# 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 (-$SO_3H$), P-Toluene sulfonic acid (PTSA), aluminium chloride ($AlCl_3$), ceric ammonium nitrate (CAN), anilinium chloride ($C_6H_5NH_3^+Cl^-$), Montmorillonite (K10), silica sulfuric acid ($SiO_2$-$OSO_3H$), 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.

Corresponding author*
Asieh Yahyazadeh
Fax: +98-131-3233262
E-Mail: yahyazadehphd@yahoo.com
[a] Department of Chemistry, College of Science, University of Guilan, Rasht, P. O. Box 41335-1914, Iran

## Introduction

Amidines have long been regarded as valuable intermediates in the synthesis of heterocyclic compounds.[1,2] 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.[3-6] They possessing anti-degenerative[7] anticancer[8,9] anti-platelet[10] and antimicrobial[11] activities. Amidine derivatives also act as serine protease inhibitors.[12] Very important compounds were prepared from amidines such as imidazole rings,[13] purins[14,15] quinazolines.[16] 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.[17] 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 J-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.

### General procedure for the preparation of imidate as precursor

Imidate was synthesized from the reaction of DAMN with trimethyl orthoformate (1:1) in dry dioxane under reflux for 2 hours. Methanol and dioxane were removed from reaction mixture by distillation as by-product. After cooling at room temperature and filtering, was added 2 mL n-hexane and allowed to stand in refrigerator for 48 hours. Precipitated yellow crystals were filtrated and were recrystallized in $CH_2Cl_2$ and Petroleum ether.

### Imidate

Light yellow needles from petroleum ether/$CH_2Cl_2$ (92%) m.p: 132-133 °C; IR (KBr) ν: 3450($NH_2$), 3300 ($NH_2$), 2900 (C-$H_{aliphatic}$), 2225 (C≡N), 1640 (C=N), 1590 (N-H), 1380 ($CH_3$), 1260 (C-N), 1250 (C-O) $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ: 7.94 (s, 1H), 6.98 (s, 2H), 3.78 (s, 3H) ppm.

### General procedure for the preparation of formamidine

A solution of synthesized imidate with amines was treated in the presence of catalyst amount in the dry ethanol under argon at room temperature. This reaction was continued until the reaction was completed. Residue was concentrated and dried under vacuum to give formamidine.

### (1Z)-N'-((Z)-2-amino-1,2-dicyanovinyl)-N-(4-ethoxy phenyl) formamidine, 2a

Light green solid, (94 %) m.p: 148-150 °C; IR (KBr) ν: 3480 (NH) 3300 (NH), 2980 ($CH_{aromatic}$), 2200 (C≡N), 1660 (N-$H_{bend}$), 1600 (C=C), 1560 (C=N), 1460 ($CH_{3\ bend}$), 1360 ($CH_{2\ bend}$), 1260 (C-N), 1160 (C-O), 820 (C-$H_{\ bend}$) $cm^{-1}$; $^1$H NMR ($CDCl_3$): 9.83 (s, 1H), 7.70 (s, 2H), 6.87 (d, J=5Hz, 2H), 6.37 (s, 2H), 4.00 (s, J=7Hz, 2H), 3.35 (s, 1H), 1.32 (t, J=7Hz, 3H) ppm.

**(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 ($CH_3$ $_{bend}$), 1260 (C-N), 1250 (C-O), 840 (C-H $_{bend}$) $cm^{-1}$; $^1$H NMR ($CDCl_3$): 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 $_{bend}$), 1600(C=C), 1465($CH_3$ $_{bend}$), 850(C-H $_{bend}$), $Cm^{-1}$; $^1$HNMR (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), 3100(C-H $_{aromatic}$), 2950(C-H $_{aliphatic}$), 2200(C≡N), 1640(N-H $_{bend}$), 1600(C=C), 1520 (C=N), 1460($CH_3$ $_{bend}$), 1280 (C-O), 860(C-H $_{bend}$), $Cm^{-1}$; $^1$HNMR ($CDCl_3$): 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 ($CH_3$ $_{bend}$), 1260 (C-N), 1240 (C-O), 830 (C-H $_{bend}$) $cm^{-1}$; $^1$HNMR (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**

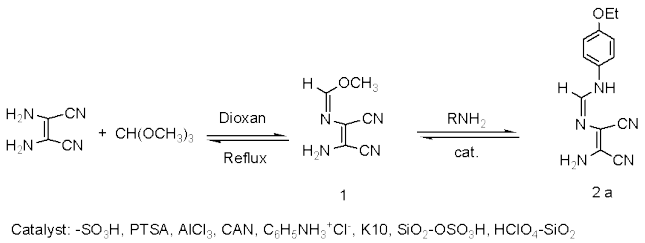
Green solid, (91%) m.p: 144-146 °C; IR (KBr): 3380 (NH), 3360 s (NH.), 2950 (C-H), 2200 (C≡N), 1680 (N-H $_{bend}$), 1600 (C=C), 1500 (C=N), 1440 ($CH_3$ $_{bend}$), 1280 (C-N), 1120 (C-O), 830 (C-H $_{bend}$) $cm^{-1}$; $^1$H NMR ($CDCl_3$): 9.16 (s, 1H), 8.54 (s, 1H), 6.89 (s, 2H), 6.31 (s, 2H), 3.96 (s, 6H, H), 3.94 (s, 3H, H).

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

Green solid, (91%) m.p: 134-136 °C; IR (KBr): 3450 (NH), 3320 s (NH.), 3100 (C-$H_{aromatic}$) 2920 (C-$H_{aliphatic}$), 2200 (C≡N), 1620 (N-H $_{bend}$), 1520 (C=N), 1440 ($CH_3$ $_{bend}$), 1280 (C-N), 735 (C-H $_{bend}$) $cm^{-1}$; $^1$H NMR (DMSO): 8.17 (s, 1H), 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.[18] 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, initial, 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-toluenesulphonic acid (PTSA), $AlCl_3$, ceric ammonium nitrate (CAN),[19] $C_6H_5NH_3^+Cl^-$,[20] K10, $SiO_2$-$OSO_3H$ (SSA), $HClO_4$-$SiO_2$ 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.[21]




**Scheme 1:** synthesis of (1*E*)-*N*'-((*Z*)-2-amino-1,2-dicyanovinyl)-*N*-(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

| Entry | Catalyst | Time, days | Yield, % |
|---|---|---|---|
| 1 | No | 20 | 40 |
| 2 | $-SO_3H$ | - | - |
| 3 | PTSA | 4 | 60 |
| 4 | $AlCl_3$ | 7 | 48 |
| 5 | CAN | 8 | 50 |
| 6 | $C_6H_5NH_3^+Cl^-$ | 3 | 67 |
| **7** | K10 | 1 | 70 |
| **8** | $HClO_4$- $SiO_2$ | 3 | 58 |
| **9** | $SiO_2$-$OSO_3H$ | 0.083 (2 h) | 87 |

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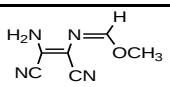
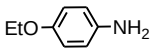
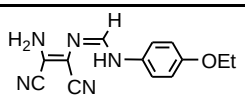
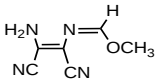
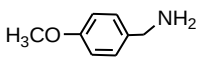
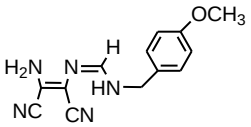
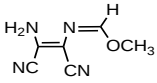
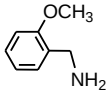
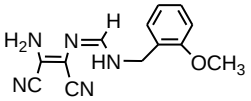
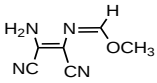
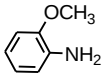
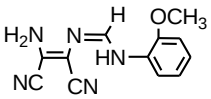
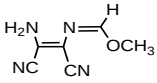
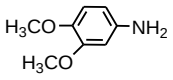
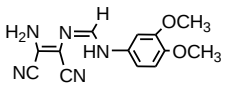
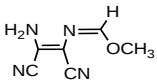
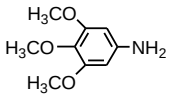
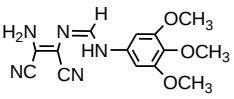
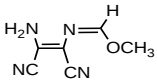
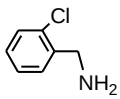
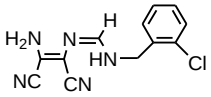
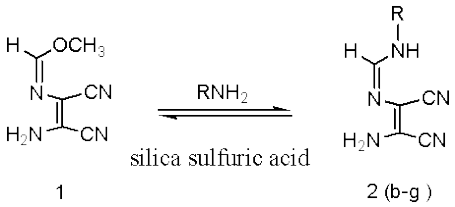
**Table 2.** Synthesis of formamidine with the usage of amines and imidate in the presence of SSA

| Entry | compd. | Imidate | Amine | Formamidine | Time, min | M. P.,°C | Yield,% |
|---|---|---|---|---|---|---|---|
| 1 | 2a |  |  |  | 120 | 148-150 | 94 |
| 2 | 2b |  |  |  | 135 | 150-152 | 87 |
| 3 | 2c |  |  |  | 130 | 148-150 | 86 |
| 4 | 2d |  |  |  | 140 | 138-140 | 90 |
| 5 | 2e |  |  |  | 110 | 142-144 | 94 |
| 6 | 2f |  |  |  | 115 | 144-146 | 91 |
| 7 | 2g |  |  |  | 165 | 134-136 | 91 |

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.




**Scheme 2.** synthesis of formamidines from imidate in the presence of silica sulfuric acid.

All of synthesized compounds were characterized by TLC, IR, $^1$H NMR. The IR vibrations of imidate showed $NH_2$ at about 3450 cm$^{-1}$, 3300 cm$^{-1}$ and the cyano at about 2225 cm$^{-1}$ and stretching vibration of C=N at about 1640 cm$^{-1}$. The other band were observed in expected place . Furthermore, $^1$H NMR of imidate revealed proton of the N=CH as a singlet peak in the region of δ7.94 ppm. The protons of the $NH_2$ appeared in singlet pattern in δ 6.98 ppm. Protons of $OCH_3$ were seen as a singlet peak in the region of δ3.78 ppm.

The infrared spectrum of (**2a-g**) confirmed the presence of the $NH_2$ and C≡N stretching vibration within the region of 3300-3480 and 2200 cm$^{-1}$ and C=C appeared at about 1600 cm$^{-1}$. The $^1$H NMR spectra showed proton of the NH in the range of δ8.17-9.83 ppm. Proton of N=CH was seen in 7.70-8.54. The protons of the aromatic rings were revealed in expected place. The protons of the $NH_2$ were seen at the region of δ 4-6.31ppm.

## Conclusions

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.

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