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Unexpected formation of *N*,*N*-disubstituted formamidines from aromatic amines, formamides and trifluoroacetic anhydride

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Abstract—An intriguing selectivity towards the formation of the formamidine was observed upon the reaction of an amine with sodium hydride and trifluoroacetic anhydride in dimethyl formamide. Various aromatic amines were reacted with a series of *N*,*N*-disubstituted formamides as a solvent under the influence of trifluoroacetic anhydride to thoroughly probe this behaviour. A trend in selectivity is discussed and a proposed mechanism for the reaction is also presented.

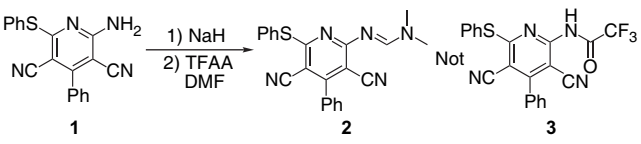
1. Introduction

The preparation of nitrogen-containing compounds such as amidines has been studied extensively owing to their importance as biologically active compounds.[1,2] Classes of compounds containing amidine substructures have found additional application as building blocks in polymer synthesis,[3] bleaching agents for paper,[4] ultraviolet light absorbers[5] and ligands in transition metal catalysis.[6] In the field of organic synthesis, formamidines serve as protecting groups for primary amines,[7] support linkers in solid phase synthesis[8] and auxiliaries in asymmetric synthesis.[9]

In the literature, a great many procedures are reported for the condensation of *N*,*N*-dialkylformamides with primary amines employing $POCl_3$, P_2O_5, PCl_5, $(COCl)_2$, $SOCl_2$ and acyl chlorides as coupling agents.[10–13] However, most of these methods have drawbacks such as low yields,[11] long reaction times,[12] harsh reaction conditions and difficulties in work up.[13] *N*,*N*-Dialkylformamide dimethylacetals are also utilised as the main reagent, in dimethylformamide (DMF), for the direct protection of primary aliphatic and aromatic amines under mild conditions.[14] Recently, Cai and co-workers reported the use of a set of sulfonylchloride coupling agents for DMF, which provided a one-step procedure for the preparation of formamidines from primary amines.[15] Delarue and Sergheraert have found that PyBOP, a well known reagent in peptide synthesis, is a convenient coupling reagent in the synthesis of formamidines from aliphatic and aromatic primary amines and DMF.[11] In this paper, we wish to add to this substantial known body of work a novel, convenient and highly efficient synthesis of a variety of formamidines using trifluoroacetic anhydride (TFAA) as the coupling agent.

2. Results and discussion

During our recent studies on the modification of the amino group present in 2-amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile **1**,[16] we observed that treatment of this amine with sodium hydride (*CAUTION* reacts violently with a proton source and can ignite spontaneously) in DMF, followed by addition of an equimolar amount of TFAA, provided the corresponding *N*′-(3,5-dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N*-dimethylformamidine **2**, instead of the expected *N*-(3,5-dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-2,2,2-trifluoroacetamide **3**, in high yield (Scheme 1).



1 2 3

Scheme 1.

We found that the optimal reaction protocol was to add sodium hydride to a solution of the amine in a minimum volume of anhydrous DMF at room temperature, followed by addition of an equimolar amount of TFAA. Once the

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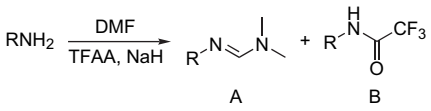
Table 1. Reaction of aromatic and aliphatic amines with DMF in the presence of TFAA



Entry	R	Molar ratio (A:B)[a]	Yield (%)
1	Phenyl	1:5	100
2	Pyrid-2-yl	1:4	100
3	3-Nitropyrid-2-yl	10:7	96
4	4-Methoxyphenyl	B only	100
5	6-Methoxypyrimidin-4-yl	B only	93
6	*C*-Pyridin-3-ylmethyl	B only	95

[a] Molar ratio determined from ^{1}H NMR data.

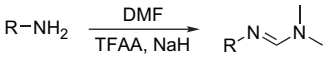
reaction was complete, cold water was added effecting precipitation of the product. Using this protocol the *N*,*N*-dimethylformamidine **2** was isolated in 95–99% yield with >95% purity.

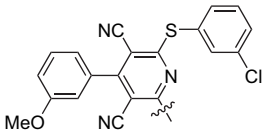
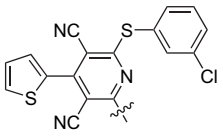
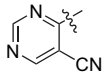
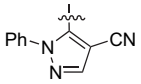
In an attempt to see whether these conditions were applicable to a broader range of starting materials, reactions of a variety of aryl and alkyl amines with DMF under similar conditions were examined (Table 1). The reactions either afforded a mixture of the corresponding formamidine together with the amide (entries 1–3), or gave only the amide (entries 4–6). For example, the reaction of aniline gave a 1:5 mixture of the *N*,*N*-dimethyl-*N*′-phenylformamidine and the *N*-phenyltrifluoroacetamide, respectively (entry 1). When using 2-aminopyridine, a mixture of *N*,*N*-dimethyl-*N*′-2-pyridinylformamidine and 2,2,2-trifluoro-*N*-2-pyridinylacetamide was produced in a 1:4 ratio, respectively (entry 2). However, the use of 2-amino-3-nitropyridine showed the presence of an electron-withdrawing group on the aromatic ring promoted formamidine formation, as a 10:7 ratio of the *N*′-(3-nitropyridinyl)-*N*,*N*-dimethylformamidine/*N*-(3-nitropyridinyl)-trifluoroacetamide mixture was obtained in this case (entry 3). Interestingly, the presence of an electron-donating group bound to the aromatic ring was found to endorse the formation of amide, as in the case of 4-methoxyaniline and 4-amino-6-methoxypyrimidine (entries 4 and 5). 3-(Aminomethyl)-pyridine was also converted into the trifluoroacetamide in excellent yield under identical conditions (entry 6).

To investigate the role of the 3-cyano functionality of amine **1** upon the observed selectivity (Scheme 1), a series of amines having similar structural features were reacted with DMF under optimised conditions (Table 2). In all cases, the corresponding *N*,*N*-dimethyformamidines were obtained in high yield with no detectable formation of the *N*-trifluoroacetamides. The reactions of 4-aminopyrimidine-5-carbonitrile and 5-amino-1-phenylpyrazole-4-carbonitrile (entries 3 and 4), not possessing the pyridine-3,5-dicarbonitrile core, also resulted in exclusive formamidine formation.

In an attempt to broaden the scope of this condensation reaction, we supposed that condensation of amines with various *N*,*N*-dialkylformamides and *N*-alkyl-*N*-arylformamides would also give rise to a range of *N*,*N*-disubstituted amidines (Table 3). Reaction of **1** with *N*,*N*-diethylformamide, pyrrolidine-1-carbaldehyde and piperidine-1-carbaldehyde, proceeded efficiently to afford the corresponding formamidines in excellent yields (entries 2–4). For the more viscous *N*-methyl-*N*-phenyl formamide the reaction also proceeded, producing the corresponding formamidine in satisfactory yield (entry 5).

Table 2. Condensation of aromatic amines with DMF using TFAA

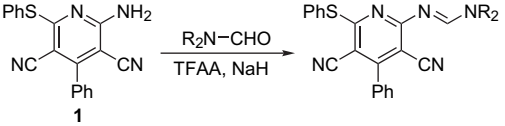


Entry	R	Yield (%)
1		96
2		95
3		99
4		82

The amino group of analogues of **1** also underwent coupling with pyrrolidine-1-carbaldehyde and piperidine-1-carboxaldehyde by this procedure, providing the desired formamidines in good to excellent yields (Table 4, entries 1–4). 4-Aminopyrimidine-5-carbonitrile reacted with *N*,*N*-diethylformamide and pyrrolidine-1-carbaldehyde to give the corresponding formamidines in 77 and 78% yield (Table 5, entries 1 and 2). Additionally, reaction of 5-amino-1-phenylpyrazole-4-carbonitrile with pyrolidine-1-carboxaldehyde furnished the corresponding formamidine in 73% yield (Table 5, entry 4).

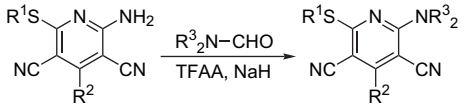
There is considerable experimental evidence indicating that the electrophilic intermediate formed in situ may be attacked by neutral amines as well as by the deprotonated forms. Therefore, we expected that free amines would condense directly with formamides in the presence of TFAA, without the need for deprotonation by NaH, to afford the corresponding

Table 3. Synthesis of formamidines by condensing **1** with various formamides



Entry	R	Yield (%)
1	Me	95–99
2	Et	93
3	–$(CH_2)_4$–	97
4	–$(CH_2)_5$–	90
5	PhMe	67

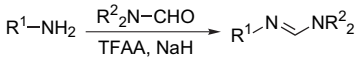
Table 4. Condensation of aromatic amines with various formamides using TFAA

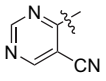
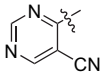
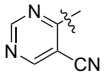
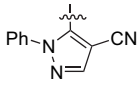


Entry	R^1	R^2	R^3	Yield (%)
1	3-Chlorophenyl	3-Methoxyphenyl	$-(CH_2)_4-$	94
2	3-Chlorophenyl	3-Methoxyphenyl	$-(CH_2)_5-$	77
3	3-Chlorophenyl	Thiophenyl	$-(CH_2)_4-$	93
4	Benzyl	Thiophenyl	$-(CH_2)_4-$	94
5	Phenyl	Phenyl	Methyl	96[a]
6	Benzyl	Thiophenyl	Methyl	91[a]
7	*p*-Benzoic acid methyl ester	*p*-Benzoic acid methyl ester	Methyl	86[a]
8	*p*-Benzoic acid methyl ester	*p*-Benzoic acid methyl ester	$-(CH_2)_4-$	78[a]

[a] Reaction without NaH.

Table 5. Condensation of aromatic amines with various formamides using TFAA



Entry	R^1	R^2	Yield (%)
1		Ethyl	77
2		$-(CH_2)_4-$	78
3		Methyl	79[a]
4		$-(CH_2)_4-$	73

[a] Reaction without NaH.

formamidines preferentially. Examination of the reaction of a variety of amines under such conditions proved this to be correct. We initially examined the reaction of **1** with DMF, in the absence of NaH, as a model system. When the amine (1 equiv) was treated with TFAA (1 equiv) at room temperature in DMF for 20 min, the corresponding *N*,*N*-dimethylformamidine was produced in excellent yield (Table 4, entry 5). The reaction of three other analogues of **1** with DMF under identical conditions afforded the expected formamidines in good to excellent yields (Table 4, entries 6–8). Interestingly, the presence of methyl ester groups in the substrates was found to be well-tolerated under these conditions. 4-Aminopyrimidine-5-carbonitrile could also be converted smoothly into the *N*,*N*-dimethylformamidine using these conditions in good yield (Table 5, entry 3). In all cases, the reaction proceeded without complication, typically taking 20 min to reach completion and producing no detectable amount of *N*-trifluoroacetamide.

These experimental results raise intriguing questions regarding the reaction mechanism. There is evidence that an amide is the only product formed in the reaction of aromatic amines with TFAA in DMF,[7] and the Vilsmeier–Haack like intermediate is the only key intermediate formed in the amidination of certain aromatic amines in DMF using PyBOP[11] and sulfonylchloride[15] coupling agents. It was decided therefore to carry out ^{1}H and ^{13}C NMR spectroscopic experiments to investigate the course of the reaction.

Inspection of the ^{1}H NMR spectrum of DMF in chloroform revealed three sharp singlets at δ=2.60, 2.80 and 7.80 ppm. These signals were due to the two methyl groups attached to the nitrogen atom and the formamide proton, respectively (Fig. 1). After an equimolar amount of TFAA was added, the peaks at δ_H=2.60 and δ_H=2.80 ppm were observed to have begun to merge together. When 2 equiv of TFAA were added, the methyl groups showed as a broad singlet at δ_H=2.65 ppm. It was very interesting to note however, that when this simple investigation was repeated with an equimolar amount or excess of Ac_2O or TFA the three sharp singlets at δ_H=2.60, 2.80 and 7.80 ppm remained unchanged (spectra not shown). Similarly, when observing the ^{13}C NMR spectrum of DMF in chloroform, three sharp peaks at δ_C=30.8, 35.9 and 161.9 ppm were observed (Fig. 2). These signals are due to the two methyl groups attached to the nitrogen atom and formamide carbon, respectively. Again, when TFAA was added, the two peaks corresponding to the methyl carbons broadened and appeared at δ_C=30.5 and 35.7 ppm. From these results it can be concluded that addition of TFAA makes the methyl groups equivalent, indicating an increase in rotational freedom.

Based on experimental results and the ^{1}H and ^{13}C NMR spectroscopic studies reported above, a mechanism for this reaction is proposed (Scheme 2). The condensation seemingly involves in situ generation of a Vilsmeier–Haack like intermediate **4**, which is in equilibrium with the

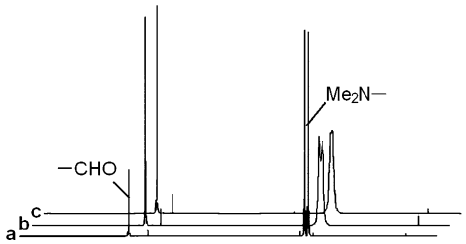


Figure 1. Changes in ^{1}H NMR spectra of (a) DMF, (b) DMF+TFAA (1:1) and (c) DMF+TFAA (1:2) in $CDCl_3$ at room temperature.

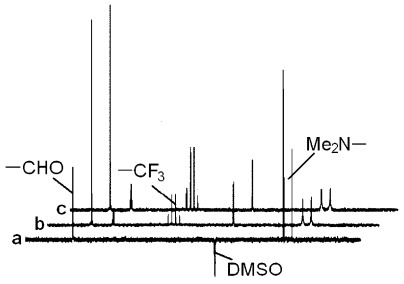
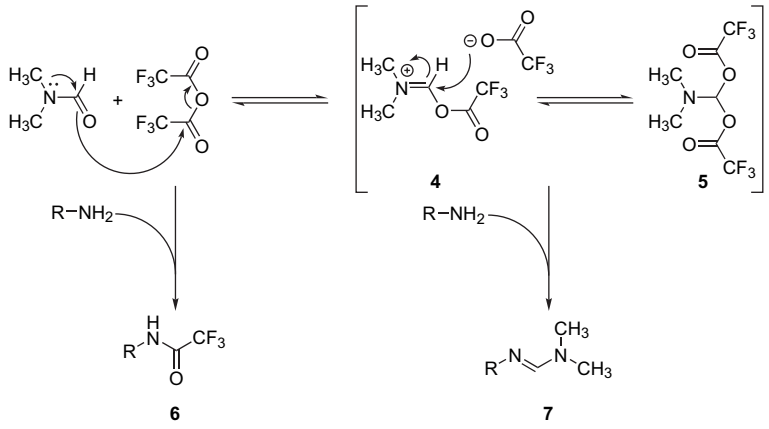


Figure 2. Changes in ^{13}C NMR spectra of (a) DMF, (b) DMF+TFAA (1:1) and (c) DMF+TFAA (1:2) in $CDCl_3$ at room temperature.



Scheme 2.

corresponding trifluoroacetyl acetal intermediate **5**, resulting from attack by a trifluoroacetic anion.[15] This would allow the two methyl groups to equilibrate through free rotation, as observed in the NMR studies. Condensation of these intermediates with an amine gives rise to a single-step synthesis of the corresponding trifluoroacetamide **6**, formamidine **7**, or a mixture of both. As found, the character of the amine nitrogen as well as the nature of the substituents on the body of the amine has a marked effect on the outcome of the reaction. Electron-withdrawing groups, especially carbonitriles in the *ortho*-position, yield amidines preferentially.

3. Conclusion

We have described a simple, convenient and efficient preparation of formamidines from various primary aromatic amines and a series of *N*,*N*-disubstituted formamides in the presence of TFAA. Advantages of the reactions presented include operational simplicity, ease of product isolation, elimination of the use of highly toxic reagents, and excellent product yields. Both the presence of the electron-withdrawing cyano group at the *ortho*-position of the amine and a nitrogen in the aromatic system have a marked effect on the outcome of the final product. However, it appears that DMF is not the solvent of choice if the trifluoroacetamide is the desired product.

4. Experimental

4.1. General details

Melting points were measured with a Bibby-Sterilin SMP10 melting point apparatus and are uncorrected. Infrared analyses were recorded using neat compounds on a Perkin–Elmer Spectrum RX1 FT-IR system equipped with a Dura Sampl*IR* II™—diamond ATR solid sample unit, measuring from 4000 to 400 cm^{-1}. Accurate mass and nominal mass measurements were measured using Waters-Micromass LCT electrospray mass spectrometer. ^1H and ^{13}C NMR analyses were performed on a Bruker AC-250 instrument in DMSO-d_6 or $CDCl_3$; chemical shifts are quoted in parts per million relative to TMS, with coupling constants quoted in Hertz. Analytical thin layer chromatography was performed on pre-coated Macherey–Nagel glass backed silica gel 60 plates (0.25 mm layer), or Merck silica gel 60 F_{254} aluminium backed plates, and visualised by ultraviolet light and potassium permanganate, or ninhydrin stains as appropriate. Commercially available reagents (including dry solvents) were used as received without further purification. Pyridine dicarbonitriles were prepared according to previously reported procedures.[16] All reactions were carried out under a nitrogen atmosphere. Isolated compounds were >95% pure by ^1H NMR analysis unless otherwise stated.

4.2. Synthesis of formamidines

4.2.1. *N*′-(3,5-Dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N*-dimethyl-formamidine (2). To a solution of 2-amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile **1** (50.0 mg, 0.15 mmol) in dry DMF (1.0 mL) was cautiously added sodium hydride (*CAUTION* reacts violently with a proton source and can ignite spontaneously) (7.4 mg, 0.31 mmol) in portions under nitrogen at room temperature. After 1 h stirring at room temperature, trifluoroacetic anhydride (50.0 mg, 0.24 mmol) was added, and the reaction was stirred at room temperature for 10 min until the reaction was deemed complete by TLC. The reaction mixture was poured into cold water (10 mL) and stirred for 5 min, the suspension formed was filtered and the crude product washed sequentially with water (10 mL) and petroleum ether (10 mL). Drying the solid in vacuo gave **2** (55.6 mg, 95% yield) as white powder; mp 216–218 °C; IR (neat) ν_{max} 2217 (s), 1624 (s), 1579 (s), 1525, 1513, 1488, 1140, 1422, 1369, 1299, 1250, 1208, 1135, 1110, 1014, 997, 916, 863, 809 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 2.95 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), 7.40–7.60 (m, 10H, ArH), 8.00 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 35.3, 41.3, 95.6, 95.6, 115.2, 115.7, 128.3, 128.6 (2C), 128.8 (2C), 129.0 (2C), 129.5, 130.5, 133.7 (2C), 136.4, 136.4, 158.2, 163.4, 165.0 ppm; ESMS *m*/*z*: 384 $(M+H)^+$; HRMS found, 384.1283, $C_{22}H_{18}N_5S$ requires 384.1284.

4.2.2. Reaction of aniline (Table 1, entry 1). Upon completion, the reaction mixture was concentrated under reduced pressure. The resultant oily residue was taken up in chloroform, filtered and all volatiles then removed under reduced pressure. Drying in vacuo gave a mixture of *N*,*N*-dimethyl-

N′-phenyl-formamidine and 2,2,2-trifluoro-*N*-phenyl-acetamide (745.8 mg, 1:5, 100%) as a white solid. *N,N-dimethyl-N′-phenyl-formamidine*: mp 87–90 °C; IR (neat) ν_{max} 3316, 3206, 1694, 1601, 1547, 1497, 1451, 1347, 1305, 1283, 1235, 1143, 1070, 1030, 1003, 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.90 (s, 3H, NCH_3), 2.99 (s, 3H, NCH_3), 7.20–7.36 (m, 5H, ArH), 8.01 (s, 1H, N═CHN) ppm; ESMS *m/z*: 149 $(M+H)^+$; HRMS found, 149.1074, $C_9H_{12}N_2$ requires 149.1079. *2,2,2-Trifluoro-N-phenyl-acetamide*: mp 87–90 °C (lit.[17] for acetamide 88–89 °C); IR (neat) ν_{max} 3317, 1700, 1601, 1548, 1497, 1451, 1347, 1307, 1283, 1233, 1169, 1141, 1078, 1030, 1003 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.20–7.36 (m, 3H, ArH), 7.55 (m, 2H, ArH), 8.77 (br s, 1H, $NHCOCF_3$) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.2 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 113.5, 118.10, 121.0, 125.5, 128.9, 129.3, 136.3, 154.1 ppm; EIMS *m/z*: 189 $(M)^+$; HRMS found, 189.041059, $C_8H_6F_3NO$ requires 189.040149.

4.2.3. Reaction of pyridin-2-yl amine (Table 1, entry 2). A mixture of *N,N*-dimethyl-*N*′-pyridin-2-yl-formamidine and 2,2,2-trifluoro-*N*-pyridin-2-yl-acetamide (136.0 mg, 1:4, 100%) was obtained as a colourless oil. *N,N-Dimethyl-N′-pyridin-2-yl-formamidine*: IR (neat) ν_{max} 3331, 3078, 2723, 1670, 1638, 1551, 1486, 1434, 1383, 1329, 1256, 1196, 1176, 1125, 989, 939 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.85 (s, 3H, NCH_3), 2.94 (s, 3H, NCH_3), 6.69 (m, 1H, ArH), 6.79 (m, 1H, ArH), 7.68 (m, 2H, ArH), 8.98 (s, 1H, N═CHN) ppm; ESMS *m/z*: 150 $(M+H)^+$; HRMS found, 150.1034, $C_8H_{12}N_3$ requires 150.1031. *2,2,2-Trifluoro-N-pyridin-2-yl-acetamide*: IR (neat) ν_{max} 3331, 3078, 2723, 1670, 1638, 1551, 1486, 1434, 1383, 1329, 1256, 1196, 1176, 1125, 989, 939 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 1H, ArH), 7.95 (m, 1H, ArH), 8.26 (m, 1H, ArH), 8.35 (d, 1H, *J*=11.2 Hz, ArH), 13.49 (br s, 1H, $NHCOCF_3$) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 111.9, 113.4, 135.90, 143.8, 143.8, 154.5, 159.6 ppm; ESMS *m/z*: 191 $(M+H)^+$; HRMS found, 191.0435, $C_8H_6F_3N_2O$ requires 191.0432.

4.2.4. Reaction of 3-nitro-pyridin-2-yl amine (Table 1, entry 3). A mixture of *N,N*-dimethyl-*N*′-(3-nitro-pyridin-2-yl)-formamidine and 2,2,2-trifluoro-*N*-(3-nitro-pyridin-2-yl)-acetamide (94.3 mg, 10:7, 96% yield) was obtained as a yellowish oil. *N,N-Dimethyl-N′-(3-nitro-pyridin-2-yl)-formamidine*: IR (neat) ν_{max} 3305, 3086, 2843, 1691, 1602, 1545, 1511, 1466, 1444, 1349, 1289, 1223, 1150, 1110, 1022 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.01 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 7.07 (m, 1H, ArH), 7.65 (m, 1H, ArH), 8.50 (m, 1H, ArH), 8.51 (s, 1H, N═CHN) ppm; ESMS *m/z*: 195 $(M+H)^+$; HRMS found, 195.0873, $C_8H_{10}N_4O_2$ requires 195.0882. *2,2,2-Trifluoro-N-(3-nitro-pyridin-2-yl)-acetamide*: ^1H NMR (250 MHz, $CDCl_3$) δ 8.08 (m, 1H, ArH), 8.37 (m, 1H, ArH), 8.61 (d, 1H, *J*=11.0 Hz, ArH), 13.50 (br s, 1H, $NHCOCF_3$) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (235 MHz, $CDCl_3$) δ 123.6, 134.9, 140.3, 140.7, 152.8, 153.5, 158.1 ppm; ESMS *m/z*: 236 $(M+H)^+$; HRMS found, 236.0288, $C_7H_5F_3N_3O_3$ requires 236.0283.

4.2.5. 2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-acetamide (Table 1, entry 4). Obtained as white crystals (171.7 mg, 100%); mp 112–114 °C (lit.,[18] 113–115 °C); IR (neat) ν_{max} 3305, 3086, 2843, 1691, 1602, 1545, 1511, 1466, 1444, 1349, 1289, 1223, 1150, 1110, 1022 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 6.88 (d, 2H, *J*=9.16 Hz, ArH), 7.45 (d, 2H, *J*=9.16 Hz, ArH), 7.92 (br s, 1H, $NHCOCF_3$) ppm (lit.[19] (400 MHz, $CDCl_3$) 3.80 (s, 3H, OCH_3), 6.90 (d, 2H, *J*=8.8 Hz, ArH), 7.46 (d, 2H, *J*=8.8 Hz, ArH), 7.87 (br s, 1H, $NHCOCF_3$)) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.4, 113.5, 114.4 (2C), 122.3 (2C), 127.95, 155.0, 157.8 ppm; EIMS *m/z*: 219 $(M)^+$; HRMS found, 219.050654, $C_9H_8F_3NO_2$ requires 219.050713.

4.2.6. 2,2,2-Trifluoro-*N*-(6-methoxy-pyrimidin-4-yl)-acetamide (Table 1, entry 5). Obtained as a yellowish solid (193.0 mg, 93% yield); mp 121–122 °C; IR (neat) ν_{max} 3441, 3388, 3296, 3148, 3011, 1636, 1589, 1544, 1493, 1468, 1410, 1364, 1297, 1275, 1212, 1029, 988 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.99 (s, 3H, OCH_3), 7.55 (s, 1H, ArH), 8.51 (s, 1H, ArH), 10.18 (br s, 1H, $NHCOCF_3$) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 54.5, 97.0, 107.5, 112.8, 117.4, 155.9, 171.8 ppm; ESMS *m/z*: 222 $(M+H)^+$; HRMS found, 222.0499, $C_7H_6F_3N_3O_2$ requires 222.0481.

4.2.7. 2,2,2-Trifluoro-*N*-pyridin-3-ylmethyl-acetamide (Table 1, entry 6). Obtained as a white solid (113.4 mg, 95%); mp 110–111 °C; IR (neat) ν_{max} 3299, 3171, 3008, 2854, 1706, 1559, 1480, 1432, 1367, 1206, 1182, 1146, 1037, 975 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.50 (d, 2H, *J*=6.1 Hz, $ArCH_2$), 7.28 (m, 1H, ArH), 7.66 (m, 1H, ArH), 8.29 (br s, 1H, $NHCOCF_3$), 8.42 (s, 1H, ArH), 8.44 (m, 1H, ArH) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.2, 113.5, 123.9, 132.3, 136.1, 148.8, 141.1, 157.9 ppm; EIMS *m/z*: 204 $(M)^+$; HRMS found, 204.050552, $C_8H_7F_3N_2O$ requires 204.051048.

4.2.8. *N*′-[6-(3-Chloro-phenylsulfanyl)-3,5-dicyano-4-(3-methoxy-phenyl)-pyridin-2-yl]-*N,N*-dimethyl-formamidine (Table 2, entry 1). Upon completion the reaction mixture was poured into cold water (10 mL) and stirred for 5 min. The precipitate formed was recovered by suction filtration and washed sequentially with water (10 mL) and petroleum ether (10 mL). Drying the solid in vacuo gave the product as a white powder (95.0 mg, 96%); mp 212–214 °C; IR (neat) ν_{max} 3605, 3531, 3076, 2924, 2222, 2206, 1625, 1602, 1578, 1519, 1488, 1456, 1415, 1372, 1327, 1308, 1260, 1228, 1205, 1187, 1170, 1132, 1106, 1038, 1018, 995, 926 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.05 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 7.65–6.95 (m, 8H, ArH), 8.16 (s, 1H, N═CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 35.4, 41.4, 55.4, 96.5, 97.1, 113.8, 115.0, 115.5, 116.6, 120.8, 129.6, 130.0, 130.0, 130.2, 133.8, 134.1, 134.6, 136.2, 157.9, 158.8 (2C), 163.4, 165.1 ppm; ESMS *m/z*: 448 $(M+H)^+$; HRMS found, 448.1005, $C_{23}H_{18}ClN_5OS$ requires 448.0999.

4.2.9. *N*′-[6-(3-Chloro-phenylsulfanyl)-3,5-dicyano-4-thiophen-2-yl-pyridin-2-yl]-*N,N*-dimethyl-formamidine (Table 2, entry 2). Yellowish powder (308.0 mg, 95%); mp 152–161 °C; IR (neat) ν_{max} 3322, 3082, 2918, 2207 (s),

1617, 1495, 1445, 1417, 1398, 1368, 1349, 1310, 1287, 1245, 1223, 1169, 1123, 1099, 1084, 1055, 1029, 994, 910 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.04 (s, 3H, NCH_3), 3.06 (s, 3H, NCH_3), 7.28–7.98 (m, 7H, ArH), 8.07 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 34.9, 41.2, 101.1, 106.8 (2C), 115.1, 115.5, 127.9, 129.1, 129.9, 130.9, 131.4, 132.5, 133.3, 134.2, 135.1, 158.0, 163.2, 164.6 ppm; ESMS *m/z*: 424 $(M+H)^+$; HRMS found, 424.0450, $C_{20}H_{15}N_5SCl$ requires 424.0457.

4.2.10. *N′*-(5-Cyano-pyrimidin-4-yl)-*N*,*N*-dimethyl-formamidine (Table 2, entry 3). Upon completion the reaction mixture was concentrated under reduced pressure, before ice-water (10 mL) was added and the resultant mixture extracted with EtOAc (2×10 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. Drying the solid in vacuo overnight gave the product as pale yellowish crystals (86.9 mg, 99%); mp 128–132 °C; IR (neat) ν_{max} 3269, 3099, 2869, 2811, 27.05, 2224, 1668, 1585, 1549, 1505, 1412, 1364, 1309, 1236, 1202, 1136, 1037, 946, 913 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.15 (s, 3H, NCH_3), 3.30 (s, 3H, NCH_3), 8.80 (s, 1H, ArH), 8.85 (s, 1H, ArH), 8.90 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 34.9, 41.0, 81.0, 100.0, 106.8, 115.6, 157.9, 161.3 ppm; ESMS *m/z*: 176 $(M+H)^+$; HRMS found, 176.0937, $C_8H_9N_5$ requires 176.0936.

4.2.11. 1-Phenyl-5-[(pyrrolidin-1-ylmethylene)-amino]-1*H*-pyrazole-4-carbonitrile (Table 2, entry 4). White solid (104.0 mg, 78% yield); mp 156 °C; IR (neat) ν_{max} 3317, 3104, 3049, 2967, 2872, 2211, 1638, 1609, 1562, 1530, 1502, 1492, 1478, 1455, 1416, 1385, 1325, 1252, 1200, 1174, 1063, 959, 910 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.95 (m, 4H, NCH_2CH_2), 3.45 (t, 2H, *J*=9.5 Hz, NCH_2), 3.55 (t, 2H, *J*=9.5 Hz, NCH_2), 7.25–7.90 (m, 6H, ArH), 8.41 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.3, 25.1, 45.8, 49.2, 116.2, 123.7, 123.9, 126.9, 128.4, 129.5, 129.9, 141.2, 141.8, 152.5, 154.5 ppm; EIMS *m/z*: 266 $(M+H)^+$; HRMS found, 266.1394, $C_{15}H_{17}N_5$ requires 266.1406.

4.2.12. *N′*-(3,5-Dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N*-diethyl formamidine (Table 3, entry 2). Upon completion the reaction mixture was poured into cold water (10 mL) and stirred for 5 min. The precipitate formed was recovered by suction filtration and washed sequentially with water (10 mL) and petroleum ether (10 mL). Drying the solid in vacuo gave the product as a white powder (139.7 mg, 93%); mp 213–215 °C; IR (neat) ν_{max} 3361, 2932, 2748, 2688, 2448, 2270, 2210 (s), 1782, 1720, 1614, 1581, 1537, 1514, 1487, 1451, 1360, 1326, 1255, 1217, 1171, 1121, 1051, 1035, 1018, 997 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (2t, 6H, *J*=8.0 Hz, $N(CH_2CH_3)_2$), 3.25 (q, 2H, *J*=8.0 Hz, NCH_2CH_3); 3.50 (q, 2H, *J*=8.0 Hz, NCH_2CH_3); 7.45–7.65 (m, 10H, ArH), 8.05 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.0, 14.4, 38.5, 40.9, 46.7, 75.0, 98.5, 99.0, 112.6, 115.1, 115.4, 125.0, 127.0, 128.5, 128.7, 129.3, 129.9, 130.3, 133.8, 136.0, 157.1, 158.5, 163.1, 165.1 ppm; ESMS *m/z*: 412 $(M+H)^+$; HRMS found, 412.1606, $C_{24}H_{22}ClN_5S$ requires 412.1596.

4.2.13. 4-Phenyl-2-phenylsulfanyl-6-[(pyrrolidin-1-ylmethylene)-amino]-pyridine-3,5-dicarbonitrile (Table 3, entry 3). Pale yellowish powder (123.0 mg, 97%); mp 228–231 °C; IR (neat) ν_{max} 3056, 2965, 2872, 2350, 2340, 2205, 1612, 1578, 1514, 1489, 1450, 1408, 1370, 1328, 1305, 1247, 1220, 1183, 1157, 1111, 1031, 1010, 986, 963 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 1.85 (t, 4H, *J*=7.5 Hz, CH_2CH_2), 3.50 (t, 4H, *J*=7.5 Hz, NCH_2), 7.55 (m, 10H, ArH), 8.15 (s, 1H, N=CH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.8, 46.5, 49.7, 97.7 (2C), 107.4, 115.3, 115.8, 128.3, 128.6 (2C), 128.8 (2C), 128.9, 129.4, 130.5, 133.7, 136.3 (2C), 154.8, 158.8, 163.4, 166.3 ppm; ESMS *m/z*: 410 $(M+H)^+$; HRMS found, 410.1446, $C_{24}H_{20}N_5O_2S$ requires 410.1439.

4.2.14. 4-Phenyl-2-phenylsulfanyl-6-[(piperidin-1-ylmethylene)-amino]-pyridine-3,5-dicarbonitrile (Table 3, entry 4). A mixture of two isomers was obtained as a white powder (139.0 mg, 90%); mp 196–197 °C; IR (neat) ν_{max} 3060, 2943, 2856, 2211 (s), 1721, 1664 (s), 1603, 1578, 1517, 1485, 1468, 1435, 1407, 1380, 1358, 1295, 1247, 1223, 1202, 1131, 1111, 1078, 1026, 997, 951, 921, 852 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) major isomer δ 1.65 (m, 6H, $CH_2CH_2CH_2$), 3.15 (t, 2H, *J*=6.4 Hz, NCH_2), 3.75 (t, 2H, *J*=6.4 Hz, NCH_2), 7.50–7.60 (m, 10H, ArH), 8.50 (s, 1H, N=CHN) ppm; (minor isomer) δ 1.60 (m, 6H, $CH_2CH_2CH_2$), 3.27 (t, 2H, *J*=6.4 Hz, NCH_2), 3.50 (t, 2H, *J*=6.4 Hz, NCH_2), 7.50–7.60 (m, 10H, ArH), 8.50 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.1, 24.7, 25.0, 26.6, 40.6, 44.5, 46.8, 52.0, 97.6 (2C), 115.3, 115.8, 128.0, 128.3, 128.6, 128.8, 128.9, 129.4, 130.5, 133.7, 136.4, 136.4, 156.6, 158.8, 163.7, 166.3 ppm; ESMS *m/z*: 424 $(M+H)^+$; HRMS found, 424.1581, $C_{25}H_{22}N_5S$ requires 424.1596.

4.2.15. *N′*-(3,5-Dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*-methyl-*N*-phenyl-formamidine (Table 3, entry 5). Yellowish solid (91.6 mg, 68%); mp 245–247 °C; IR (neat) ν_{max} 3051, 2216 (s), 1621, 1606 (s), 1584, 1546, 1515, 1488, 1441, 1419, 1349, 1309, 1283, 1252, 1211, 1117, 1039, 1017, 998, 979, 912, 823, 800, 790, 761 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.50 (s, 3H, NCH_3), 7.15–7.60 (m, 15H, ArH), 8.55 (s, 1H, N=CHN) ppm; ^{13}C NMR (250 MHz, $CDCl_3$) δ 15.2, 35.2, 65.8, 98.8, 98.9, 114.9, 115.5, 121.0, 126.5, 127.7, 128.6, 128.7, 128.9, 129.0, 129.2, 129.3, 129.5, 129.6, 129.9, 130.7, 130.9, 133.4, 135.7, 136.3, 143.4, 156.7, 163.3 ppm; ESMS *m/z*: 468 $(M+Na)^+$; HRMS found, 468.1240, $C_{27}H_{19}N_5SNa$ requires 468.1259.

4.2.16. *N′*-(5-Cyano-pyrimidin-4-yl)-*N*,*N*-diethyl-formamidine (Table 5, entry 1). Upon completion the reaction mixture was concentrated under reduced pressure, before ice-water (10 mL) was added and the resultant mixture extracted with EtOAc (2×10 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. Drying the solid in vacuo overnight gave the product as yellowish crystals (156.0 mg, 77%); mp 152–154 °C; IR (neat) ν_{max} 3060, 2943, 2211 (s), 1664, 1603 (s), 1517, 1485, 1468, 1380, 1326, 1295, 1247, 1223, 1202, 1131, 1111, 1078, 1026, 997, 951 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (m, 6H, $N(CH_3)_2$), 3.45 (q, 2H, *J*=7.5 Hz, NCH_2), 3.70 (q, 2H, *J*=7.5 Hz, NCH_2), 8.55 (s, 1H, ArH), 8.70 (s, 1H, ArH), 8.80 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.2, 14.4, 41.0, 47.1,

101.6, 115.5, 156.3, 160.8, 167.6 ppm; ESMS *m/z*: 204 $(M+H)^+$; HRMS found, 204.1244, $C_{10}H_{14}N_5$ requires 204.1249.

4.2.17. 4-[(Pyrrolidin-1-ylmethylene)-amino]-pyrimidine-5-carbonitrile (Table 5, entry 2). Yellowish solid (81.4 mg, 78%); mp 164–166 °C; IR (neat) ν_{max} 3276, 3098, 2872, 2705, 2225, 1668, 1586, 1550, 1506, 1412, 1366, 1310, 1236, 1201, 1136, 1037, 946, 914, 833 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.85 (m, 4H, CH_2CH_2), 3.60 (t, 2H, J=6.5 Hz, NCH_2), 3.75 (t, 2H, J=6.5 Hz, NCH_2), 8.85 (s, 1H, N=CHN), 8.90 (s, 1H, ArH), 9.04 (s, 1H, ArH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.8, 24.4, 89.8, 99.6, 113.7, 115.3, 155.2, 158.1, 159.2, 166.8 ppm; ESMS *m/z*: 202 $(M+H)^+$; HRMS found, 202.1091, $C_{10}H_{12}N_5$ requires 202.1093.

4.2.18. *N*′-(4-Cyano-2-phenyl-2*H*-pyrazol-3-yl)-*N*,*N*-dimethyl-formamidine (Table 5, entry 4). White solids (98.6 mg, 82%); mp 144–147 °C; IR (neat) ν_{max} 3229, 3008, 2919, 2207, 1749, 1624, 1591, 1526, 1509, 1492, 14.52, 14.16, 1406, 1309, 1340, 1259, 1200, 1155, 1116, 1087, 1062, 1022, 991, 958 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 2.95 (s, 3H, NCH_3), 3.10 (s, 3H, NCH_3), 7.25–7.80 (m, 5H, ArH), 8.00 (s, 1H, ArH), 8.25 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 35.7, 40.1, 78.2, 115.6, 123.2, 123.8, 126.8, 128.6, 129.5, 138.5, 141.8, 154.8, 156.6 ppm; EIMS *m/z*: 239 $(M)^+$; HRMS found, 239.1175, $C_{13}H_{13}N_5$ requires 239.1170.

4.2.19. 2-(3-Chloro-phenylsulfanyl)-4-(3-methoxy-phenyl)-6-[(pyrrolidin-1-ylmethylene)-amino]-pyridine-3,5-dicarbonitrile (Table 4, entry 1). Upon completion the reaction mixture was poured into cold water (10 mL) and stirred for 5 min. The precipitate formed was recovered by suction filtration and washed sequentially with water (10 mL) and petroleum ether (10 mL). Drying the solid in vacuo gave the product as a pale yellowish powder (115.9 mg, 96%); mp 172–175 °C; IR (neat) ν_{max} 3082, 2973, 2221 (s), 1610 (s), 1575 (s), 1520, 1508, 1488, 1450, 1428, 1369, 1328, 1307, 1289, 1236, 1214, 1186, 1154, 1118, 1037, 994, 964 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.65–2.15 (m, 4H, CH_2CH_2), 3.35–3.70 (m, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 6.90–7.50 (m, 7H, ArH), 7.65 (s, 1H, ArH), 8.34 (s, 1H, N=CHN) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 24.3, 24.9, 43.1, 46.7, 49.9, 97.3, 97.8, 115.4, 115.9, 127.8, 129.2, 129.6, 130.0 (2C), 130.1, 131.2, 133.0, 133.7, 134.1, 136.2, 137.8, 151.1, 154.6, 163.7, 165.5 ppm; ESMS *m/z*: 474 $(M+H)^+$; HRMS found, 474.1138, $C_{25}H_{21}ClN_5OS$ requires 374.1155.

4.2.20. 2-(3-Chloro-phenylsulfanyl)-4-(3-methoxy-phenyl)-6-[(piperidin-1-ylmethylene)-amino]-pyridine-3,5-dicarbonitrile (Table 4, entry 2). A mixture of two isomers was obtained as a white powder (95.1 mg, 77%); mp 185–186 °C; IR (neat) ν_{max} 3480, 3330, 3213 (s), 2215, 1635 (s), 1610, 1518, 1384, 1243, 994, 775 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) (major isomer) δ 1.60 (m, 6H, $CH_2CH_2CH_2$), 3.22 (t, 2H, J=4.8 Hz, NCH_2), 3.72 (t, 2H, J=4.8 Hz, NCH_2), 7.60 (m, 8H, ArH), 8.10 (s, 1H, N=CHN) ppm; (minor isomer) δ 1.74 (m, 6H, $CH_2CH_2CH_2$), 3.40 (t, 2H, J=4.8 Hz, NCH_2), 3.66 (t, 2H, J=4.8 Hz, NCH_2), 7.60 (m, 8H, ArH), 7.92 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.1, 25.6, 26.7, 40.0, 44.7, 46.8, 52.2, 55.4, 97.6, 113.8, 115.0, 115.6, 116.6, 120.8, 129.5, 130.0, 130.2, 133.8, 134.1, 134.7, 136.1, 156.3, 158.8, 159.5, 163.7, 165.0 ppm; ESMS *m/z*: 488 $(M+H)^+$; HRMS found, 488.1300, $C_{26}H_{23}ClN_5OS$ requires 488.1312.

4.2.21. 2-(3-Chloro-phenylsulfanyl)-6-[(pyrrolidin-1-ylmethylene)-amino]-4-thiophen-2-yl-pyridine-3,5-dicarbonitrile (Table 4, entry 3). Pale yellow powder (95 mg, 77%); mp 214–216 °C; IR (neat) ν_{max} 3083, 2966, 2870, 2204 (s), 1660, 1606 (s), 1574, 1527, 1439, 1399, 1367, 1350, 1323, 1300, 1245, 1229, 1152, 1113, 1070, 1029, 993, 965 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.88 (m, 4H, CH_2CH_2); 3.48 (m, 4H, NCH_2), 7.29 (m, 1H, ArH), 7.62 (m, 4H, ArH), 7.78 (m, 1H, ArH), 7.89 (d, 1H, J=6.5 Hz, ArH), 8.24 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.8, 43.1, 46.0, 98.9, 90.0, 114.9, 115.4, 124.0, 128.8, 128.8, 130.2, 130.3, 130.6, 131.5, 133.0, 133.8, 134.7, 135.4, 150.0, 159.5, 160.9 ppm; ESMS *m/z*: 450 $(M+H)^+$; HRMS found, 450.0609, $C_{22}H_{17}ClN_5S_2$ requires 450.0614.

4.2.22. 2-Benzylsulfanyl-6-[(pyrrolidin-1-ylmethylene)-amino]-4-thiophen-2-yl-pyridine-3,5-dicarbonitrile (Table 4, entry 4). Greenish powder (113.0 mg, 94%); mp 164–166 °C dec; IR (neat) ν_{max} 3317, 3092, 2981, 2876, 2485, 2208, 1608, 1531, 1490, 1462, 1448, 1397, 1366, 1324, 1301, 1278, 1228, 1204, 1152, 1073, 1052, 1029, 1009, 977 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 1.90 (m, 4H, NCH_2CH_2), 3.55 (t, 2H, J=5.5 Hz, NCH_2), 3.70 (t, 2H, J=5.5 Hz, NCH_2), 4.60 (s, 2H, $ArCH_2$), 7.15–7.50 (m, 6H, ArH), 7.55 (d, 1H, J=6.5 Hz, ArH), 7.95 (d, 1H, J=6.5 Hz, ArH), 9.00 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 23.7, 24.5, 33.9, 46.4, 49.8, 96.3, 96.6, 115.3, 115.8, 127.2, 128.4, 128.5, 128.7, 130.8, 131.3, 132.6, 136.9, 150.4, 155.0, 160.5, 163.3, 165.6 ppm; ESMS *m/z*: 430 $(M+H)^+$; HRMS found, 430.1167, $C_{23}H_{20}N_5S$ requires 430.1160.

4.3. Synthesis of formamidines without NaH

4.3.1. *N*′-(3,5-Dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N*-dimethyl-formamidine (Table 4, entry 5). To a stirred solution of 2-amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile **1** (50.0 mg, 0.22 mmol) in dry DMF (1.0 mL) was added TFAA (50.0 mg, 0.24 mmol) under nitrogen at room temperature. After the mixture was stirred for 20 min at room temperature it was poured into cold water (10 mL) and stirred for 5 min, the suspension was filtered and the precipitated crude product washed with water (10 mL). Drying the solid in vacuo overnight gave **2** (57.3 mg, 96%).

4.3.2. *N*′-(6-Benzylsulfanyl-3,5-dicyano-4-thiophen-2-yl-pyridin-2-yl)-*N*,*N*-dimethyl-formamidine (Table 4, entry 6). Yellowish powder (256.0 mg, 89%): mp 202–204 °C; IR (neat) ν_{max} 3440, 3318, 3216, 2212, 1719, 1619, 1518, 1491, 1449, 1419, 1397, 1367, 1340, 1314, 1286, 1245, 1222, 1124, 1098, 1055, 1008, 982 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.15 (s, 3H, NCH_3), 3.25 (s, 3H, NCH_3), 4.60 (s, 2H, $ArCH_2$), 7.10–7.65 (m, 7H, ArH), 7.95 (d, J=7.5 Hz, ArH), 8.90 (s, 1H, N=CHN) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 33.9, 35.0, 41.1, 96.4, 96.7, 115.3, 115.8, 127.3,

127.8, 128.5, 129.3, 130.7, 130.8, 131.2, 131.3, 132.6, 136.9, 150.4, 158.2, 163.3, 165.7 ppm; ESMS *m/z*: 404 $(M+H)^+$; HRMS found, 404.0998, $C_{21}H_{18}N_5S_2$ requires 404.1004.

4.3.3. *N′*-[3,5-Dicyano-4-(phenyl-4-carboxylic acid methyl ester)-6-(phenylsulfanyl-4-carboxylic acid methyl ester)-pyridin-2-yl)-*N*,*N*-dimethyl-formamidine (Table 4, entry 7). A mixture of two isomers was obtained as a faint yellowish solid (203.4 mg, 78%); mp 145–147 °C; IR (neat) ν_{max} 2935, 2217 (s), 1723, 1624 (s), 1569, 1527, 1494, 1437, 1401, 1371, 1275, 1251, 1182, 1135, 1105, 1014, 987, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) (major isomer) δ 3.05 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 3.94 (s, 3H, $COOCH_3$), 3.95 (s, 3H, $COOCH_3$), 7.58 (d, 2H, *J*=8.5 Hz, ArH), 7.70 (d, 2H, *J*=8.5 Hz, ArH), 8.01 (s, 1H, N=CHN), 8.10 (d, 2H, *J*=8.5 Hz, ArH), 8.20 (d, 2H, *J*=8.5 Hz, ArH) ppm; (minor isomer) δ 2.92 (s, 3H, NCH_3), 3.05 (s, 3H, NCH_3), 3.88 (s, 3H, $COOCH_3$), 3.91 (s, 3H, $COOCH_3$), 7.40 (d, 2H, *J*=9.2 Hz, ArH), 7.50 (d, 2H, *J*=9.2 Hz, ArH), 7.89 (s, 1H, N=CHN), 8.04 (d, 2H, *J*=9.2 Hz, ArH), 8.07 (d, 2H, *J*=9.2 Hz, ArH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 35.4, 40.9, 52.5 (2C), 97.8, 98.0, 114.7, 115.2, 128.6, 129.8, 130.1, 130.4, 130.6, 131.1, 132.0, 132.2, 133.8, 136.1, 137.7, 156.2, 157.8, 157.9, 163.4, 165.4, 166.1, 166.3 ppm; ESMS *m/z*: 500 $(M+H)^+$; HRMS found, 522.1192, $C_{26}H_{21}N_5O_4NaS$ requires 522.1212.

4.3.4. 4-{3,5-Dicyano-2-[(pyrrolidin-1-ylmethylene)-amino]-6-*p*-methylcarboxylester sulfanyl-pyridin-4-yl}-benzoic acid methyl ester (Table 4, entry 8). A mixture of two isomers was obtained as a pale yellowish solid (194.2 mg, 78%); mp 187–190 °C dec; IR (neat) ν_{max} 2954, 2876, 2216, 1714, 1613, 1519, 1503, 1449, 1363, 1329, 1274, 1245, 1192, 1157, 1106, 1013, 965 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) (major isomer) δ 1.83 (m, 4H, $2NCH_2CH_2$), 3.42 (t, 2H, *J*=6.5 Hz, NCH_2), 3.57 (t, 2H, *J*=6.5 Hz, NCH_2), 3.88 (s, 3H, $COOCH_3$), 3.89 (s, 3H, $COOCH_3$), 7.52 (d, 2H, *J*=9.2 Hz, ArH), 7.60 (d, 2H, *J*=9.2 Hz, ArH), 8.01 (s, 1H, N=CHN), 8.04 (d, 2H, *J*=9.2 Hz, ArH), 8.12 (d, 2H, *J*=9.2 Hz, ArH); (minor isomer) δ 1.83 (m, 4H, $2NCH_2CH_2$), 3.42 (t, 2H, *J*=6.5 Hz, NCH_2), 3.46 (t, 2H, *J*=6.5 Hz, NCH_2), 3.85 (s, 3H, $COOCH_3$), 3.88 (s, 3H, $COOCH_3$), 7.31 (d, 2H, *J*=9.2 Hz, ArH), 7.38 (d, 2H, *J*=9.2 Hz, ArH), 7.94 (d, 2H, *J*=9.2 Hz, ArH), 8.00 (d, 2H, *J*=9.2 Hz, ArH), 8.01 (s, 1H, N=CHN) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 24.2, 24.9, 46.7, 49.8, 52.5, 97.7, 98.0, 114.8, 115.3, 125.9, 127.4, 128.8, 129.8, 130.2, 130.8, 131.1, 132.0, 134.0, 135.8, 137.8, 153.1, 154.6, 157.9, 161.0, 163.4, 165.3, 166.2, 166.4 ppm; ESMS *m/z*: 526 $(M+H)^+$; HRMS found, 526.1550, $C_{28}H_{24}N_5O_4S$ requires 526.1549.

4.3.5. *N′*-(5-Cyano-pyrimidin-4-yl)-*N*,*N*-dimethyl-formamidine (Table 5, entry 3). Pale yellowish solid (83.4 mg, 79%).

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