 Hz, 1H), 6.27 (s, 2H), 3.75(s, 3H), 3.72 (s, 3H) ppm.

(1Z)-N’-((Z)-2-amino-1,2-dicyanovinyl)-N-(3,4,5-trimethoxyphenyl)formamidine 2f

Green solid, (91%) m.p: 144-146 °C; IR (KBr): 3380 (NH), 3320 s (NH), 3100 (C-H aromatic) 2920 (C-H aliphatic), 2210 (C=N), 1620 (N-H bend), 1570 (C-C), 1510 (C-N), 1375 (CH3 bend), 1260 (C-N), 1240 (C-O), 830 (C-H bend) cm⁻¹; ¹H NMR (CDCl3): 9.16 (s, 1H), 8.54 (s, 1H), 6.89 (s, 2H), 6.31 (s, 2H), 3.96 (s, 6H, H), 3.94 (s, 3H, H).

(1Z)-N-(2-chlorobenzyl)-N’-((Z)-2-amino-1,2-dicyanovinyl)-formamidine 2g

Green solid, (85%) m.p: 150-152 °C; IR (KBr): 3480 (NH), 3360 (N-H), 2950 (C-H), 2200 (C=N), 1630 (N-H bend), 1600 (C=C), 1500 (C=N), 1440 (CH3 bend), 1280 (C-N), 1120 (C-O), 830 (C-H bend) cm⁻¹; ¹H NMR (CDCl3): 7.75(d, J=2.8 HZ, 1H), 7.45 (s, 2H), 7.31 (t, J=2.8 HZ, 2H), 6.12 (s, 2H), 4.58 (d, J=4.4 HZ, 2H).

**Result and discussion**

The methods currently available for the preparation of amidines often involve multistep processes with long reaction times. In this research, we focused our efforts to provide a convenient route for synthesis amidine from imidate at the least time with high yields. To reach this aim, initially, imidate was obtained from the reaction of diaminomaleonitrile (DAMN) with trimethyl orthoformate in refluxing dioxane. Synthesized imidate were reacted with 4-ethoxybenzenamine in the presence of different catalysts that have been shown in the Scheme 1. In this section of work, the main scope was investigation about the effect of different catalysts on the rate of reaction. Some of catalysts such as sulphonic acids such as p-toluene sulphonic acid (PTSA), AICl₃, ceric ammonium nitrate (CAN), C₆H₅NH₃⁺Cl⁻, K₂O, SiO₂-OSO₃H (SSA), HClO₄-SiO₂ were tested on reaction that have been shown in Table 1. This reaction without any catalyst took 20 days. The usage of other catalysts decreased the time of reaction about several days. It was observed that the reaction proceeded efficiently in the presence of silica sulfuric acid (SSA) at room temperature about 2 hours, giving formamidines in excellent yields. SSA was afforded from silica gel and chlorosulfonic acid as described previously.

**Scheme 1**: synthesis of (1E)-N’-((Z)-2-amino-1,2-dicyanovinyl)-N-(3,4-ethoxyphenyl)formamidine from imidate in the presence of different catalysts.

To demonstrate the generality of this method, we examined the reaction of imidate with various amines in the presence of SSA in dry ethanol under argon at room temperature (Scheme 2, Table 2). This method is effective for the preparation of formamidine derivatives from both electron-rich as well as electron-deficient.

**Table 1.** Catalytic evolution for synthesis formamidine from imidate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time, days</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>-SO₃H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>PTSA</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>AICl₃</td>
<td>7</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>CAN</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>C₆H₅NH₃⁺Cl⁻</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>K₂O</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>HClO₄-SiO₂</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>9</td>
<td>SiO₂-OSO₃H</td>
<td>0.083 (2 h)</td>
<td>87</td>
</tr>
</tbody>
</table>

Table 2. Synthesis of formamidine with the usage of amines and imidate in the presence of SSA

<table>
<thead>
<tr>
<th>Entry</th>
<th>compd.</th>
<th>Imidate</th>
<th>Amine</th>
<th>Formamidine</th>
<th>Time, min</th>
<th>M. P.,°C</th>
<th>Yield,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H₂N</td>
<td>EtO</td>
<td>H₂N</td>
<td>120</td>
<td>148-150</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>H₂N</td>
<td>H₃CO</td>
<td>H₂N</td>
<td>135</td>
<td>150-152</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>H₂N</td>
<td>OCH₃</td>
<td>H₂N</td>
<td>130</td>
<td>148-150</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>H₂N</td>
<td>OCH₃</td>
<td>H₂N</td>
<td>140</td>
<td>138-140</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>H₂N</td>
<td>H₃CO</td>
<td>H₂N</td>
<td>110</td>
<td>142-144</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>H₂N</td>
<td>OCH₃</td>
<td>H₂N</td>
<td>115</td>
<td>144-146</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>H₂N</td>
<td>Cl</td>
<td>H₂N</td>
<td>165</td>
<td>134-136</td>
<td>91</td>
</tr>
</tbody>
</table>

In general, when R represented the electron with donor groups such as amino and ethoxy groups the yield and purity of the product were obviously better, and short reaction time was required.

In conclusion, we tried to find efficient and new method for preparing formamidine. Different catalysts were tested to afford amidine from imidate. Effect of Catalysts on the rate of reaction was considered. Compared to other catalyst, SSA can decrease the time of reaction about several hours. So, SSA was chosen as best catalyst in this reaction and was examined on synthesis of different amidines. The Synthesis of all amidines in high yield only took about 2 hours.

Acknowledgment

We are grateful to the University of Guilan Research Council for the partial support of this work.

References

Synthesis and characterization of formamidine derivatives


Received: 18.04.2013. Accepted: 21.06.2013.