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Dication $C(R^1)$–$N(R^2)_2$ Synthons and their use in the Synthesis of Formamidines, Amidines, and α-Aminonitriles

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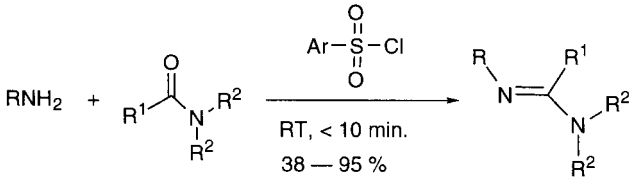
Abstract—A combination of amides and 2-pyridinesulfonyl chloride was evaluated as synthons of the dication $C(R^1)$–$N(R^2)_2^{2+}$. When the substrates were primary amines, high yields of formamidines and amidines were obtained. When the substrates were α-aminoamides, α-aminonitriles were obtained. Through this process, naturally occurring α-aminoacids can be transformed into chiral α-aminonitriles with complete retention of stereochemical configuration. All reactions proceed rapidly at room temperature, and normally finish within 10 min, with yields ranging from 80 to 95% for most cases. Among the sulfonyl chlorides examined, 2-pyridinesulfonyl chloride stands out in both reaction rate and selectivity of formamidine or amidine versus sulfonyl amide. The scope and limitations of the reaction among different types of amides as synthons and amines as substrates were examined.

Formamidines, derivatives of the unstable imidic acid, have been used as pharmacological agents,[1] primarily as pesticides like amitraz[2] and histamine receptor antagonists.[3] Their application as building blocks in polymers,[4] bleaching agents for paper,[5] and ligands in transition metal complexes[6] has also been noted. Their use as intermediates in organic synthesis is quite diversified,[7] including as auxiliaries in asymmetric synthesis,[8] as protecting groups for primary amines,[9] as nitrogen-based nucleophiles,[10] and as support linkers in solid phase synthesis.[11] A few general methods are available for the synthesis of compounds of this type. Coupling of *N*,*N*-dialkylformamides with primary amines by a number of coupling agents including P_2O_5, PCl_5, PCl_3, $SOCl_2$, and acyl chlorides has been realized.[12] In other situations, ethyl *N*-cyanoformimidate was used to form N^2-aryl-N^1-cyanoformamidines, which were converted to a variety of N^2-aryl-N^1-alkylformamidines with excess alkyl or dialkylamines.[13] Thiophenylimidic esters were recently used in an alternative synthesis of formamidines.[14] *N*,*N*-dialkylformamide dimethylacetals have also been used to couple with primary amines directly under neutral conditions.[15] Earlier phenylisocyanate was reacted with *N*,*N*-dimethylformamide to generate the formamidine through a four-membered heterocyclic intermediate.[16] This reaction was further generalized to use other aryl isocyanates as starting materials.[17] Quite unexpectedly, (diaminomethyl)di-*tert*-butylphosphine reacts with primary amines to generate formamidines and di-*tert*-butyl-hydrophosphine in moderate yields.[18] Selective reduction of tri-substituted ureas has also been used to synthesize 3-substituted formamidines in a number of cases.[19] 1,1-Addition of amines to isocyanides catalyzed by AgCl at low temperature generates stereospecific isomers of formamidines, which are different from those generated by other methods.[20] In our effort to evaluate the application of the dication $C(R_1)$–$N(R_2)_2$ synthons, we found a convenient and highly efficient synthesis of a variety of formamidines, amidines and α-aminonitriles. Part of the results has been reported.[21] Since our initial report, other work using phosphorus-based coupling agents such as PyBroP (Tri-pyrrole bromophosphorus bromide) has appeared in the literature for the synthesis of formamidines.[22] Application of the synthons from the combination of *N*,*N*-dimethylacrylamide/triflic anhydride and *N*,*N*-dimethylformamide/triflic anhydride on activated aromatic systems such as thiophenes[23] or activated methylene groups such as cyclopentadienes[24] has also been reported. An interesting twist of the synthons has been used in the synthesis of *N*,*N*-dibenzylformamidines.[25] A general scheme for the reaction of this paper is shown in Scheme 1. We report the scope and limitation of the reaction in the synthesis of formamidines, amidines and α-aminonitriles. The synthon $C(R^1)$–$N(R^2)_2^{2+}$ was generated from the combination of an amide $C(R^1)(O)$–$N(R^2)_2$ and a



Scheme 1.

Keywords: dication $C(R^1)$–$N(R^2)_2$; α-aminonitriles; synthons.
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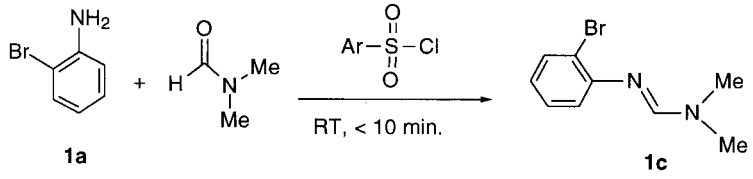
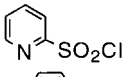
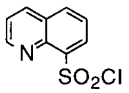
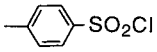


Scheme 2.

Table 1. Evaluation of coupling agents for the formation of **1c**

Entry	Coupling agent		Time (min)	Yield (%)	Entry	Coupling agent		Time (min)	Yield (%)
1		**1b**	1–2	95	4		**4b**	20–30	89
2		**2b**	2–5	90	5	CH_3COCl	**5b**	2–5	<1[a]
3	CH_3SO_2Cl	**3b**	<1	76[b]	6	PhCOCl	**6b**	20–30	<1[a]

[a] Pure amide was obtained.
[b] A by-product, methyl sulfonyl amide, was formed.

coupling agent, either a sulfonyl chloride or acyl chloride. Before our communication, only one report using the modified Vilsmayer–Haack reagent $R_2NC(O)–H+ClSO_2Ph$ in the synthesis of trisubstituted N-(X-2-benzothiazolyl)formamidines appeared.[26] A isolated case for amide dehydration to nitriles upon dehydrative formamidine formation was also reported.[27]

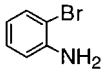
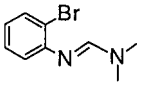
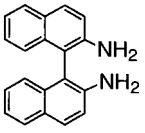
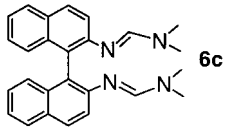
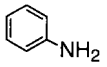
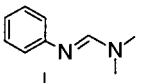
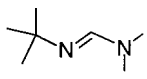
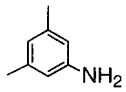
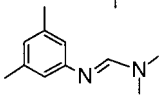
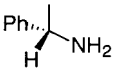
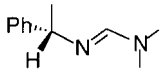
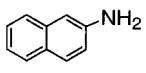
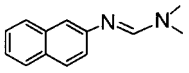
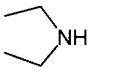
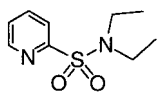
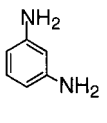
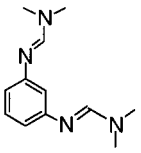
Evaluation of coupling agents

We used a reaction of forming formamidine as a typical example to evaluate the efficiency of either a sulfonyl chloride or an acyl chloride (Scheme 2). The reactivity of 2-pyridinesulfonyl chloride and *p*-toluenesulfonyl chloride is optimal for the synthesis of formamidines, with the former slightly favorable in rate and yield. Increasing the reactivity of the sulfonyl chloride by using methylsulfonyl chloride increases the rate of the reaction, but decreases the yield of formamidine, and formation of sulfonyl amide is observed as shown in entry 3 in Table 1. Lowering the reactivity of sulfonyl chloride by using 8-quinolinesulfonyl chloride slows the reaction, although no difference in selectivity is observed. However, acetyl chloride is a rather poor coupling agent as shown in entry 5 and 6. Overall, sulfonyl chlorides are better coupling agents than acyl chlorides. No experiments based on acyl chlorides were performed any further. The order of reagent addition is not important for this reaction.

Scope of formamidine formation

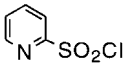
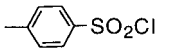
We selected the best coupling agent, 2-pyridinesulfonyl

Table 2. Scope of formamidine synthesis (all reaction finished within 5 min)

Entry	Amine		Product		Yield (%)	Entry	Amide		Product		Yield (%)
1		**1a**		**1c**	95	6		**6a**		**6c**	91
2		**2a**		**2c**	95	7	*t*-Bu-NH_2	**7a**		**7c**	38[a]
3		**3a**		**3c**	90	8		**8a**		**8c**	50[a]
4		**4a**		**4c**	91	9		**9a**		**9c**	80[b]
5		**5a**		**5c**	94						

[a] 37% amide was isolated.
[b] Sulfonamide was the only product isolated.

Table 3. Evaluation of coupling agents for the formation of **7c** (all reaction finished within 5 min)

Entry	Coupling agent	Yield (%)	Entry	Coupling agent	Yield (%)
1	 **1b**	38[a]	3	CH_3COCl **5b**	<1[b]
2	 **4b**	<1[b]			

[a] 37% amide was isolated.
[b] Pure amide was formed. No formamidine was detected by GCMS.

chloride, to evaluate the scope of the formamidine synthesis. A variety of aromatic and aliphatic amines was first evaluated. The results are summarized in Table 2. It is clear that aromatic amines are better substrates than aliphatic amines for this reaction in selectivity. The primary side products are those of sulfonyl amides generated directly from the reaction of the sulfonyl chloride and the amines. For aromatic amines, no side products have been observed. However, the amides become the major products even with quite hindered aliphatic amines such as *tert*-butyl amine. The stability of the formamidines from aliphatic amines is much reduced. They are decomposed to the corresponding amines when exposed to untreated silica gel. Diamines are transformed into di-formamidines with the same efficiency as the mono-ones. No effort was made to synthesize the mono-amine mono-formamidine compounds. Secondary amines, as expected, form amides only.

In our effort to determine whether aliphatic amines prefer a different coupling agent for this reaction, we evaluated a few of coupling agents on formation of **7c**. The results are summarized in Table 3. Although not much difference is observed between 2-pyridinesulfonyl chloride and *p*-toluenesulfonyl chloride for aromatic substrates, only the former gave any formamidine **7c**. The other coupling agents gave almost exclusively amides. This enforces our selection of 2-pyridinesulfonyl chloride in the subsequent evaluation of the scope of this reaction.

Tolerance of functional groups

In order to test the generality of the formamidine synthesis, different functional groups were added into the amine substrates, including pyridine, phenol, and ester groups. The results are summarized in Table 4. Both pyridine and phenol or a combination of the two groups are well tolerated for this reaction. No products from the direct reaction between the OH group and 2-pyridinesulfonyl chloride were observed. When the phenol group is at the ortho position of the formamidine group, the products are easily cyclized to form the corresponding oxazoles upon air oxidation. However, conjugated ester groups promote hydrolysis of the formed formamidines even in basic conditions. This is consistent with the electron-withdrawing property of the group which activates the formamidine group toward nucleophilic attack considerably. The corresponding formamides are formed. When 2-nitroaniline was used, only a small amount of the formamidine was formed; most of the starting material was unchanged. Attempted reaction of β-aminoalcohols, such as 2,2-diphenyl-2-amino-ethanol, gave a mixture of products under the same conditions as those for simple formamidine synthesis. No effort was made to purify each compound in the mixture.

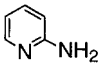
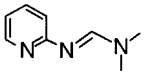
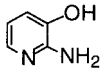
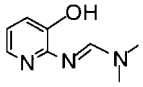
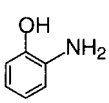
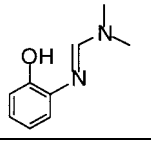
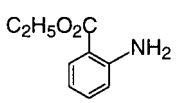
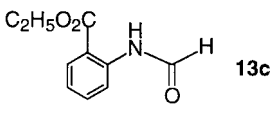
Reaction of derivatives of α-aminoacids

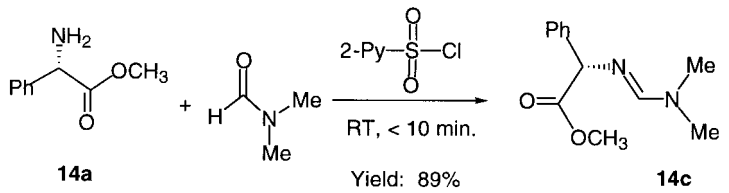
When α-aminoacids were used as amine substrates, no reaction was observed. However, α-aminoesters undergo clean transformation into α-formamidino esters (Scheme 3). No loss of optical purity for the transformation and no side products of sulfonamides have been observed for this class of substrates. It is quite interesting to note that a nearby electron-withdrawing ester group has such a strong influence on the course of the reaction, as compared with other aliphatic amines such as *tert*-butyl amine.

Synthesis of enantio-pure α-aminonitriles from α-aminoacids

When the substrates were changed to α-aminoamides, we observed quantitative transformation into the formamidines of α-aminonitriles instead (Scheme 4). This transformation involves forming and breaking of 10 bonds, and is complete in less than 10 min, with complete retention of the stereochemical configuration at the α-carbon center. Both aromatic and aliphatic α-aminoamides proceed with high efficiency. However, no reaction was observed when benzamide was used under identical conditions.

Table 4. Tolerance of functional groups in formamidine synthesis (all reactions finished within 5 min)

Entry	Amine	Product	Yield (%)	Entry	Amine	Product	Yield (%)
1	 **10a**	 **10c**	87	3	 **12a**	 **12c**	79
2	 **11a**	 **11c**	88	4	 **13a**	 **13c**	63



Scheme 3.

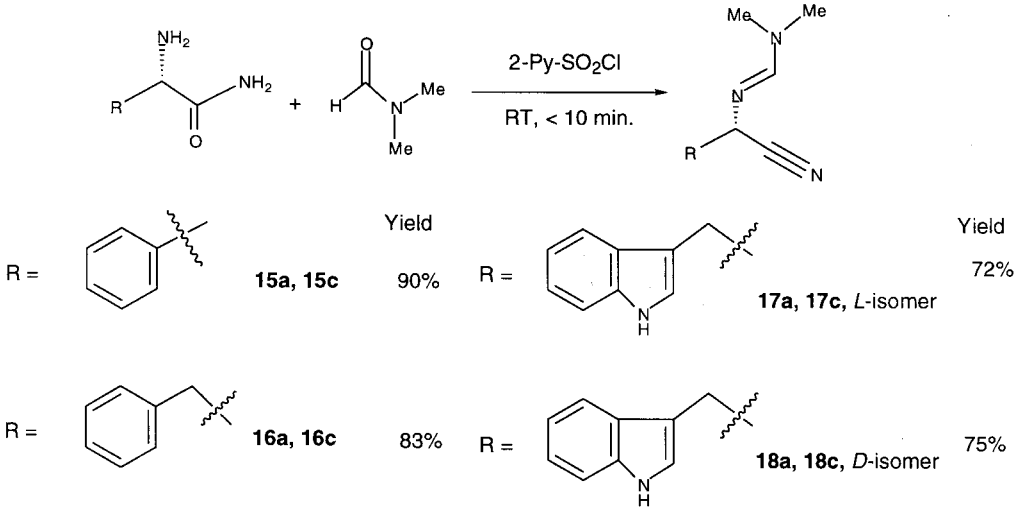
The reaction products were characterized by ^{1}H, $^{13}C\{^{1}H\}$, MS, and high resolution MS. It is interesting to note that attempts to measure the IR band of the –CN group fail to give any notable peak around 2000–2400 cm^{-1}. The stretching vibrations from the cyano group of α-aminonitriles appear in the region 2210–2250 cm^{-1} in their IR spectra.[28] When an hydroxyl or acetyl group is the substitutent on nitrogen in the α-aminonitrile molecule, the intensity of this band is considerably reduced. Our experiments enforce the conclusion that IR spectroscopy is not always a reliable method for confirming the structure of α-aminonitriles. However, the presence of an IR absorption band in the region does suggest the existence of a –CN group because of limited overlap from other groups.

This reaction represents the reverse of the Strecker synthesis.[29] Since the starting materials were synthesized from α-aminoacids (Scheme 5), it seems that there is no synthetic value for this reaction. However, it provides a cheap source of chiral pools from naturally occurring α-aminoacids. Earlier work on the use of α-aminonitriles has been reviewed.[30] For example, they can serve as precursors to chiral α-aminoaldehydes, chiral α-aminoalcohols, and chiral diamines, and all of them are difficult to make through other synthetic routes, and are important intermediates in organic synthesis. Chiral α-aminonitriles have been used extensively as precursors for the synthesis of amidine peptides, thiazoline peptides, and tetrazole peptides, which show interesting biological properties.[31]

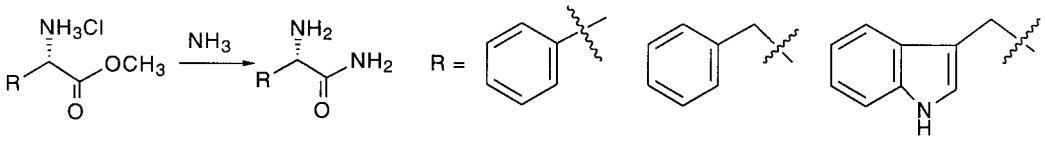
Synthesis of chiral α-aminonitriles has been previously realized from the dehydration of *N*-substituted α-aminoamides with phosphorus oxychloride.[32] The reaction conditions include introduction of an *N*-*o*-nitrophenylsulfenyl group (NPS), dehydration of the amide group, and de-protection of the NPS group, with an overall yield of 10–40%. Some earlier investigators employed benzyloxycarbonyl, phthaloyl, or acetyl as an *N*-protecting group.[33]

Exploration of stoichiometric reaction and variation of substituents on nitrogen of amides in the synthons

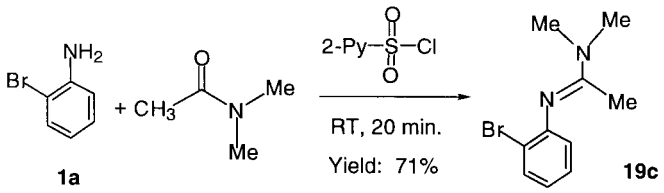
In the effort to expand the scope further, we studied the formamidine formation reaction using solvents other than neat *N*,*N*-dimethylformamide to explore the possibility of using a stoichiometric quantity. It turned out that neat DMF is critical to the success of the reaction. For example, no



Scheme 4.



Scheme 5.



Scheme 6.

reaction was observed in a CH_2Cl_2/DMF (1:1) mixture. It is also interesting to note that *N*,*N*-diethylformamide under the same conditions gave no indication of the formation of the corresponding formamidines. Other amides evaluated such as $CH_2{=}CHC(O)NMe_2$ also gave no formamidines or amidines, whether the amino substrates are 2-bromoaniline or 2-hydroxyaniline.

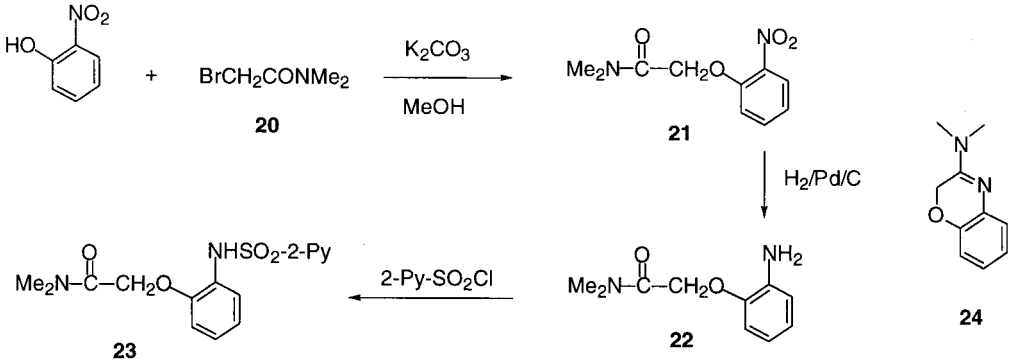
Formation of amidines

Success of the formamidine formation prompted us to evaluate the synthesis of amidines. Under the same conditions as those for the formation of formamidines, the reaction of 2-bromoaniline gave the corresponding amidine in high yield (Scheme 6). However, the reaction rate slows down substantially. Other amines evaluated as substrates such as aniline, 4-nitroaniline and 3,5-dimethylaniline gave only the corresponding amides, without any participation of *N*,*N*-dimethylacetamide. The reaction of α-aminoamides, however, gave products too unstable to be isolated.

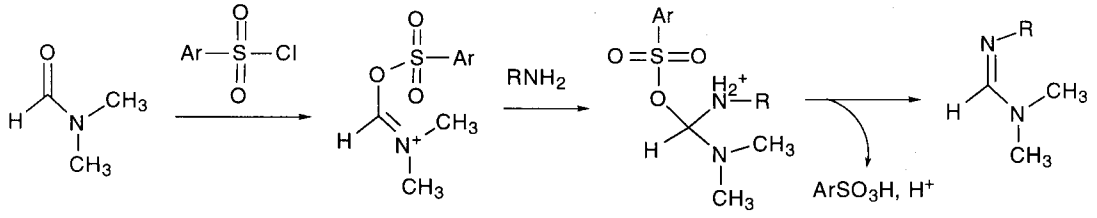
Attempts to synthesize cyclic amidines such as **24** as shown in Scheme 7 fail to give the cyclic amidine under a variety of solvents including CH_2Cl_2, CH_2Cl_2/HCl, CH_3COOH, and in neat state (2-pyridinesulfonyl chloride is a liquid at RT). Exclusive formation of the sulfonamide is observed. It appears that the sulfonyl chloride has a greater reactivity for an amino group than for an amide group at the same concentration. This is consistent with our observation that formation of formamidines is only observed in neat DMF. Any dilution of the amide group will tilt the balance in favor of sulfonamide formation.

Compared with the experimental conditions of 100–120° for P_2O_5, PCl_5, or $SOCl_2$ as coupling agents, this reaction is advantageous for its mild experimental conditions, high chemical yields, and short reaction times. In all of our reactions, only one isomer is observed. The structures of all unknown formamidines were confirmed by high resolution MS, ^{1}H NMR, and/or $^{13}C\{^1H\}$ NMR. Comparison of the NMR spectra of **2c** and **4c** with literature assignments confirms the formation of the trans isomers. This is consistent with a thermodynamically controlled reaction. In analogy with the mechanism proposed for the formation of formamidines by other coupling agents,[34] a proposed mechanism is shown on Scheme 8.

In conclusion, we have described a simple, convenient, and efficient preparation of formamidines from primary amines and *N*,*N*-dimethylformamide in the presence of sulfonyl chlorides. Its advantages lie in: (a) the straightforwardness and simplicity of the procedure; (b) the mildness of the reaction conditions and excellent yields; and (c) the short reaction time and chemoselectivity. The reaction scope of formamidine formation is quite general with the amine



Scheme 7.



Scheme 8. A possible mechanistic model.

substrates, including compatibility with a variety of functional groups. However, only DMF gives synthetically useful and general reactions. Even a change from methyl to ethyl in the formamide shuts down the formation of formamidines all together. For α-aminoesters, clean transformation into the corresponding formamidines is observed without any interference from the ester group. The stereochemical configuration of the α-carbon is maintained. For α-aminoamides, we observed a clean transformation into α-aminonitriles with retention of the stereocenter. These reactions expand the use of naturally occurring α-aminoacids as chiral pools in organic synthesis. Only limited in success was achieved in the synthesis of amidines by this strategy. A mechanism consistent with the observations of analogous coupling agents and all the experimental results in this study is proposed.

Experimental

2-Pyridinesulfonyl chloride was synthesized according to a literature preparation with 84% isolated yield.[35] This compound is not stable at rt, and normally is kept in a freezer. The other sulfonyl chlorides are commercially available and used as received. DMF was purchased from Fisher Scientific; *N*,*N*-diethylformamide, *N*,*N*-dimethyl acrylamide, 2-bromoaniline, *p*-toluenesulfonyl chloride, methylsulfonyl chloride, 8-quinolinesulfonyl chloride, acetyl chloride, benzoyl chloride, aniline, 3,5-dimethyl aniline, 2-naphthyl amine, 1,3-phenylenediamine, 1,1′-binaphthyl-2,2′-diamine, *t*-butyl amine, 2-aminopyridine, 2-hydroxy-aniline, 3-hydroxy-2-aminopyridine, ethyl 2-aminobenzoate, *N*,*N*-dimethylacetamide, 2-nitrophenol, *N*,*N*-dimethyl bromoacetamide, and Pd/C were from Aldrich. Dihydrogen (H_2) and chlorine (Cl_2) were from Aga gases (Hammond, IN). All α-aminoamides were synthesized according to a literature procedure from α-aminoacids or α-aminoesters, which were obtained from Aldrich.[36]

^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on Bruker 200, 400, and 500 MHz and Varian 300 MHz NMR spectrometers. All chemical shifts were referenced by the residual solvent peak(s) of deuterated solvents. All low resolution MS data were obtained from a HP 5897 Mass spectrometer, and all high resolution MS data from Mass Spectrometry Center of The University of Illinois at Urbana.

General procedure for the formation of formamidine **1c**–**14c**: All reactions were performed with 0.10 mmol of amines and 0.15 mmol of Ar-SO_2Cl in 0.5 mL DMF at rt. Isolated yields were based on amines. After 1.5 equiv. of a sulfonyl chloride was dissolved in DMF for 5 min, an amine (1.0 equiv.) was added at room temperature. The reaction mixture was stirred for the specified time listed in the tables or checked by TLC until the reaction was finished. After the solvent was removed, K_2CO_3 solution (4M) was added. The mixture was then extracted with ether. The ether solution was dried over Na_2SO_4 and the solvent was removed to generate the pure product. All of the products were characterized by ^1H NMR, $^{13}C\{^1H\}$ NMR, MS, and HRMS.

General procedure for the formation of formamidine **15c**–**17c**: All reactions were performed with 0.10 mmol of amines and 0.30 mmol of Ar-SO_2Cl in 0.5 mL DMF at rt. The products were isolated by 20×20 cm TLC plates.

***N*,*N*-Dimethyl 2′-bromoanilino formamidine (1c).** ^1H NMR in CD_3CN, δ, 7.91 (s, 1H, N=CH–N), 7.73 (dd, $^3J_{HH}$=6.1 Hz, $^5J_{HH}$=0.7 Hz, 1H, Ar-H), 7.51–7.46 (m, 2H, Ar-H), 7.31 (td, $^3J_{HH}$=5.8 Hz, $^5J_{HH}$=1.4 Hz, 1H, Ar-H), 3.48 (s, 3H, CH_3), 3.29 (s, 3H, CH_3). MS data, 226, 228 (20%, M^+), 211, 213 (5%, $M-CH_3^+$), 186, 184, 182 (20%, $M-N(CH_3)_2$), 157, 155 ($M-CH(N)-NMe_2^+$), 147 (100%, $M-Br^+$), 132, 131 ($M-Br-Me^+$), 106 (40%), 76 (20%). HRMS for $C_9H_{11}BrN_2$, found: 226.009; calcd: 226.011.

***N*,*N*-Dimethyl anilino formamidine (2c).** ^1H NMR in CD_3CN, δ, 7.59 (s, 1H, N=CH–N), 7.22 (td, $^3J_{HH}$=7.0 Hz, $^5J_{HH}$=1.8 Hz, 2H, Ar-H), 6.95 (t, $^3J_{HH}$=7.2 Hz, 1H, Ar-H), 6.90 (d, $^3J_{HH}$=8.4 Hz, 2H, Ar-H), 2.96 (s, 6H, CH_3). MS data, 148 (55%, M^+), 133 (25%, $M-CH_3^+$), 120 (20%), 106 (40%), 104 (40%, $M-NMe_2^+$), 77 (100%, Ph^+), 73 (90%). HRMS for $C_9H_{12}N_2$, found: 148.100; cald: 148.100.

***N*,*N*-Dimethyl 3′,5′-dimethylanilino formamidine (3c).** ^1H NMR in CD_3CN, δ, 7.56 (s, 1H, N=CH–N), 6.62 (s, 1H, Ar-H), 6.52 (s, 2H, Ar-H), 2.94 (s, 6H, NCH_3), 2.23 (s, 6H, CH_3). MS data, 176 (100%, M^+), 175 (65%, $M-H^+$), 161 (40%, $M-CH_3^+$), 148 (40%), 134 (90%), 105 (60%, $M-CH(N)-NMe_2^+$), 91(26%), 79 (57%), 77 (55%). HRMS for $C_{11}H_{16}N_2$, found: 176.131; calcd: 176.131.

***N*,*N*-Dimethyl 2′-naphthylamino-formamidine (4c).** ^1H NMR in CD_3CN, δ, 7.78–7.71 (m, 4H, Ar-H), 7.40 (td, $^3J_{HH}$=7.2 Hz, $^5J_{HH}$=1.2 Hz, 1H, Ar-H), 7.30 (td, $^3J_{HH}$=8.4 Hz, $^5J_{HH}$=1.5 Hz, 1H, Ar-H), 7.26 (d, $^5J_{HH}$=1.8 Hz, 1H, Ar-H), 7.20 (dd, $^3J_{HH}$=8.7 Hz, $^5J_{HH}$=2.1 Hz, 1H, Ar-H), 3.01 (s, 6H, CH_3). MS data, 198 (80%, M^+), 183 (30%, $M-CH_3^+$), 170 (40%), 156 (100%), 127 (70%, $M-CH(N)-NMe_2^+$). HRMS for $C_{13}H_{14}N_2$, found: 198.116; calcd: 198.116.

1,3-Di-(*N*,*N*-dimethylformamidino)benzene (5c). ^1H NMR in CD_3CN, δ, 7.61 (s, 2H, N=CH–N), 7.07 (t, $^3J_{HH}$=7.8 Hz, 1H, Ar-H), 6.53 (dd, $^3J_{HH}$=7.5 Hz, $^4J_{HH}$=1.8 Hz, 2H, Ar-H), 6.46 (t, $^5J_{HH}$=2.4 Hz, 1H, Ar-H), 2.96 (s, 12H, CH_3). MS data, 218 (100%, M^+), 203 (10%, $M-CH_3^+$), 190 (30%), 176 (20%), 172 (15%, $M-NMe_2^+$), 158 (10%), 147 (15%), 131 (30%, $M-2\times NMe_2+H^+$). HRMS for $C_{12}H_{18}N_4$, found: 218.154; calcd: 218.153.

2,2′-Di-(*N*,*N*-dimethylformamidino)-1,1′-binaphthyl (6c). ^1H NMR in CD_3OD, δ, 7.81 (t, $^3J_{HH}$=8.4 Hz, 4H, Ar-H), 7.42 (s, 2H, N=CH–N), 7.25 (td, $^3J_{HH}$=7.3 Hz, $^4J_{HH}$=0.9 Hz, 2H, Ar-H), 7.24 (d, $^3J_{HH}$=8.7 Hz, 2H, Ar-H), 7.13 (td, $^3J_{HH}$=7.5 Hz, $^4J_{HH}$=1.2Hz, 2H, Ar-H), 7.02 (d, $^3J_{HH}$=8.7 Hz, 2H, Ar-H), 2.55 (s, 12H, CH_3). MS data, 394 (68%, M^+), 350 (20%, $M-NMe_2^+$), 323 (53%, $M-CH(N)-NMe_2^+$), 307 (30%, $M-2\times NMe_2+H^+$), 294 (35%), 278 ($M-CH(N)-NMe_2-NMe_2-H^+$), 265 (70%), 252 (35%, $M-2\times CH(N)-NMe_2^+$), 224 (20%), 197 (40%). HRMS for $C_{26}H_{26}N_4$, found: 394.214; calcd: 394.216.

***N*,*N*-Dimethyl *tert*-butylamino-formamidine (7c).** ^{1}H NMR in CD_3CN, δ, 7.87 (N=CH–N), 2.90 (s, NCH_3), 2.78 (s, NCH_3), 2.27 (s, CH_3). MS data, 128 (20%, M^+), 113 (100%, $M-CH_3^+$).

***N*,*N*-Dimethyl α-methylbenzylamino-formamidine (8c).** ^{1}H NMR in $CDCl_3$, δ, 7.58 (s, 1H, N=CH–N), 7.38–7.12 (m, 5H, Ph), 4.42 (q, $^3J_{HH}$=6.8 Hz, 1H, –CH–N), 3.00 (s, 6H, NCH_3), 1.57 (d, $^3J_{HH}$=6.8 Hz, 3H, C–CH_3).

***N*,*N*-Diethyl 2-pyridinesulfonamide (9c).** ^{1}H NMR in $CDCl_3$, 8.66 (dd, $^3J_{HH}$=4.6 Hz, $^4J_{HH}$=1.8 Hz, 1H, Ar-H), 7.93 (dt, $^3J_{HH}$=7.9 Hz, $^4J_{HH}$=1.7 Hz, 1H, Ar-H), 7.86 (dt, $^3J_{HH}$=7.7 Hz, $^4J_{HH}$=1.7 Hz, 1H, Ar-H), 7.43 (ddd, $^3J_{HH}$=7.0 Hz, $^4J_{HH}$=4.7 Hz, $^5J_{HH}$=1.1 Hz, 1H, Ar-H), 3.39 (q, $^3J_{HH}$=7.2 Hz, 4H, CH_2), 1.13 (t, $^3J_{HH}$=7.2 Hz, CH_3). MS data, 199 (2%, $M-CH_3^+$), 169, 107 (26%, $M-C_5H_4N-C_2H_5^+$), 78 (78%, $C_5H_4N^+$), 79 (61%, $C_5H_5N^+$), 72 (100%, $N(CH_2CH_3)_2^+$).

2-(*N*′,*N*′-Dimethylformamidino) pyridine (10c). ^{1}H NMR in CD_3CN, δ, 8.42 (s, 1H, N=CH–N), 8.17 (dd, $^3J_{HH}$=4.5 Hz, $^5J_{HH}$=1.8 Hz, 1H, Ar-H), 7.53 (dd, $^3J_{HH}$=5.7 Hz, $^5J_{HH}$=0.9 Hz, 1H, Ar-H), 6.84 (dd, $^3J_{HH}$=4.5 Hz, $^5J_{HH}$=1.5 Hz, 1H, Ar-H), 6.80 (dd, $^3J_{HH}$=7.2 Hz, $^5J_{HH}$=0.9 Hz, 1H, Ar-H), 3.06 (s, 3H, CH_3), 3.00 (s, 3H, CH_3). MS data, 149 (20%, M^+), 134 (35%, $M-CH_3^+$), 119 (5%, $M-2\times CH_3^+$), 105 (15%, $M-NMe_2^+$), 93 (50%), 78 (70%, $M-CH(N)-NMe_2^+$), 73 (100%). HRMS for $C_8H_{11}N_3$, found: 149.096; calcd: 149.095.

2-(*N*′,*N*′-Dimethylformamidino) phenol (11c). ^{1}H NMR in CD_3COCD_3, δ, 7.93 (s, 1H, N=CH–N), 6.96 (dd, $^3J_{HH}$=9.9 Hz, $^4J_{HH}$=2.2 Hz, 1H, Ar-H), 6.80 (td, $^3J_{HH}$=7.4 Hz, $^4J_{HH}$=1.5 Hz, 1H, Ar-H), 6.73 (dd, $^3J_{HH}$=7.9 Hz, $^4J_{HH}$=1.6 Hz, 1H, Ar-H), 6.67 (td, $^3J_{HH}$=7.5 Hz, $^4J_{HH}$=1.6 Hz, 1H, Ar-H), 3.11 (s, 3H, CH_3), 3.020 (s, 3H, CH_3). ^{13}C{^{1}H} NMR in CD_3COCD_3, δ, 153.3 (N=CH–N), 150.9 (C–O), 138.2 (CC), 123.1 (CH), 120.1 (impurity), 119.6 (CH), 115.9 (CH), 113.3 (CH), 39.8 (CH_3), 33.9 (CH_3). MS data, 164 (70%, M^+), 147 (18%, $M-OH^+$), 120 (100%, $M-N(CH_3)_2^+$). HRMS for $C_9H_{12}N_2O$, found: 164.094607; calcd: 164.094963. HRMS for M−2H, $C_9H_{10}N_2O$, found: 162.079; calcd: 162.079.

3-Hydroxy-2-(*N*′,*N*′-dimethylformamidino) pyridine (12c). ^{1}H NMR in $CDCl_3$, δ, 8.60 (s, 1H, N=CH–N), 7.76 (dd, $^3J_{HH}$=5.2 Hz, $^4J_{HH}$=1.7 Hz, 1H, Ar-H), 7.10 (td, $^3J_{HH}$=7.9 Hz, $^4J_{HH}$=1.7 Hz, 1H, Ar-H), 6.82 (dd, $^3J_{HH}$=7.8 Hz, $^4J_{HH}$=5.1 Hz, 1H, Ar-H), 3.15 (s, 3H, CH_3), 3.11 (s, 3H, CH_3). MS data, 165 (50%, M^+), 150 (18%, $M-CH_3^+$), 121 (100%, $M-N(CH_3)_2^+$), 110 (100%, 3-OH-2-NH_2-Py^+), 94 (30%, 3-OH-2-0-Py^+), 82 (60%, C_4H_4NO, 71 (30%, $CH(=N)(-NMe_2)^+$), 55 (75%, $C_3H_3O^+$). HRMS for $C_8H_{11}N_3O$, found: 165.090; calcd: 165.090. HRMS for M−2H, $C_8H_9N_3O$, found: 163.074; calcd: 163.075.

Ethyl 2-(formylamino) benzoate (13c). ^{1}H NMR in $CDCl_3$, δ, 11.0 (brs, 1H, NH), 8.70 (d, $^3J_{HH}$=8.4 Hz, 1H, CH(O)), 8.51 (s, 1H, CHO), 8.06 (d, $^3J_{HH}$=8.0 Hz, 1H, Ar-H), 7.55 (t, $^3J_{HH}$=7.8 Hz, 1H, Ar-H), 7.12 (t, $^3J_{HH}$=7.7 Hz, 1H, Ar-H), 4.39 (q, $^3J_{HH}$=7.0 Hz, 2H, OCH_2), 1.42 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 168.1 (CCO_2), 159.9 (HCON), 140.9 (CC), 135.0 (CH), 131.3 (CH), 123.5 (CH), 121.6 (CH), 115.9 (CC), 61.9 (OCH_2), 14.6 (CH_3). MS data, 193 (10%, M^+), 165 (40%, $M-CO^+$), 119 (100%, $M-HCO_2CH_2CH_3$), 92 (30%, $C_6H_4NH+H^+$), 65 (20%, $C_5H_5^+$). HRMS for $C_{10}H_{11}NO_3$, found: 193.074; calcd: 193.074.

Methyl L-phenyl alanine α-(*N*′,*N*′-dimethylformamidino) carboxylate (14c). ^{1}H NMR in $CDCl_3$, δ, 7.40–7.18 (m, 6H, Ar-H and HCN_2), 4.89 (s, 1H, CH–N), 3.61 (s, 3H, OCH_3), 2.83 (s, 6H, NCH_3). MS data, 220 (1%, M^+), 205 (1%, $M-Me^+$), 161 (100%, $M-CO_2CH_3^+$). HRMS for $C_{12}H_{16}N_2O_2$, found: 220.121; calcd: 220.121.

L-Phenyl alanine α-(*N*′,*N*′-dimethylformamidino) nitrile (15c). ^{1}H NMR in $CDCl_3$, δ, 7.59 (s, 1H, N=CH–N), 7.44–7.36 (m, 5H, Ar-H), 5.42 (s, 1H, –CH(CN)–N), 2.95 (s, 6H, CH_3). ^{13}C{^{1}H} NMR, δ, in $CDCl_3$, 156.9 (CHN_2), 137.9, 129.3, 128.8, 127.3, 119.9 (CN), 58.0. MS data, 187 (100%, M^+), 161 (5%, $M-CN^+$), 147 (30%, $M-2CH_3^+$), 116 (95%, $M-CH(=N)NMe_2^+$), 106 (100%, $Ph-CHNH_2^+$), 89 (Ph-C^+), 77 (50%, Ph^+), 71 (70%, $CH(=N)NMe_2^+$). HRMS, $C_{11}H_{13}N_3$, found: 187.111; calcd: 187.111.

L-Phenyl alanine α-aminoamide (15a).[36] ^{1}H NMR in $CDCl_3$, δ, 7.43–7.27 (m, 5H, Ar-H), 6.92 (brs, 1H, NH), 6.08 (brs, 1H, NH), 4.52 (s, 1H, $CH(NH_2)$), 1.87 (s, 6H, CH_3).

L-Benzyl alanine α-(*N*′,*N*′-dimethylformamidino) nitrile (16c). ^{1}H NMR in CD_3COCD_3, δ, 7.39 (m, 2H, *o*-H), 7.33 (m, 2H, *m*-H), 7.32 (s, 1H, N=CH–N), 7.20 (m, 1H, *p*-H), 4.43 (m, 1H, –CH(CN)–N), 3.02 (m, 2H, CH_2), 2.85 (s, 6H, CH_3). ^{13}C{^{1}H} NMR in CD_3COCD_3, δ, 157.2 (CHN_2), 137.3, 130.2, 128.5, 127.1, 120.9 (CN), 56.9, 42.9. MS data, 201 (15%, M^+), 186 (1%, $M-CH_3^+$), 174 (8%, $M-HCN^+$), 110 (100%, $M-CH_2Ph^+$), 91 (35%, $PhCH_2^+$), 77 (10%, Ph^+), 65 (20%, $C_5H_5^+$). HRMS, $C_{12}H_{15}N_3$, found: 201.126; calcd: 201.127.

L-Benzyl alanine α-aminoamide (16a).[36] ^{1}H NMR in $CDCl_3$, δ, 7.35–7.23 (m, 5H, Ar-H), 7.12 (brs, 1H, NH), 5.69 (brs, 1H, NH), 3.62 (dd, $^3J_{HH}$=9.7 Hz, $^3J_{HH}$=4.0 Hz, 1H, CH(NH)), 3.28 (dd, $^3J_{HH}$=13.7 Hz, $^3J_{HH}$=4.0 Hz, 1H, CH_2), 2.72 (dd, $^3J_{HH}$=13.7 Hz, $^3J_{HH}$=9.5 Hz, 1H, CH_2), 1.34 (brs, 2H, NH_2).

L-Tryptophan α-(*N*′,*N*′-dimethylformamidino) nitrile (17c). ^{1}H NMR in CD_3COCD_3, δ, 10.16 (brs, 1H, N–H), 7.64 (dd, $^3J_{HH}$=6.4 Hz, 1H, Ar-H), 7.40 (td, $^3J_{HH}$=6.6 Hz, 1H, Ar-H), 7.40 (s, 1H, N=CH–N), 7.29 (d, $^4J_{HH}$=1.8 Hz, 1H, Ar-H), 7.11 (td, $^3J_{HH}$=6.4 Hz, $^4J_{HH}$=0.8 Hz, 1H, Ar-H), 7.03 (td, $^3J_{HH}$=6.0 Hz, $^4J_{HH}$=0.8 Hz, 1H, Ar-H), 4.47 (t, $^3J_{HH}$=5.7 Hz, 1H, –CH(CN)–N), 3.22 (ABd, $^2J_{HH}$=14.8 Hz, $^3J_{HH}$=6.2 Hz, 1H, CH_2), 3.13 (ABd, $^2J_{HH}$=14.2 Hz, $^3J_{HH}$=5.8 Hz, 1H, CH_2), 2.85 (s, 6H, CH_3). ^{13}C{^{1}H} NMR in CD_3COCD_3, δ, 157.1 (CHN_2), 137.0, 128.1, 124.4, 124.2, 121.6, 121.5, 119.1, 119.0, 111.7, 111.6, 110.5, 56.8, 33.1. MS data, 240 (4%, M^+), 130 (100%, $M-CH(CN)(=N-CHNMe_2)^+$). HRMS for $C_{14}H_{16}N_4$, found: 240.138; calcd: 240.137. HPLC analysis on a chiracel OD column by isopropanol/hexane (5/95) gave a retention time of 31.1 min.

L-Tryptophan α-aminoamide (17a).[36] ^{1}H NMR in CD_3COCD_3, δ, 8.30 (brs, 1H, ArN–H), 7.68 (d, $^3J_{HH}$=7.8 Hz, 1H, Ar-H), 7.38 (d, $^3J_{HH}$=7.7 Hz, 1H, Ar-H), 7.25–7.08 (m, 4H, Ar-H, N–H), 5.66 (brs, 1H, N–H), 3.73 (dd, $^3J_{HH}$=4.1 Hz, $^3J_{HH}$=9.2 Hz, 1H, CH(N)), 3.39 (dd, $^3J_{HH}$=4.1 Hz, $^3J_{HH}$=14.2 Hz, 1H, CH_2), 2.94 (dd, $^3J_{HH}$=9.2 Hz, $^3J_{HH}$=14.2 Hz, 1H, CH_2), 1.47 (brs, 2H, NH_2).

D-Tryptophan δ-(*N′*,*N′*-dimethylformamidino) nitrile (18c). ^{1}H NMR in CD_3COCD_3, δ, 10.14 (brs, 1H, N–H), 7.62 (dd, $^3J_{HH}$=7.9 Hz, $^4J_{HH}$=0.4 Hz, 1H, Ar-H), 7.38 (td, $^3J_{HH}$=7.2 Hz, $^4J_{HH}$=0.6 Hz, 1H, Ar-H), 7.37 (s, 1H, N=CH–N), 7.27 (d, $^4J_{HH}$=2.2 Hz, 1H, Ar-H), 7.09 (td, $^3J_{HH}$=6.5 Hz, $^4J_{HH}$=0.9 Hz, 1H, Ar-H), 7.01 (t, $^3J_{HH}$=5.6 Hz, $^4J_{HH}$=0.8 Hz, 1H, Ar-H), 4.47 (t, $^3J_{HH}$=5.7 Hz, 1H, –CH(CN)–N), 3.21 (ABd, $^2J_{HH}$=14.8 Hz, $^3J_{HH}$=7.5 Hz, 1H, CH_2), 3.10 (ABd, $^2J_{HH}$=14.2 Hz, $^3J_{HH}$=6.7 Hz, 1H, CH_2), 2.81 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR in CD_3COCD_3, δ, 157.1, 137.0, 128.1, 124.4, 124.2, 121.7, 121.5, 119.1, 119.0, 111.7, 111.6, 110.5, 56.8, 33.1. MS data, 240 (4%, M^+), 130 (100%, M−CH(CN)(=N–$CHNMe_2)^+$). HRMS for $C_{14}H_{16}N_4$, found: 240.137; calcd: 240.137. HPLC analysis on a chiracel OD column by isopropanol/hexane (5/95) gave a retention time of 32.8 min.

D-Tryptophan α-aminoamide (18a).[36] ^{1}H NMR in CD_3COCD_3, δ, 8.23 (brs, 1H, ArN–H), 7.68 (d, $^3J_{HH}$=7.6 Hz, 1H, Ar-H), 7.38 (d, $^3J_{HH}$=8.0 Hz, 1H, Ar-H), 7.25–7.08 (m, 4H, Ar-H, N–H), 5.57 (brs, 1H, N–H), 3.73 (dd, $^3J_{HH}$=4.1 Hz, $^3J_{HH}$=9.2 Hz, 1H, CH(N)), 3.40 (dd, $^3J_{HH}$=4.1 Hz, $^3J_{HH}$=14.2 Hz, 1H, CH_2), 2.94 (dd, $^3J_{HH}$=9.2 Hz, $^3J_{HH}$=14.2 Hz, 1H, CH_2), 1.45 (brs, 2H, NH_2).

***N*,*N*-Dimethyl 2′-bromoanilino acetamidine (19c).** 2-Bromoaniline (0.10 mmol) was dissolved in 0.25 mL *N*,*N*-dimethyl acetamide. 2-Pyridinesulfonyl chloride (0.20 mmol) was added into the above solution in one portion. The mixture was stirred at rt for about 20 min. The products were worked up as described above for the synthesis of formamidines. ^{1}H NMR in CD_3CN, δ, 7.49 (dd, $^3J_{HH}$=8.0 Hz, $^4J_{HH}$=1.4 Hz, 1H, Ar-H), 7.19 (td, $^3J_{HH}$=7.4 Hz, $^4J_{HH}$=1.4 Hz, 1H, Ar-H), 6.79 (td, $^3J_{HH}$=7.7 Hz, $^4J_{HH}$=1.6 Hz, 1H, Ar-H), 6.71 (dd, $^3J_{HH}$=7.9 Hz, $^4J_{HH}$=1.6 Hz, 1H, Ar-H), 3.03 (s, 6H, NMe_2), 1.80 (s, 3H, CH_3). MS data, 240, 242 (12%, M^+), 196, 198 (45%, $M-NMe_2^+$), 161 (100%, $M-Br^+$), 155, 157 (30%, $M-CH_3C(=N)NMe_2^+$). HRMS for $C_{10}H_{13}N_2$, found: 240.026; calcd: 240.026.

***N*,*N*-Dimethyl 2-bromoacetamide (20).**[37] 2-Bromo acetyl bromide (4 g, 20 mmol) and dimethyl ammonium chloride (2.43 g, 30 mmol) were suspended in CH_2Cl_2 (35 mL). Triethyl amine (3.5 g, 35 mmol) was added dropwise. The resulting mixture was stirred overnight, and filtered. Upon removal of the solvent, the solid was extracted with diethyl ether. Removal of the solvent gave **16**, with 89% yield. ^{1}H NMR in $CDCl_3$, δ, 4.08 (s, 2H, CH_2), 3.10 (s, 3H, CH_3), 2.99 (s, 3H, CH_3).

***N*,*N*-Dimethyl 2′-nitrophenoxo acetamide (21).**[37] 2-Nitrophenol (209 mg, 1.5 mmol) and *N*,*N*-dimethyl 2-bromoacetamide (500 mg, 3.0 mmol) were dissolved in acetone. K_2CO_3 (5 equiv.) was added. The mixture was refluxed overnight or as needed for complete reaction as checked by TLC. The mixture was purified on a silica gel column eluated by ethyl acetate. The product was contaminated by *N*,*N*-dimethyl 2-bromoacetamide. ^{1}H NMR in $CDCl_3$, δ, 7.85 (d, $^3J_{HH}$=8.1 Hz, 1H, Ar-H), 7.52 (t, $^3J_{HH}$=7.6 Hz, 1H, Ar-H), 7.19 (d, $^3J_{HH}$=8.3 Hz, 1H, Ar-H), 7.08 (t, $^3J_{HH}$=7.7 Hz, 1H, Ar-H), 4.85 (s, 2H, CH_2), 3.14 (s, 3H, CH_3), 2.97 (s, 3H, CH_3).

***N*,*N*-Dimethyl 2′-aminophenoxo acetamide (22).**[37] *N*,*N*-Dimethyl 2′-nitrophenoxo acetamide (**19**) was dissolved in methanol, and hydrogenated by H_2 catalyzed by Pd/C (10% Pd). The product was purified by a silica gel column elauated by ethyl acetate/hexane (1:1). The yield was 90%. ^{1}H NMR in $CDCl_3$, δ, 6.85 (t, $^3J_{HH}$=8.1 Hz, 1H, Ar-H), 6.83 (d, $^3J_{HH}$=8.1 Hz, 1H, Ar-H), 6.74 (d, $^3J_{HH}$=7.5, 1H, Ar-H), 6.70 (t, $^3J_{HH}$=7.0 Hz, 1H, Ar-H), 4.73 (s, 2H, CH_2), 4.02 (brs, 2H, NH_2), 3.06 (s, 3H, CH_3), 3.00 (s, 3H, CH_3).

***N*,*N*-Dimethyl 2′-(2″-pyridylsulfonamido)phenoxo acetamide (23).** *N*,*N*-Dimethyl 2′-aminophenoxo acetamide (**22**) (12 mg, 0.062 mmol) was dissolved in CH_2Cl_2, or CH_3COOH, or in neat state. 2-Pyridinesulfonyl chloride (1.5–3 equiv.) was added in one portion at rt. The product was purified by a silica gel column. The yield was 90%. ^{1}H NMR in $CDCl_3$, δ, 8.85 (s, 1H, NH), 8.65 (d, $^3J_{HH}$=4.5 Hz, 1H, Ar-H), 7.98 (d, $^3J_{HH}$=7.7 Hz, 1H, Ar-H), 7.82 (t, $^3J_{HH}$=6.9 Hz, 1H, Ar-H), 7.64 (dd, $^3J_{HH}$=7.1 Hz, $^4J_{HH}$=2.4 Hz, 1H, Ar-H), 7.42 (dd, $^3J_{HH}$=7.5 Hz, $^4J_{HH}$=4.6 Hz, 1H, Ar-H), 7.02–6.96 (m, 2H, Ar-H), 6.84 (dd, $^3J_{HH}$=7.3 Hz, $^4J_{HH}$=2.5 Hz, 1H, Ar-H), 4.64 (s, 2H, CH_2O), 2.98 (s, 6H, NCH_3).

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