

## 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 amidines **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. Shriner 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

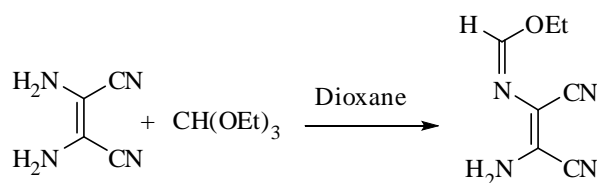
High-resolution <sup>1</sup>H NMR (500 MHz), <sup>13</sup>C NMR (125 MHz)

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<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O)

A mixture of diaminomaleonitrile (1g, 9.25 mmol) and triethyl orthoformate (1.37 mL, 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 recrystallised 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<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O: C, 51.2; H, 4.9; N, 34.1%]; *m/z* (EI) 165 (M+1)<sup>+</sup> 94.2%, 119 (M-OC<sub>2</sub>H<sub>5</sub>)<sup>+</sup>

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Scheme 1.

32.9%, 81 [(M+1)-C<sub>4</sub>H<sub>6</sub>NO]<sup>+</sup> 96.3%, 29 [(M+1)-C<sub>6</sub>H<sub>6</sub>N<sub>3</sub>O]<sup>+</sup> 100%;  $\delta_{\text{H}}$  (300 MHz, d<sub>6</sub>-DMSO) 1.30 (t, 3H, <sup>3</sup>J<sub>6,7</sub> 7Hz, H7), 4.30 (q, 2H, <sup>3</sup>J<sub>7,6</sub> 7Hz, H6), 7.00 (br. s, 2H, NH<sub>2</sub>), 7.97 (s, 1H, H5) ppm;  $\nu_{\text{max}}$  (Nujol mull) 3410 m, 3300 s, 3160 m (N-H str.), 2220 s, 2200 s (C≡N str.), 1600 m (N-H bend), 1470 m, 1360 s, 1260 m, 1130 s, 800 m and 750 m cm<sup>-1</sup>.

## 2.2. General procedure for the preparation of the *N*-Aryl-*N'*-[2-amino-1,2-dicyanovinyl]formamidines 2a-d.

The aromatic amines (1.01g, 6.07 mmol) were added to a suspension of **1** (1.00 g, 6.09 mmol) in dry ethanol, which contained silica sulfuric acid as 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 formimidate had disappeared (usually 3 to 4h) 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 amidines 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

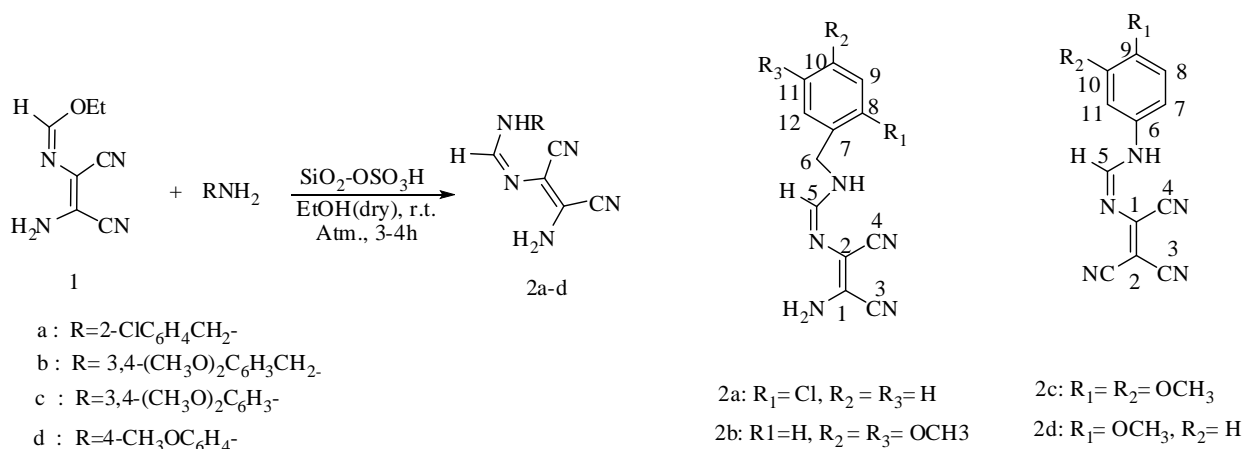
(2-Chlorobenzyl)-(Z)-*N*-[2-amino-1,2-dicyanovinyl]formamidine 2a: m.p. 108-110 °C (decomp.). Yield 92%. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, TMS Int. Ref. ppm)  $\delta$ : 4.58 (d, 2H, <sup>3</sup>J<sub>6,NH</sub> = 6.5Hz, H6), 6.80 (s, 2H, NH<sub>2</sub>), 7.40-7.44 (complex, m, 2H, H11 & H12), 7.45-7.56 (complex, m, 2H, H9 & H10), 7.78 (d, 1H, <sup>3</sup>J<sub>5,NH</sub> = 6.5Hz, H5), 8.16-8.24 (br. d, 1H, <sup>3</sup>J<sub>NH,5</sub> = 6.5Hz, NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, ppm)  $\delta$ : 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 C<sub>12</sub>H<sub>10</sub>N<sub>5</sub>Cl requires C, 55.6; H, 3.8; N, 27.0, Cl, 13.5 %]; m/z (FAB) 260 (M+1)<sup>+</sup> 65.5%, 259 (M)<sup>+</sup> 78%, 224 (M-Cl)<sup>+</sup> 18.2%, 165 [(M-1)-C<sub>4</sub>H<sub>3</sub>N<sub>3</sub>]<sup>+</sup> 100%, 164 (M-C<sub>4</sub>H<sub>4</sub>N<sub>3</sub>)<sup>+</sup> 90.8%, 142 (12.12%), 125(81.8%), 119 (30.3%), 109 (9.0%); IR (Nujol mull,  $\nu_{\text{max}}$  cm<sup>-1</sup>): 3420 s, 3380 s, 3320 s, 3180 m (NH str.), 3000 m, 2980 m, 2950 m, 2220 s (CN str.), 2200 s (CN str.), 1655 s (C=N 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%. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, ppm)  $\delta$ : 3.95 (s, 3H,

OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.68 (d, 2H, <sup>3</sup>J<sub>6,NH</sub> = 6Hz, H6), 6.40 (s, 2H, NH<sub>2</sub>), 6.78-7.02 (m, 3H, H8, H9 & H12), 7.62 (d, 1H, <sup>3</sup>J<sub>5,NH</sub> 6Hz, H5), 8.08-8.16 (br. d, 1H, <sup>3</sup>J<sub>5,NH</sub> = 6 Hz, NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, ppm)  $\delta$ : 43.9 (C6, by DEPT 135), 55.5 and 55.7 (C13 & C14), 110.4 (C1), 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 C<sub>14</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub> C, 58.9; H, 5.3; N, 24.6 %]; m/z (EI) 286 (M+1)<sup>+</sup> 3.2%, 245 [(M+1)-CH<sub>2</sub>N<sub>2</sub>]<sup>+</sup> 1.8%, 168 [(M+1)-C<sub>5</sub>H<sub>2</sub>N<sub>4</sub>]<sup>+</sup> 9.8%, 151 (M- C<sub>5</sub>H<sub>4</sub>N<sub>5</sub>)<sup>+</sup> 100%; IR (Nujol mull,  $\nu_{\text{max}}$  cm<sup>-1</sup>): 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%. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, ppm)  $\delta$ : 3.60 (s, 6H, 2 x OCH<sub>3</sub>), 6.25 (br. s, 2H, NH<sub>2</sub>), 6.76 (d, 1H, <sup>3</sup>J<sub>8,7</sub> = 8.5Hz, H8), 7.45-7.70 (br. Complex, m, 3H, H7, H11 & H5), 9.70 (br.s, 1H, NH), <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, ppm)  $\delta$ : 59.4 and 59.7 (C12 & C13), 110.0 (C1), 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 C<sub>13</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub> C, 57.6; H, 4.8; N, 25.8 %]; m/z (EI) 272 (M+1)<sup>+</sup> 8.9%, 271 (M)<sup>+</sup> 47.8%, 270 (M-1)<sup>+</sup> 11.0%, 244 [(M-1)-CN]<sup>+</sup> 32.9%, 164 [(M-1)-C<sub>4</sub>H<sub>2</sub>N<sub>4</sub>]<sup>+</sup> 37.6%; IR (Nujol mull,  $\nu_{\text{max}}$  cm<sup>-1</sup>): 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%. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, ppm)  $\delta$ : 3.78 (s, 3H, OCH<sub>3</sub>), 6.40 (br. s, 2H, NH<sub>2</sub>), 6.92 (d, 2H, <sup>3</sup>J<sub>8,7</sub> = 8Hz, H8 & H10), 7.42-7.90 (br. Complex, m, 3H, H7, H11 & H5), 9.90 (br. s, 1H, NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, ppm)  $\delta$ : 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 C<sub>12</sub>H<sub>11</sub>N<sub>5</sub>O C, 59.8; H, 4.6; N, 29.0 %]; m/z (EI) 242 (M+1)<sup>+</sup> 100%, 241 (M)<sup>+</sup> 2.8%, 215 (M-CN)<sup>+</sup> 40.9%, 136 [(M+1)- C<sub>4</sub>H<sub>2</sub>N<sub>4</sub>]<sup>+</sup> 4.9%, 124 [(M+1)-C<sub>5</sub>H<sub>2</sub>N<sub>4</sub>]<sup>+</sup> 44.9%, 108 [(M+1)- C<sub>5</sub>H<sub>4</sub>N<sub>5</sub>]<sup>+</sup> 4.3%; IR (Nujol mull,  $\nu_{\text{max}}$  cm<sup>-1</sup>): 3470 w, 3450 s, 3345 s, 3300 m, 3250 s, 3120 m (NH str.), 2215 s



Scheme 2.

(CN str.), 2195 s (CN str.), 1650 m (C=N str.), 1600 m (NH bend), 1575 w, 1515 m, 1310 s, 1290 m, 1245 s, 1220 s, 1175 m, 1030 s, 960 w, 820 s, 785 s.

### 3. Results and discussion

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 by recrystallisation from dichloromethane and petroleum ether and has been characterized.

The <sup>1</sup>H NMR spectrum showed the presence of the ethyl protons with the expected pattern and the NH<sub>2</sub> and CH protons as singlets at δ7.00 and 7.98 ppm respectively. In the <sup>13</sup>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<sup>-1</sup>.

Having obtained the imidate **1** in good yield it was then treated with arylamine and benzylamine in a 1:1 molar ratio in ethanol in the presence of a catalytic amount of silica sulfuric acid 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 to be pure by TLC, <sup>1</sup>H NMR, <sup>13</sup>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 formamidines (**2a-d**) with the usage of amines and imidate in the presence of SSA.

Entry	Substrate (imidate)	amine	Product formamidines (2a-f)	m.p. (°C)	Reaction Time (min)	Yield (%)
a				108-110	240	92
b				124-126	150	94
c				138-140	180	96
d				123-124	220	93

Initial fragmentation, involve loss of the amidine segment ( $M-C_5H_4N_5$ )<sup>+</sup>. The <sup>1</sup>H NMR spectra of compound **2a** and **2b** in [<sup>2</sup>H<sub>6</sub>]dimethyl sulfoxide ([<sup>2</sup>H<sub>6</sub>]DMSO) had some interesting features. The two benzylic protons (H<sub>6</sub>) 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*<sub>H,NH</sub> 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<sub>2</sub>O exchange, after which the two doublets (HC=N & CH<sub>2</sub>) appeared as sharp singlets. The <sup>13</sup>C NMR spectrum show two peaks of relatively low intensity at δ118.8-120.1 and δ119.9-121.4 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<sup>-1</sup> characteristic of CN stretching vibrations, together with an NH and a C=N stretching vibration at 3480-3120 and 1655-1640 cm<sup>-1</sup> 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.

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