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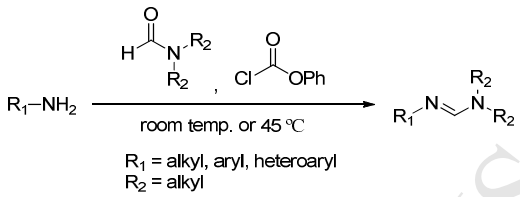

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Unexpected route for the synthesis of *N*,*N*-dialkyl formamidines using phenyl chloroformate and *N*,*N*-dialkyl formamides.

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ABSTRACT

An unexpected route for the synthesis of *N,N*-dialkyl formamidines has been reported by the reaction of amines with *N,N*-dialkylformamides and phenyl chloroformate.

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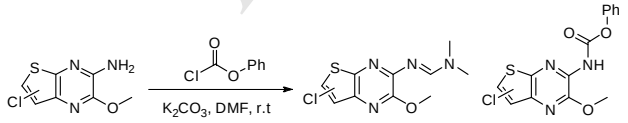
1. Introduction

Formamidines are the key intermediates for the construction of heterocycles[1] and functional group transformations.[2] They have also been employed as pharmacological agents,[3] protecting groups for primary amines[4], and as a support linker in solid phase synthesis.[5] The use of formamidines as chiral auxiliaries in asymmetric synthesis[6] and as ligand for metal-catalyzed hydrosilyation and epoxidation has also been reported.[7] The methods for the synthesis of formamidines can largely be divided into three categories. The first involves the use of *N*,*N*-dialkylformamide dialkylacetals with or without a catalytic amount of acid. The second involves coupling agents such as $POCl_3$, P_2O_5, PCl_5, $(COCl)_2$, $SOCl_2$, acid chlorides, sulfonylchlorides, PyBOP and trifluoroacetic anhydride.[8] The last involves the use of isolated iminium salt like vilsmeier reagent, which is related to the method reported herein.[9] Recently, a new approach using NaI and TBHP to make *N*-sulfonyl formamidine has been reported.[10] As a part of our medicinal chemistry research program we required carbamate **3** for which we attempted the reaction of phenyl chloroformate with amine **1** (Scheme 1). It was expected that the nucleophilic substitution would lead to the carbamate. However the product obtained was confirmed as formamidine **2**, strongly suggesting the formation of a reactive intermediate between *N*,*N*-dimethylformamide and phenyl chloroformate which was reacting with amines (Scheme 2). These findings have not been reported, and have encouraged us to investigate the formamidine synthesis.

2. Results and discussion

We initially selected 3-aminopyridine and aminopyrazine to study the optimal conditions. The reaction proceeded well, but extraction with EtOAc was difficult due to its good solubility in water. To solve the problem, we used 6-chloro-2-aminopyrazine as a model substrate since it is well extracted with EtOAc. After selecting a model compound, we investigated the necessity of K_2CO_3 in the methodology and found that K_2CO_3 was not necessary for the reacton (Table 1, entries 1-4). Instead, the reaction required more phenyl chloroformate for completion. In the absence of the base, the product can be obtained as HCl salt via simple filtration, which makes the purification much easier. Two other chloroformates were also screened to compare their reactivity. Among the chloroformates (Table 1, entries 4 and 5), *p*-nitrophenyl chloroformate was found to show similar results to that of phenylchloroformate, but ethyl chloroformate gave poor yields. Considering the price of the two aryl chloroformates, phenyl chloroformate was found to be the reagent of choice for the reaction.

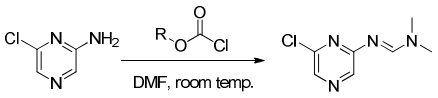
To study the reaction details, DMF and phenyl chloroformate were mixed (1:1 molar ratio) and stirred for 5 minutes, and diluted into $CDCl_3$. The ^{1}H-NMR spectrum indicated the existence of iminium salt, and that the DMF was completely consumed. However we were unable to confirm the intermediacy of either **4** or **5** because bubbles, suspected as CO_2 were observed in the mixture while stirring. A literature survey revealed the



Scheme 1.

isolation of a iminium salt **4**, which is used as a chlorinating agent.[11] We also can isolate the intermediate **4** from the described procedure. It was thus concluded that the intermediate **5** formed initially underwent decarboxylation to form the intermediate **4**. The isolation of the intermediate **4** answers the formation of the formamidines (Scheme 2).

Table 1. Reaction condition screening.[a]



Entry	Base [equiv.]	R [equiv.]	Time [min]	Yield[b] [%]
1	K_2CO_3 (2.7)	Ph (2.0)	5	79
2	K_2CO_3(3.0)	Ph (2.2)	5	85
3	-	Ph (2.0)	5	86[c]
4[d]		Ph (2.0)	5	84[c]
5	-	Et (2.0)	5	12
6[e]	-	*p*-NitroPh (2.0)	5	84

[a] Reaction conditions: DMF (1 ml) and chloroformate were stirred for 5 minutes with base or not before addition of the 6-chloro-2-aminopyraizne (1 mmol). [b] isolated yield. [c] obtained as HCl salt. [d] DMF (0.5 ml). [e] DMF (2 ml).

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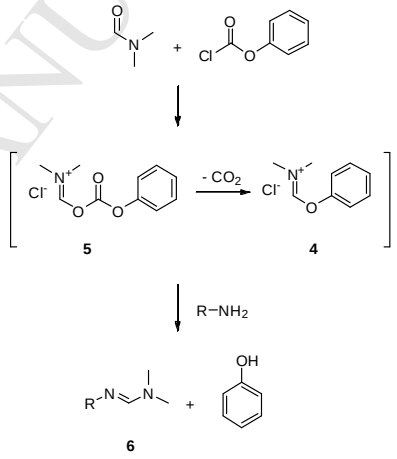
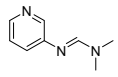
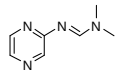
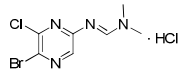
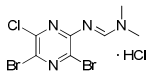
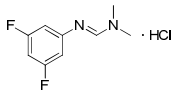
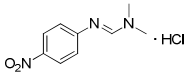
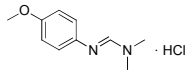
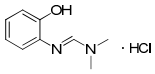
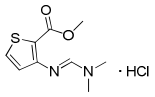
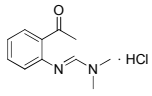
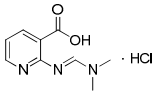
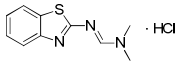
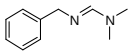
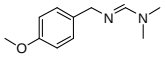
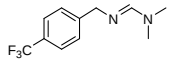


Scheme 2.

We started to explore the scope and limitiations of the method (Table 2). It was found that a greater equivalent of the phenyl chloroformate has to be used as the nucleophilicity of amines decreases (Table 2, entries 1-4). In the case of trihaloaminopyrazine (Table 2, entry 4), the reaction worked well but the product could not be obtained due to its instability, both in the protic solvent and in the air. It easily turned back to the amine. Nitro, methoxy, hydroxy, methyl ester, carboxylic acid and acetyl-substituted aryls also gave the desired products (Table 2, entries 6-11). When methyl 3-amino-2-thiophenecarboxylate was tested (Table 2, entry 9), the product was not generated as salt. So, we employed a silica gel column after aqueous work-up. However, we failed to obtain the product, because the formamidine was converted to methyl 3-formamidothiophene-2-carboxylate in the column. A similar tendency was also reported when ethyl 2-aminobenzoate was used as a substrate.[8a] To avoid the hydrolysis, after extraction, the product was collected as HCl salt using HCl in diethyl ether. Finally, benzyl amines were conducted (Table 2, entries 13-15). Since the product was not precipitated as salt, we had to purify it by column chromatography.

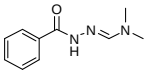
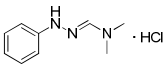
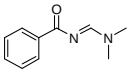
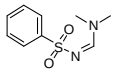
Table 2. Scope of the method.[a]

Entry	product		Time [min]	Yield[b] [%]
1[c]		**6b**	5	81
2[c]		**6c**	5	87
3[d]		**6d**	20	71
4[e]		**6e**	20	-
5		**6f**	5	87
6		**6g**	5	95
7		**6h**	5	79
8		**6i**	5	70
9		**6j**	5	90
10		**6k**	5	59
11		**6l**	10	60
12		**6m**	10	86
13		**6n**	5	50
14		**6o**	5	40
15		**6p**	10	59

[a] Reaction conditions: DMF (1 ml) and phenyl chloroformate (2 eq) were stirred for 5 minutes at rt before addition of the amines (1 mmol). [b] isolated yield. [c] phenyl chloroformate (1.5 eq) was used. [d] 4.5 eq of phenyl chloroformate. [e] 7 eq of phenyl chloroformate.

In addition to aryl and alkyl amines, we have also screened phenylhydrazide, phenylhydrazine, benzamide and phenylsulfonamide (Table 3) to demonstrate further use of the method. Phenylhydrazide and phenylhydrazine gave good results but benzamide gave only *N*-formylbenzamide in 9% yield. The rest of the unreacted benzamide was recovered. Phenylsulfonamide was found to be unsuccessful.

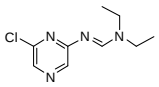
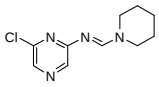
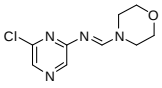
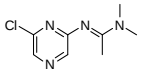
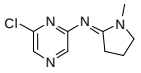
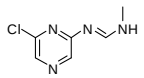
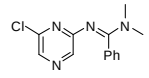
Table 3. Expansion of the substrate.[a]

Entry	product		Time [min]	Yield[b] [%]
1		**7a**	10	64
2		**7b**	5	95
3		**7c**	10	-
4[c]		**7d**	10	16

[a] Reaction conditions: DMF (1 ml) and phenyl chloroformate (2 eq) were stirred for 5 minutes at rt before addition of the substrates (1 mmol). [b] isolated yield. [c] 3 eq of K_2CO_3

Other *N*,*N*-disubstituted amide analogues were tested with 6-chloro-2-aminopyrazine (Table 4). They were also suitable for formation of the formamidins. But *N*,*N*-dimethylacetamide, *N*-methylformamide, NMP and *N*,*N*-dimethylbenzamide were found to be not good for the formation of iminium intermediate with phenyl chloroformate, giving poor yield or no product.

Table 4.
Reaction of 6-chloro-2-aminopyrazine with various amides.[a]

Entry	amide	product		Time [min]	Yield[b] [%]
1[c, d]			**8a**	5	85
2[c]			**8b**	5	81
3[c, e]			**8c**	5	67
4			**8d**	20	-
5			**8e**	20	7
6			**8f**	20	-[f]
7			**8g**	20	-[g]

[a] Reaction conditions: amide (1 ml) and phenyl chloroformate (2 eq) were stirred for 10 minutes at rt before addition of 6-chloro-2-aminopyrazine (1 mmol). [b] isolated yield. [c] 45 °C. [d] 3.5 eq of phenyl chloroformate. [e] 1.5 ml of 4-formylmorpholine. [f] No reaction. [g] decomposition.

3. Conclusion

In conclusion, we have discovered that phenyl chloroformate can be used for the synthesis of the formamidines. Mild conditions, short reaction time and generality verified with various substrates make this method attractive. Also it is

noteworthy that DMF or its derivatives are not good choice as solvent if chloroformates have to be used for the synthesis of the carbamate.

4. Experimental

4.1. General

All reactions were carried out under an air atmosphere. All commercial reagents and solvents were used as received without further purification. The reactions were monitored by TLC using silica gel plates and column chromatography was performed with Merck silica gel 60 (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE III 500. Chemical shift values (δ) are given in parts per million using residual solvent as internal standard. Mass spectra were obtained on an Agilent 6400 Triple Quadrupole Mass spectrometer instrument using ESI. Melting points were measured with a Stuart SMP40 apparatus. IR spectra were recorded on a Smiths IdentifyIR.

4.2. General procedure for the preparation of *N,N*-dimehtyl formamidines 6, 7

To the DMF (1 ml) was added dropwise phenyl chloroformate (2 eq). The mixture was stirred for 5 minutes at room temperature. Then 6-chloro-2-aminopyrazine (1 mmol) was introduced to the mixture. After 5 minutes, the solvent (isopropyl alcohol: diethyl ether, v/v = 1:2) was poured into the mixture. The precipitated product **6a** was filtered off, washed with the solvent and dried.

*4.2.1. N'-(6-chloropyrazin-2-yl)-N,N-dimethylformamidine hydrochloride (**6a**).* White solid; mp 224-226 °C (decomp.); ^{1}H NMR (500 MHz, MeOD) δ 9.09 (t, *J* = 0.7 Hz, 1H), 8.64 (d, *J* = 0.6 Hz, 1H), 8.58 (d, *J* = 0.5 Hz, 1H), 3.57 (d, *J* = 0.6 Hz, 3H), 3.45 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 154.11, 148.22, 146.78, 142.47, 134.28, 45.51, 38.90; LC/MS (ESI) *m/z* 185 $[M+H]^+$; IR (ATR): *v* = 3037, 3012, 2689, 1700, 1541, 1383, 1305, 1156, 818 cm^{-1}; Anal. Calcd for $C_7H_{10}Cl_2N_4$: C, 38.03; H, 4.56; N, 25.34. Found: C, 37.6; H, 4.7; N, 25.1. HRMS (ESI) *m/z* calcd for $C_7H_{10}ClN_4$ $[M+H]^+$ 184.0594, found 184.0596;

*4.2.2. N,N-dimethyl-N'-(pyridin-3-yl)formamidine (**6b**).* To the DMF was added dropwise phenyl chloroformate. The mixture was stirred for 5 minutes in room temperature. Then 3-aminopyridine was introduced to the mixture. After 5 minutes, the mixture was basified with K_2CO_3(aq), extracted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography to give the product. colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 – 8.21 (m, 2H), 7.52 (s, 1H), 7.28 – 7.23 (m, 1H), 7.17 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.05 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 153.80, 147.93, 143.68, 143.16, 128.07, 123.52, 40.30, 34.52; LC/MS (ESI) *m/z* 150 $[M+H]^+$; IR (ATR): *v* = 2921, 2808, 1628, 1573, 1473, 1372, 1266, 1233, 1104, 807, 712 cm^{-1};

*4.2.3. N,N-dimethyl-N'-(pyrazin-2-yl)formamidine (**6c**).* Slightly yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.26 (d, *J* = 1.4 Hz, 1H), 8.09 (dd, *J* = 2.7, 1.5 Hz, 1H), 8.05 (d, *J* = 2.7 Hz, 1H), 3.09 (d, *J* = 1.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.18, 156.20, 142.14, 141.60, 137.86, 40.97, 34.83; LC/MS (ESI) *m/z* 151 $[M+H]^+$; IR (ATR): *v* = 3045, 2931, 1614, 1568, 1379, 1099, 1007, 836 cm^{-1};

*4.2.4. N'-(5-bromo-6-chloropyrazin-2-yl)-N,N-dimethylformamidine hydrochloride (**6d**).* White solid; mp 263-266 °C (decomp.); ^{1}H NMR (500 MHz, MeOD) δ 9.05 (s, 1H), 8.44 (s, 1H), 3.56 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 154.21, 148.70, 145.93, 135.81, 134.05, 45.51, 38.89; LC/MS (ESI) *m/z* 263 $[M+H]^+$; IR (ATR): *v* = 2975, 2637, 1692, 1417, 1297, 1163, 1024, 832 cm^{-1}; Anal. Calcd for $C_7H_9BrCl_2N_4$: C, 28.03; H, 3.02; N, 18.68. Found: C, 28.17; H, 3.01; N, 18.52;

*4.2.5. N'-(3,5-difluorophenyl)-N,N-dimethylformamidine hydrochloride (**6f**).* White solid; mp 278-281 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.74 (s, 1H), 7.15 (m, 2H), 6.93 (tt, *J* = 9.0, 2.2 Hz, 1H), 3.48 (s, 3H), 3.34 (d, *J* = 0.6 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 165.05 (dd, J_{CF} = 247.7, 14.6 Hz), 155.44, 141.22 (t, J_{CF} = 13.1 Hz), 104.00 (m), 102.58 (t, J_{CF} = 26.0 Hz), 44.74, 38.00; LC/MS (ESI) *m/z* 185 $[M+H]^+$; IR (ATR): *v* = 3019, 2823, 1695, 1611, 1113, 986 cm^{-1}; Anal. Calcd for $C_9H_{11}ClF_2N_2$: C, 48.99; H, 5.03; N, 12.70. Found: C, 49.3; H, 5.1; N, 12.6.;

*4.2.6. N'-(4-nitrophenyl)-N,N-dimethyl-formamidine hydrochloride (**6g**).* White solid; mp 280-282 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.87 (s, 1H), 8.34 (d, *J* = 9.1 Hz, 2H), 7.67 (d, *J* = 9.1 Hz, 2H), 3.52 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 154.10, 145.57, 142.69, 125.12, 119.22, 43.52, 36.76; LC/MS (ESI) *m/z* 194 $[M+H]^+$; IR (ATR): *v* = 2883, 1701, 1597, 1516, 1311, 854, 748 cm^{-1}; Anal. Calcd for $C_9H_{12}ClN_3O_2$: C, 47.07; H, 5.27; N, 18.3. Found: C, 47.4; H, 5.1; N, 18.0;

*4.2.7. N'-(4-methoxyphenyl)-N,N-dimethylformamidine hydrochloride (**6h**).* Slightly yellow solid; mp 203-205 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.46 (s, 1H), 7.41 – 7.26 (m, 2H), 7.05 – 6.90 (m, 2H), 3.81 (s, 3H), 3.41 (s, 3H), 3.27 (d, *J* = 0.6 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 160.10, 155.30, 131.54, 122.76, 116.00, 56.08, 44.16, 37.42; LC/MS (ESI) *m/z* 179 $[M+H]^+$; IR (ATR): *v* = 2970, 2810, 1689, 1507, 1341, 1236, 1019, 794 cm^{-1}; Anal. Calcd for $C_{10}H_{15}ClN_2O$: C, 55.50; H, 7.04; N, 13.05. Found: C, 55.91; H, 7.02; N, 13.04; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}N_2O$ $[M+H]^+$ 179.1184, found 179.1178;

*4.2.8. N'-(2-hydroxyphenyl)-N,N-dimethylformamidine hydrochloride (**6i**).* Slightly orange solid; mp 155-157 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.42 (s, 1H), 7.28 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.19 (ddd, J = 8.2, 7.5, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.91 (td, *J* = 7.8, 1.3 Hz, 1H), 3.45 – 3.37 (m, 3H), 3.29 (d, *J* = 0.6 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 157.09, 151.45, 129.75, 125.69, 124.85, 121.17, 117.54, 44.20, 37.09; LC/MS (ESI) *m/z* 165 $[M+H]^+$; IR (ATR): *v* = 3075, 2966, 1689, 1344, 1281, 1131, 748, 681 cm^{-1}; Anal. Calcd for $C_9H_{13}ClN_2O$: C, 53.87; H, 6.53; N, 13.96. Found: C, 53.3; H, 6.8; N, 13.9; HRMS (ESI) *m/z* calcd for $C_9H_{13}N_2O$ $[M+H]^+$ 165.1028, found 165.1025;

*4.2.9. Methyl N'-(thiophen-3-yl)-N,N-dimethylformamidine-2-carboxylate hydrochloride (**6j**).* To the DMF was added dropwise phenyl chloroformate. The mixture was stirred for 5 minutes at room temperature. Then methyl 3-amino-2-thiophenecarboxylate was introduced to the mixture. After 5 minutes, the mixture was basified with K_2CO_3(aq), extracted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was diluted with diethyl ether and HCl (3 M in diethyl ether) was added. The solution was heated at 35 °C for 10 min. The precipitated product **6j** was filtered off, washed with the solvent (isopropyl alcohol: diethyl ether, v/v = 1:2) and dried. Slightly yellow solid; mp 175-177 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.99 (s, 1H), 7.90 (d, *J* = 5.4 Hz, 1H), 7.49 (d, *J* = 5.5 Hz, 1H), 3.94 (s, 3H), 3.52 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 165.03, 155.44, 142.70, 134.78, 120.79, 116.49, 53.20, 44.52, 37.17; LC/MS (ESI) *m/z* 213 $[M+H]^+$; IR (ATR): *v* = 3452, 3052, 1671, 1584, 1450, 1279, 787 cm^{-1}; Anal. Calcd for $C_9H_{13}ClN_2O_2S$: C, 43.46; H, 5.27; N, 11.26. Found: C, 42.57; H, 5.76; N, 11.27; HRMS (ESI) *m/z* calcd for $C_9H_{13}N_2O_2S$ $[M+H]^+$ 213.0698, found 213.0701;

*4.2.10. N'-(2-acetylphenyl)-N,N-dimethylformamidine hydrochloride (**6k**).* White solid; mp 167-169 °C (decomp.); ^{1}H NMR (500 MHz, MeOD) δ 9.11 (s, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.82 – 7.73 (m, 2H), 7.51 – 7.42 (m, 1H), 3.54 (s, 3H), 3.38 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 205.26, 154.36, 138.93, 136.63, 134.06, 127.13, 124.59, 118.08, 44.47, 37.37, 28.55; LC/MS (ESI) *m/z* 191 $[M+H]^+$; IR (ATR): *v* = 3374, 2882, 1683, 1630, 1307, 1255, 774 cm^{-1} Anal. Calcd for $C_{11}H_{15}ClN_2O$: C, 58.28; H, 6.67; N, 12.36. Found: C, 56.3; H, 7.0; N, 11.8; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}N_2O$ $[M+H]^+$ 191.1184, found 191.1183;

*4.2.11. N'-(pyridin-2-yl)-N,N-dimethylformamidine-3-carboxylic acid hydrochloride (**6l**).* White solid; mp 214-216 °C (decomp.); ^{1}H NMR (500 MHz, MeOD) δ 9.47 (s, 1H), 8.61 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.54 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.43 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.58 (s, 3H), 3.41 (d, *J* = 0.7 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 168.72, 152.65, 151.53, 149.37, 141.01, 121.39, 112.16, 43.57, 36.49; LC/MS (ESI) *m/z* 194 $[M+H]^+$; IR (ATR): *v* = 3033, 2280, 1826, 1688, 1638, 1210, 778 cm^{-1}; Anal. Calcd for $C_9H_{12}ClN_3O_2$: C, 47.07; H, 5.27; N, 18.30. Found: C, 47.04; H, 5.28; N, 18.26;

*4.2.12. N'-(benzo[d]thiazol-2-yl)-N,N-dimethylformamidine hydrochloride (**6m**).* White solid; mp 197-200 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.57 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.48 – 7.40 (m, 1H), 3.43 (s, 3H), 3.32 (d, *J* = 3.4 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 176.00, 162.64, 138.89, 129.44, 126.86, 126.61, 124.24, 115.84, 42.69, 36.93; LC/MS (ESI) *m/z* 206 $[M+H]^+$; IR (ATR): *v* = 2425, 1637, 1535, 1458, 1394, 1186, 773 cm^{-1}; Anal. Calcd for $C_{10}H_{12}ClN_3S$: C, 49.69; H, 5.00; N, 17.38. Found: C, 49.11; H, 5.01; N, 17.32; HRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_3S[M+H]^+$ 206.0752, found 206.0755;

*4.2.13. N'-benzyl-N,N-dimethylformamidine (**6n**).* Slightly yellow oil; ^{1}H NMR (500 MHz, MeOD) δ 7.52 (s, 1H), 7.29 (m, 2H), 7.24 (m, 2H), 7.21 (m, 1H), 4.39 (s, 2H), 2.90 (s, 6H); ^{13}C NMR (126 MHz, MeOD) δ 158.75, 142.90, 129.29, 128.55, 127.64, 59.47, 38.18; LC/MS (ESI) *m/z* 163 $[M+H]^+$; IR (ATR): *v* = 3031, 1658, 1383, 1238, 696 cm^{-1};

*4.2.14. N'-(4-methoxybenzyl)-N,N-dimethylformamidine (**6o**).* Slightly yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.39 (s, 2H), 3.77 (s, 3H), 2.89 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.43, 155.69, 133.96, 128.76, 113.82, 58.19, 55.37, 37.54; LC/MS (ESI) *m/z* 193 $[M+H]^+$; IR (ATR): *v* = 2933, 2836, 1646, 1510, 1242, 1059, 816 cm^{-1};

*4.2.15. N'-(4-(trifluoromethyl)benzyl)- N,N-dimethylformamidine (**6p**).* Slightly yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.37 (m, 3H), 4.49 (s, 2H), 2.89 (s, *J* = 19.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.17, 146.57, 128.55 (q, J = 32.2 Hz), 127.67, 125.11 (q, J_{CF} = 3.8 Hz), 124.43 (q, J_{CF} = 271.7 Hz), 59.08, 37.77; LC/MS (ESI) *m/z* 231 $[M+H]^+$; IR (ATR): *v* = 2871, 1648, 1321, 1108, 1065, 1017, 819 cm^{-1};

*4.2.16. N'-benzoyl-N,N-dimethylformohydrazonamide (**7a**).* the procedure is same with **6c**. Slightly yellow solid; mp 171-173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.90 (s, 1H), 7.79 – 7.73 (m, 2H), 7.46 – 7.41 (m, 1H), 7.40 – 7.33 (m, 2H), 2.86 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.30, 164.84, 157.95, 134.53, 131.12, 128.60, 126.97, 37.92; LC/MS (ESI) *m/z* 192 $[M+H]^+$; IR (ATR): *v* = 3216, 3064, 2905, 1603, 1572, 1355, 1110, 902, 694 cm^{-1};

*4.2.17. N,N-dimethyl-N'-phenylformohydrazonamide hydrochloride (**7b**).* Slightly yellow solid; mp 201-203 °C; ^{1}H NMR (500 MHz, MeOD) δ 8.32 (s, 1H), 7.28 (t, *J* = 7.1 Hz, 2H), 7.03 – 6.86 (m, 3H), 3.35 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 159.82, 147.06, 128.96, 121.53, 113.44, 42.60, 36.27; LC/MS (ESI) *m/z* 164 $[M+H]^+$; IR (ATR): *v* = 3190, 2977, 2770, 1707, 1486, 770, 753, 703 cm^{-1}; Anal. Calcd for $C_9H_{14}ClN_3$: C, 54.14; H, 7.07; N, 21.04. Found: C, 54.1; H, 7.2; N, 21.10;

*4.2.18. N,N-dimethyl-N'-(phenylsulfonyl)formamidine (**7d**).* White solid; mp 128-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.91 – 7.84 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.42 (m, 2H), 3.12 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.33, 142.52, 131.94, 128.81, 126.56, 41.61, 35.64; LC/MS (ESI) *m/z* 213 $[M+H]^+$; IR (ATR): *v* = 2930, 1613, 1280, 1145, 1086, 906, 846, 685 cm^{-1};

4.3. General procedure for reaction of 6-chloro-2-aminopyrazine with amides

To the *N,N*-diethylformamide (1 ml) was added dropwise phenyl chloroformate (3.5 eq). The mixture was stirred for 10 minutes at room temperature. Then 6-chloro-2-aminopyrazine (1 mmol) was introduced to the mixture. After 5 minutes at 45 °C, the mixture was basified with K_2CO_3(aq), extracted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography to give the product.

*4.2.19. N'-(6-chloropyrazin-2-yl)-N,N-diethylformamidine (**8a**).* Slightly yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.12 (s, 1H), 8.04 (s, 1H), 3.59 (q, J = 7.2 Hz, 2H), 3.40 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.04, 155.89, 146.72, 139.11, 135.72, 46.52, 40.09, 14.93, 12.48; LC/MS (ESI) *m/z* 213 $[M+H]^+$; IR (ATR): *v* = 2975, 2936, 2875, 1605, 1387, 1158, 1115 cm^{-1};

*4.2.20. 6-chloro-N-(piperidin-1-ylmethylene)pyrazin-2-amine (**8b**).* Slightly yellow solid; mp 71-73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.12 (s, 1H), 8.04 (s, 1H), 3.73 (m, 2H), 3.44 (m, 2H), 1.67 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.03, 155.48, 146.74, 138.98, 135.76, 51.54, 44.02, 26.69, 25.21, 24.51; LC/MS (ESI) *m/z* 225 $[M+H]^+$; IR (ATR): *v* = 3069, 2941, 2855, 1696, 1607, 1353, 1157, 1000, 858 cm^{-1};

*4.2.21. 6-chloro-N-(morpholinomethylene)pyrazin-2-amine (**8c**).* Slightly yellow solid; mp 121-123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 3.82 (m, 2H), 3.75 (m, 4H), 3.51 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.33, 155.43, 146.79, 139.01, 136.64, 67.15, 66.35, 50.04, 43.70; LC/MS (ESI) *m/z* 227 $[M+H]^+$; IR (ATR): *v* = 2980, 2911, 2867, 1609, 1389, 1348, 1162, 1104, 1006, 848 cm^{-1};

*4.2.22. 6-chloro-N-(1-methylpyrrolidin-2-ylidene)pyrazin-2-amine (**8e**).* Slightly yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.00 (s, 1H), 3.45 (t, *J* = 7.1 Hz, 2H), 3.06 (s, 3H), 2.94 (t, *J* = 7.9 Hz, 2H), 2.06 (dt, *J* = 15.2, 7.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.47, 158.76, 146.37, 139.50, 134.69, 51.38, 31.80, 29.69, 19.88; LC/MS (ESI) *m/z* 211 $[M+H]^+$; IR (ATR): *v* = 2925, 2870, 2175, 1590, 1469, 1379, 1288, 1158, 1001, 921 cm^{-1};

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Supplementary data

Copies of the ^{1}H NMR and ^{13}C NMR spectra of the compounds.

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