Silica sulfuric acid as an efficient and reusable heterogeneous catalyst for the synthesis of formamidines from the diaminomaleonitrile

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Abstract
Silica sulfuric acid as an efficient and reusable heterogeneous catalyst has been used for the preparation of amidades 2 from formimidate 1 by reaction with aromatic amines at room temperature in good to excellent yields. Imidate was prepared by treatment of equimolar quantities of triethyl orthoformate and diaminomaleonitrile in refluxing dioxane. All the compounds were characterized fully by spectroscopic techniques.

Keywords: Silica sulfuric acid, Heterogeneous catalyst, Imidate, Amidine, Diaminomaleonitrile.

1. Introduction
Formamidines have been implicated to be crucial intermediate in the formation of imidazoles and adenines [1-5]. Some amidines have also been found to be active towards adrenergic receptors. Shrir and Neumann have reviewed chemistry and synthesis of amidines [6]. Synthesis and characterization of several alkyl, aryl formamidine and also the amidrazone have been reported previously [7-11]. Various aryl and benzyl formamidines of type 2a-d by the reaction of imidate 1 with aromatic amines have been prepared in the present of a catalytic amount of anilinium chloride [8-9]. We decided that we could prepared various aryl and benzyl amidines of type 2a-d by reaction of imidate 1 with aromatic amines in the present of silica sulfuric acid as recyclable solid acid catalyst. During recent years, the use of silica sulfuric acid as a catalyst in organic synthesis has attracted great interest from many chemists [12]. Silica sulfuric acid can enhance the reactivity and selectivity of many types of reactions, such as oxidation [13], carbon-carbon bond formation [14], cycloaddition [15], and protection and deprotection [16]. Silica supported sulfuric acid was prepared from the reaction of silica gel with chlorosulfonic acid [13, 17].

2. Experimental
High-resolution \(^1\)H NMR (500 MHz), \(^{13}\)C NMR (125 MHz) spectra were obtained via a Bruker 500 DRX-Avance NMR spectrometer. The compounds were dissolved in deuterated DMSO as NMR solvent. IR data were obtained with a Shimadzu 470 spectrometer. Mass spectra were recorded using a GC-MS Agilent Technologies QP-5973N MSD instrument. The elemental analysis was determined on a Leco CHNS-900 analyzer. The Melting points of crystalline compounds were measured with an electrothermal melting point apparatus and have not been corrected. Purification of 1,4-dioxane and diethyl ether were refluxed with adding Na (1% w/v) and benzophenone (0.2% w/v) under an inert atmosphere until the blue colour of the benzophenone appeared. Dry dioxane was distilled, and store over 4A molecular sieves in the dark.

2.1. Typical procedure for the Preparation of Ethyl-(Z)-N-(2-amino-1,2-dicyanovinyl)formimidate (1, C\(_7\)H\(_8\)N\(_4\)O)
A mixture of diaminomaleonitrile (1g, 9.25 mmol) and triethyl orthoformate (1.37 mL, 1.22g, 9.24 mmol) in dioxane (2 mL) was heated in a round bottom flask fitted with a short vigreux column, distillation head, condenser and receiver. Ethanol, mixed with dioxane, was removed continuously until the temperature in the distillation head reached 99 °C. The brown solution in the distillation pot was allowed to cool and was then filtered. A white, needle-shaped crystal (1.42g, 8.70 mmol, 94%) was obtained after recrystallisation from dichloromethane and petroleum ether. m.p. 132-133 °C (decomp.), [lit., [12] 135-137 °C]; [Found: C, 51.3; H, 4.8; N, 34.2. Calc. for C\(_7\)H\(_8\)N\(_4\)O: C, 51.2; H, 4.9; N, 34.1%]; m/z (EI) 165 (M+1)^+ 94.2%, 119 (M-O\(_2\)C\(_2\)H\(_3\))^+.
2.2. General procedure for the preparation of the N-Aryl-N’-2-amino-1,2-dicyanovinyl]formamidines 2a-d.

The aromatic amines (1.01 g, 6.09 mmol) were added to a suspension of 1 (1.00 g, 6.09 mmol) in dry ethanol, which contained silica sulfuric acid as a new catalyst (0.02 g) for this reaction. The mixtures were stirred at room temperature until TLC (9:1 chloroform/ethanol eluant) showed that all the formimide that had disappeared (usually 3 to 4 h) and the catalyst recovered by filtration, was washed with ethanol (10 mL), dried at room temperature and reused four times for the same reaction. The amides were isolated by filtration and the filtrate was evaporated to furnish the crude product which was further purified by usual crystallization procedure in absolute ethanol. The most cases the products 2a-d were pale green to white.

The selected spectral data

(2-Chlorobenzyl)-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine 2a: m.p. 108-110 °C (decomp.). Yield 92%. 1H NMR (300 MHz, DMSO-d6, TMS Int. Ref. ppm) δ: 4.58 (d, 2H, JNH = 6.5Hz, H6), 6.80 (s, 2H, NH2), 7.40-7.44 (complex, m, 2H, H11 & H12), 7.45-7.56 (complex, m, 2H, H9 & H10), 7.78 (d, 1H, JNH = 6.5Hz, H5), 8.16-8.24 (br. d, 1H, JNH = 6.5Hz, NH); 13C NMR (75 MHz, DMSO-d6, ppm) δ: 45.9 (C6), 110.0 (C1), 119.1 (C2), 120.1 (C3), 121.4 (C4), 131.2 (C11), 132.9 (C12), 133.0 (C10), 133.5 (C9), 136.6 (C8), 139.7 (C7), 154.5 (C5); [Found: C, 55.5; H, 3.7; N, 27.3; Cl, 13.6. Calc. for C11H8NO4Cl requires C, 55.6; H, 3.8; N, 27.0, Cl, 13.5%]; m/z (FAB) 260 (M+) 65.5%, 259 (M+) 78.4%, 224 (M+Cl) 18.1%, 165 [(M-1-C6H4N2)]+ 100%, 164 (M-C6H4N2)+ 90.8%, 142 (12.12%), 125 (81.8%), 119 (30.3%), 109 (9.0%); IR (Nujol mull, vmax cm⁻¹): 3420 s, 3380 s, 3320 s, 3180 m (NH str.), 3080 s, 2980 m, 2950 s, 2220 s (CN str.), 1655 s (C=C str.), 1580 m (NH bend), 1470 m, 1460 s, 1450 s, 1430 m, 1380 s, 1360 s, 1260 s, 1235 w, 1220 w, 1170 m, 1060 s, 1040 s, 1015 s, 980 w, 950 s, 815 s, 790 m, 760 s.

(3,4-Dimethoxybenzyl)-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine 2b: m.p.124-126 °C (decomp.). Yield 94%. 1H NMR (300 MHz, DMSO-d6, ppm) δ: 3.95 (s, 3H, OCH3), 3.97 (s, 9H, OCH3), 4.68 (d, 2H, JNH = 6Hz, H6), 6.40 (s, 2H, NH2), 6.78-7.02 (m, 3H, H8, H9 & H10), 7.62 (d, 1H, JNH = 6Hz, H5), 8.08-8.16 (br. d, 1H, JNH = 6 Hz, NH); 13C NMR (75 MHz, DMSO-d6, ppm) δ: 34.9 (C8, by DEPT 135), 55.5 and 55.7 (C13 &C14),110.4 (C11), 115.8 and 116.1 (C9, C12), 119.3 and 120.4 (C3 & C4), 121.1 (C2), 124.1 (C8), 135.2 (C7), 152.0 and 152.7 (C10 & C11), 154.4 (C5); [Found: C, 59.2; H, 5.5; N, 24.3. Calc. for C13H12N2O3 C, 58.9: H, 5.3; N, 24.6%]; m/z (EI) 286 (M+) 3.2%, 245 [(M+1)-CH2N2] 1.8%, 168 [(M+1)-C6H4N2] 9.8%, 151 (M-C6H4N2) 100%; IR (Nujol mull, vmax cm⁻¹): 3480 s, 3380 s (NH str.), 2225 s (CN str.), 2205 s (CN str.), 1645 s (C=N str.), 1600 m (NH bend), 1520 m, 1275 s, 1250 m, 1230 w, 1170 s, 1155 w, 1040 s, 980 m, 965 w, 880 s, 850 s, 815 s, 780 s.

(3,4-Dimethoxyphenyl)-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine 2c: m.p.138-140 °C (decomp.). Yield 96%. 1H NMR (300 MHz, DMSO-d6, ppm) δ: 3.60 (s, 6H, 2 x OCH3), 6.25 (br. s, 2H, NH2), 6.76 (d, 1H, JNH = 8.5Hz, H8), 7.45-7.70 (br. Complex, m, 3H, H7, H11 & H5), 9.70 (br. s, 1H, NH); 13C NMR (75 MHz, DMSO-d6, ppm) δ: 59.4 and 59.7 (C12 &C13), 110.0 (C11), 116.0 (C7), 116.3 (C8), 116.6 (C11), 119.0 and 120.0 (C3 & C4), 122.5 (C2), 137.1 (C6), 149.0 (C5), 153.0 and 153.3 (C9 &C10); [Found: C, 57.9; H, 4.8; N, 25.4. Calc. for C19H13N2O2 C, 57.6; H, 4.8; N, 25.8%]; m/z (EI) 272 (M+) 89.8%, 271 (M-1) 47.8%, 270 (M-2) 11.0%, 244 [(M-1)-(CN)] 32.9%, 164 [(M-1)-C6H4N2] 37.6%; IR (Nujol mull, vmax cm⁻¹): 3470 s, 3340 s, 3235 s (NH str.), 2230 s (CN str.), 2195 s (CN str.), 1640 m (C=N str.), 1600 m (NH bend), 1580 s, 1510 s, 1300 s, 1255 s, 1230 s, 1165 s, 1145 s, 1130 s, 1025 s, 965 w, 935 s, 830 s, 795 s, 765 s.

(4-Methoxyphenyl)-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine 2d: m.p. 123-124 °C (decomp.). Yield 93%. 1H NMR (300 MHz, DMSO-d6, ppm) δ: 3.78 (s, 3H, OCH3), 6.40 (br. s, 2H, NH2), 6.92 (d, 2H, JNH = 8Hz, H8 & H10), 7.42-7.90 (br. Complex, m, 3H, H7, H11 & H5), 9.90 (br. s, 1H, NH); 13C NMR (75 MHz, DMSO-d6, ppm) δ: 59.1 (C12),109.0 (C1), 118.1 (C8 & C10), 118.8 and 119.9 (C3 & C4), 122.3 (C2), 124.5 (C7 & C11), 136.6 (C6), 150.9 (C5), 159.1 (C9); [Found: C, 59.7; H, 4.5; N, 28.7. Calc. for C11H13N2O2 C, 59.8; H, 4.6; N, 29.0%]; m/z (El) 242 (M+1) 100%, 241 (M+) 2.8%, 215 (M-CN) 40.9%, 136 [(M+1)-C6H4N2] 4.9%, 124 [(M-1)-C6H4N2] 44.9%, 108 [(M-1)-C6H4N2] 4.3%; IR (Nujol mull, vmax cm⁻¹):3470 w, 3450 s, 3345 s, 3300 m, 3250 s, 3120 m (NH str.), 2215 s.
Imidate 1 was prepared from diaminomaleonitrile and triethyl orthoformate in refluxing dry dioxane to give formimidate in 84% yield according to the procedure described in the patent literature [18] (Scheme 1). In our hands we have obtained 94% yields for this reaction. The pure imidate 1 is obtained as white needle-shaped crystals from dichloromethane and petroleum ether and has been characterized.

The $^1$H NMR spectrum showed the presence of the ethyl protons with the expected pattern and the NH$_2$ and CH protons as singlets at 8.70 and 7.98 ppm respectively. In the $^{13}$C NMR spectrum two peaks were observed due to the two cyano groups at δ=118.8 and 118.7 ppm and in the infrared spectrum the CN vibrations are seen as strong absorptions at 2220 and 2200 cm$^{-1}$.

Having obtained the imidate 1 in good yield it was then treated with arylamine and benzylamine in a 1:1 molar ratio with SSA as an efficient and reusable heterogeneous catalyst [13-17] for this reaction (Scheme 2) (Table 1). The reaction mixture was stirred under an inert atmosphere at room temperature. A homogeneous solution was obtained and within 20 minutes a white solid precipitated out. The product was filtered off after 3-4 hours. It was washed with diethyl ether and was found be pure by TLC, $^1$H NMR, $^{13}$C NMR and IR spectroscopy.

The elemental analysis results of amidine 2 were satisfactory. The mass spectrum showed a peak at $m/z$ 260, 286, 272 and 242 for 2a, 2b, 2c and 2d, respectively.

### Table 1. Structures of formamidine (2a-d) with the usage of amines and imidate in the presence of SSA.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (imidate)</th>
<th>amine</th>
<th>Product formamidine (2a-f)</th>
<th>m.p. (°C)</th>
<th>Reaction Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H$_2$N=N=H</td>
<td></td>
<td>H$_2$N=N=H</td>
<td>108-110</td>
<td>240</td>
<td>92</td>
</tr>
<tr>
<td>b</td>
<td>H$_2$N=N=H</td>
<td>Cl</td>
<td>H$_2$N=N=H</td>
<td>124-126</td>
<td>150</td>
<td>94</td>
</tr>
<tr>
<td>c</td>
<td>H$_2$N=N=H</td>
<td></td>
<td>H$_2$N=N=H</td>
<td>138-140</td>
<td>180</td>
<td>96</td>
</tr>
<tr>
<td>d</td>
<td>H$_2$N=N=H</td>
<td>Cl</td>
<td>H$_2$N=N=H</td>
<td>123-124</td>
<td>220</td>
<td>93</td>
</tr>
</tbody>
</table>
Initial fragmentation, involve loss of the amidine segment (M-C_5H_4N_5)⁺. The ¹H NMR spectra of compound 2a and 2b in [¹H_6]dimethyl sulfoxide ([¹H_6]DMSO) had some interesting features. The two benzylic protons (H_6) appeared as a doublet at δ=4.58 and 4.68 ppm respectively, caused by a coupling to the NH proton which appeared as a broad doublet at δ8.08-8.16 ppm. The HC=N proton was also a doublet (J_H,NH 6.0-6.5 Hz), at δ7.62-7.78 ppm and showed a small additional coupling (<1Hz) to the benzylic protons. The fact that the HC=N and the benzylic protons are coupled to NH was also confirmed by D_2O exchange, after which the two doublets (HC=N & CH_2) appeared as sharp singlets. The ¹³C NMR spectrum show two peaks of relatively low intensity at δ1118.8-120.1 and δ1199.9-121.4 ppm due to the two cyano groups and a peak due to HC=N at δ149.0-154.5 ppm in the amidine molecule. The infrared spectrum of amidine 2a-d showed two strong absorption in the region 2195-2230 cm⁻¹ characteristic of CN stretching vibrations, together with an NH and a C=N stretching vibration at 3480-3120 and 1655-1640 cm⁻¹ respectively.

4. Conclusion

In summary, an efficient protocol for the preparation of formamidines derivatives was described. The reactions were carried out at room temperature and produce the corresponding products in good to excellent yield. Also the catalyst could be successfully recovered and reusable.

Acknowledgments

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

References