The Use of Chloroformamidine Hydrochloride as a Reagent for the Synthesis of Guanidines from Electron Deficient Aromatic Amines

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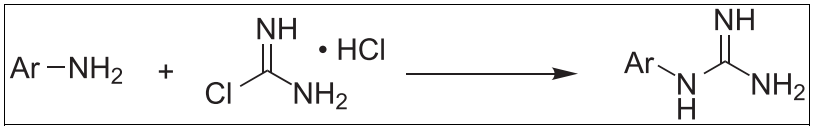

In efforts to optimize a manufacturing process for an internal development compound, a clean, efficient approach to guanidine synthesis using chloroformamidine hydrochloride was identified. To investigate the general utility of this methodology towards electron-deficient aromatic amines, a set of favorable conditions were developed from a series of screens, and the scope of the reaction was probed. The successful application of this chemistry to a variety of pyridines, anilines, and heterocyclic compounds highlights its use as an improved, alternative guanylation method for this often challenging set of aromatic amines.

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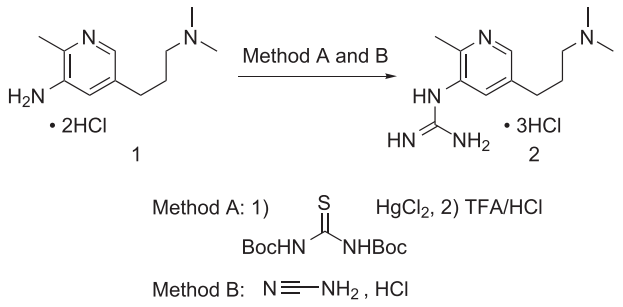
Guanidines are of great importance in the pharmaceutical industry due to their many synthetic applications, often being utilized as heterocyclic precursors, strong bases and catalysts, and their alkaloids have exhibited a broad range of antimicrobial and antitumor activities [1]. For these reasons, much effort has gone into the development of facile, efficient guanylating reagents. Many methods for the synthesis of substituted guanidines reported in the literature often perform well with electron-rich amines, but only modestly, if at all, with electron-deficient aromatic amines [1]. This paper reports a clean, convenient one-pot synthesis of guanidines from electron-deficient aromatic amines using chloroformamidine hydrochloride as the guanylating reagent.

The methodology presented herein evolved from the need to identify and develop a scalable synthesis for a guanidine intermediate **2** associated with an internal development project (Scheme 1) [2]. The initial focus for this transformation was on utilizing the two most common approaches to guanidines from electron-deficient aromatic amines. Our first attempts involved the reaction of pyridine amine **1** with bis-Boc-thiourea in the presence of activating agents such as $HgCl_2$, $CuCl_2$, or Mukaiyama's reagent, followed by deprotection of the resulting Boc-protected guanidine (Scheme 1, *Method A*) [3]. The use of stoichiometric amounts of metal salts, removal of by-products, poor atom efficiency, column chromatography, and low yields made this method inappropriate for further scale up.

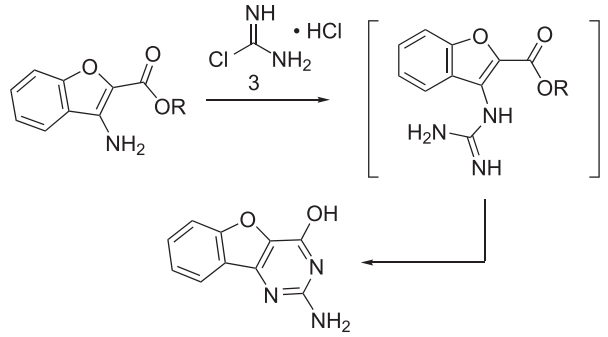
The second guanylation strategy utilized cyanamide activated by an acid, often HCl, to generate the formamidine species *in situ* followed by reaction with an amine to affect guanidine formation (Scheme 1, *Method B*) [4]. The main limitation encountered was the small number of solvent options associated with commercially available acid solutions and water in aqueous acids. Many of those solvents hindered reagent and substrate solubility, reaction temperature, and hence reaction completion. In addition, degradation of the active formamidine reagent occurred over time as a result of reaction with the nucleophilic solvents used. When this method was attempted on starting material **1**, this degradation was significant with EtOH as solvent and portionwise dosing of 12 equivalents of cyanamide over 26 h resulted in only 45% conversion to **2**. Further addition of cyanamide did not provide notable improvement. These inefficiencies coupled with the difficult separation of **1** from **2** reiterated the need for an alternate methodology for the guanidine synthesis.

A literature search to identify alternative guanylation options provided examples of pyrimidine cyclizations from aromatic amines with an adjacent carboxylate (Scheme 2) [5] or other functional groups such as nitriles [6], using isolated chloroformamidine hydrochloride **3**. In these examples, **3** presumably undergoes attack by the free amine to form a guanidine intermediate, which immediately cyclizes to afford a fused pyrimidine moiety. Although isolation of the presumed guanidine intermediate was not mentioned, without functionality at the carbon beta to the amine position, the reaction would stop at the guanidine intermediate and it could potentially be isolated. Further supporting the potential of this methodology, use of preformed **3** would

Scheme 1. Desired transformation to guanidine intermediate 2.



Scheme 2. Pyrimidine synthesis using chloroformamidine hydrochloride.

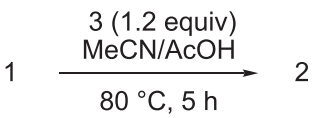


circumvent the solvent and degradation issues observed in previous attempts with *in situ* generation of **3,** which already showed moderate success with substrate **1**.

More recently, Chen *et al.* reported an example of direct guanidination of a complicated aliphatic amine utilizing **3** [7]. Benefits mentioned in this reference also support our efforts to apply the same methodology for electron-deficient aromatic guanidine synthesis.

Applying the reported pyrimidine cyclization conditions to compound **1** using **3**, a user friendly, stable solid prepared according to the literature [5,8], was highly successful (Scheme 3). With dioxane or MeCN as solvent, the reaction resulted in the exclusive formation of the desired guanidine moiety **2** under reflux with slight excess of **3**. The only issue observed was low solubility of **3** and product **2** in the solvents utilized, which resulted in heterogeneous reaction mixtures even at high temperature. The solubility issue was readily resolved by introduction of another polar solvent, with the optimal solvent combination for **1** being MeCN/AcOH 10/1. Under these conditions, full conversion was achieved at 80°C in less than 5 h, and **2** was isolated in 88% yield by filtration as the tris-HCl salt with >99% purity. This new procedure for **2** was then successfully scaled up to multiple kilograms in GMP productions. The simple translation of this method to our previously challenging chemical transformation of **2** encouraged us to further investigate its utility as an effective guanylation technique with other electron-poor aromatic amine substrates.

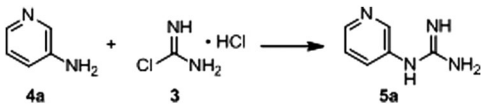
Scheme 3. Application of chloroformamidine hydrochloride conditions to development compound 1.



Our work began with a comprehensive screen of the reaction conditions utilizing 3-aminopyridine **4a**, a compound with structural simplicity and similarity to **1**, as the model substrate. The primary focus of the initial studies was to identify the optimal solvent or solvent systems, temperature(s), and chloroformamidine equivalents for this transformation. The screen was heavily focused on polar solvents because of the observed relative low solubility of **3** in many common organic solvents and was carried out over an elevated temperature range (60–120°C) for the same reason. Attempts with acetic acid (Table 1, entry 1) showed good solubility and conversion to the desired guanidine product. Unfortunately, acetic acid also proved to be reactive with **4a**, resulting in the formation of an undesired side product. The same was observed for solvents such as DMF, DMSO, NMP, and DMAc (Table 1, entries

Table 1

Screening of guanylation on model substrate 4a.



Entry[a]	Solvent	Temperature (°C)	Conversion (%)[b] 5a	4a	Imp(s).
1	AcOH	60	29	2	69
2	DMF	100	40	4	56
3	NMP	100	17	9	74
4	IPA	80	11	89	0
5	*t*-butanol	100	66	25	9
6[c]	MeCN	80	65	29	6
7[d]	MeCN/AcOH	80	71	1	28
8[c,d]	MeCN/sulfolane	80	>99	<1	0
9[c]	dioxane	100	64	36	0
10[c,d]	dioxane/AcOH	100	94	6	0
11	sulfolane	100	97	2	1

[a]All reactions conducted on a 2.1 mmol scale, using 1.2 eq. of **3** (Entry 5 used 1.8 eq. and Entry 10 used 1.4 eq.), in 10 vol. solvent (sampled over 24 h – table displays best conversion),
[b]Conversion was determined by LC/MS of the in-process reaction mixture,
[c]Heterogeneous reaction at certain temperatures,
[d]Solvent ratio 10 : 1

2 and 3) [9]. However, in these instances, the reactions did not achieve full conversion, and multiple impurities were observed. Several higher boiling alcoholic solvents such as Isopropyl Alcohol (IPA) (Table 1, entry 4) were screened, but low conversion and undesired side-reactions were encountered. Fewer impurities were observed with the more hindered alcoholic solvents such as *tert*-butanol (Table 1, entry 5). Despite preliminary favorable results, *tert*-butanol was not included in the solvent list for later studies due an observed phase separation that occurred between the solvent and reagents at temperatures above 80°C.

Use of MeCN and dioxane (Table 1, entries 6 and 9), both non-reactive solvents towards **3**, showed clean, conversion to **5a**, with minimal side products observed. Similar to compound **1**, low solubility of **3** occurred in these solvents at certain temperatures, which resulted in heterogeneous reaction mixtures, and led to slow conversion of **1**. These issues were eliminated, and higher conversions were achieved by introducing a minimal amount of acetic acid or sulfolane (Table 1, entries 7, 8, 10).

The introduction of sulfolane as a co-solvent also highlighted its potential as a primary solvent. Sulfolane (Table 1, entry 11) demonstrated better solubility over the MeCN and dioxane solvent systems. In addition, reactivity of sulfolane with **4a** and **3** was minimal compared with the other high boiling solvents DMF, DMSO, NMP, and DMAc, leading to higher conversion and a cleaner purity profile.

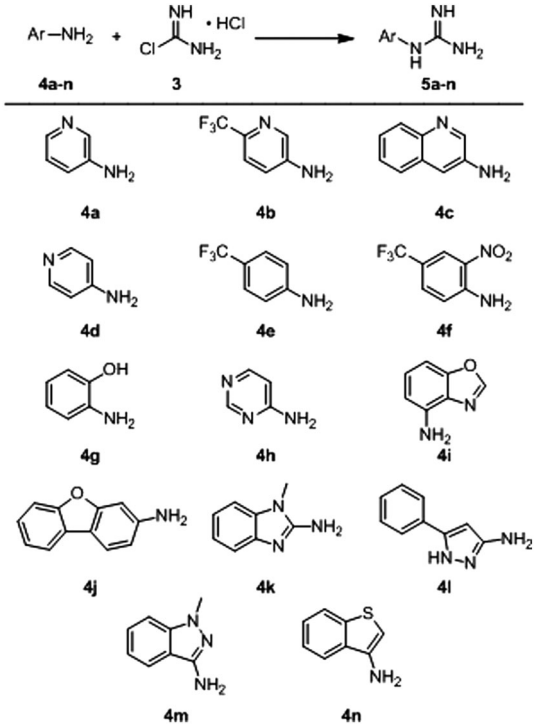
In attempts to further improve product conversion, the optimal amount of **3** was investigated in the preferred solvents highlighted by the first screen. Studies commenced using a minimum of 1.2 equivalents of **3** because of potential decomposition and previously observed participation in side-reactions [8]. Results showed an improvement in product conversion when **3** was increased from 1.2 to 1.4 equivalents, especially at lower temperatures. Additional increases in **3** over 1.4 equivalents, however, did not offer consistent progress. Moreover, product isolation became increasingly difficult with the need to remove excess amounts of **3** present, and hence, 1.4 equivalents of **3** were chosen to be the standard amount for further experimentation [10].

The scope of the guanylation reaction was then explored by applying the current best conditions to a set of pyridines, anilines, and heteroaromatic amines with various electron withdrawing and donating substituents as illustrated in Table 2. It should be noted that for the substrate screen, reactions were progressed until conversion of starting material ceased or significant impurity formation was observed. Also, column chromatography was often used to purify the desired products.

Reaction outcome with various aminopyridine substrates proved heavily dependent on the position of the amine group relative to the pyridine nitrogen. The excellent yields of **5a** and **c** (Table 2, entries 1 and 3) demonstrated that guanylation is very successful when the amine is in the 3-position. The addition of an electron withdrawing group

Table 2

Scope of guanidine synthesis.



Entry[a]	SM	Solvent	Conversion (%)[b] **5a-n**	Isolated yield (%)
1[d,g]	**4a**	sulfolane	97	95
2	**4b**	MeCN	79	68
3	**4c**	MeCN	>99	91
4[d]	**4d**	dioxane/ AcOH	8	0
5	**4e**	dioxane	98	83
6[d]	**4f**	dioxane	78	55
7	**4g**	MeCN/ AcOH	61	59
8[e]	**4h**	sulfolane	0	0
9[c]	**4i**	sulfolane	74	48
10[g]	**4j**	MeCN	80	59
11[f]	**4k**	MeCN/dioxane/ sulfolane	0	0
12[d]	**4l**	MeCN/AcOH	54[h]	0
13	**4m**	MeCN	>99	47
14	**4n**	sulfolane	69	42

[a]All screening reactions were run using 0.5 g of **4** and 1.40 eq. of **3** at 80°C,
[b]Conversion was determined by LC/MS of the in-process reaction mixture,
[c]60°C,
[d]100°C,
[e]120°C,
[f]100% impurity formation,
[g]Isolated as HCl salt (all others isolated as the freebase),
[h]The conversion accounts for two compounds with the desired mass corresponding to the two potential products

to 3-aminopyridine hindered reaction slightly but still managed to afford **5b** (Table 2, entry 2) in a 68% yield. Contrary to the 3-aminopyridine substrates, reactions with pyridines containing the amine moiety at the 2- or 4-position were poor presumably because of conjugation effects. Some formation of the desired guanidine product was observed with 4-aminopyridine **4d** (Table 2, entry 4), while 2-aminopyridine showed virtually none. Prolonged heating to force the reaction only resulted in impurity formation.

The aniline substrates all proved to efficiently undergo guanylation using the current system. Most successful was the electron-deficient aniline **4e** (Table 2, entry 5), with 83% yield of **5e**. The more challenging **4f** (Table 2, entry 6), an aniline bearing multiple electron withdrawing groups, exhibited slower reactivity than **4e**, which was expected because of its highly electron-deficient nature, but did offer reasonable conversion and isolated yield of 55% desired product **5f** after chromatography. Substrate **4g** with an electron donating group (Table 2, entry 7) resulted in a slightly lower, but still moderate yield compared with **4e** because of impurity formation, however, no functional group intolerance with the hydroxyl group was observed.

Some commercial heteroaromatic amines were also explored as part of substrate scope investigation. The less reactive aminopyrimidine **4h** (Table 2, entry 8) showed essentially no conversion to desired product **5h** under the optimal conditions, potentially because of conjugation effects, and resulted in only impurity formation under forced conditions. Substrates **4i** and **4j** (Table 2, entries 9 and 10) with the amine group on the benzene portion of the compound proved successful. Moderate yields (48% and 59%, respectively) were obtained because of difficult isolation. Further investigation into the effect of amino group position on a heterocycle with more than one heteroatom showed this to have a significant influence on the reaction. Heterocycles with multiple heteroatoms were prone to significant impurity formation, especially when the amine moiety is located between the two heteroatoms as can be seen with **4k** (Table 2, entry 11). Heterocyclic substrates with multiple reactions sites such as **4l** (Table 2, entry 12) underwent reaction at both sites. However, when the additional sites were blocked, as in **4m** (Table 2, entry 13), the reaction showed complete conversion. Unfortunately, only a 55% yield was obtained because of loss of material during the difficult isolation and the free basing process. Guanylation was also possible with electron-rich heterocycles such as **4n** (Table 2, entry 14), albeit with slightly lower conversion and yield due to impurity formation.

In summary, carrying out this methodology on a variety of different aromatic amines successfully proved the use of chloroformamidine hydrochloride as a facile reagent for the guanylation. This approach provides a clean and efficient alternative to the current guanylation methods, more specifically for the often difficult electron-deficient aromatic amines, and also expands upon the number of solvent options benefitting reaction temperature and substrate solubility.

EXPERIMENTAL

General methods. All starting materials and reagents were purchased commercially and used without further purification. NMR spectra were taken on either a 300 or 400 MHz NMR spectrometer. All HPLC analyses were performed using an LC/MSD system equipped with a reverse-phase column and a flow rate of 1.0 mL/min. Purification of compounds was performed on an automated liquid chromatography purification system using pre-packed silica columns or a preparative HPLC system. Because of the unknown stability of the new compounds synthesized, high-resolution mass spectrometry (HRMS) was performed in-house instead of elemental analysis, which would have required shipping the compounds off-site. All HRMS data were acquired using a mass spectrometer coupled with ultra-high performance liquid chromatography (UHPLC) and charged aerosol detector (CAD).

Chloroformamidine hydrochloride(3). 1,4-Dioxane (4.16 mol, 0.325 L) and cyanamide (0.714 mol, 30.0 g) were added to a jacketed glass reactor and cooled to 0°C while stirring at 450 rpm. A solution of 4.0 *M* hydrochloric acid in 1,4-dioxane (2.34 mol, 0.584 L) was added dropwise maintaining reaction temperature below 20°C. Upon addition completion, the mixture was stirred at room temperature for 2 h. The reaction was filtered and solids washed with another portion of 1,4-dioxane (2.08 mol, 0.162 L) . The cake was then dried in vacuo at 40°C resulting in 78.3 g (95.4%) of a white solid. *Anal.* Calcd. for $CH_4Cl_2N_2$: C, 10.45, H, 3.51, N, 24.37, Cl, 61.68. Found: Batch 1 (20.0 g scale) C, 10.93, H, 3.28, N, 24.39, Cl, 61.63, Batch 2 (30.0 g scale) C, 10.27, H, 3.30, N, 24.54, Cl, 61.81.

General procedure for the synthesis of mono-substituted guanidines. To a scintillation vial was added amine **4** (1.00 equivalent), solvent (5–25 volumes), and chloroformamidine HCl **3** (1.40 equivalent). The vial was flushed with nitrogen and heated with stirring at 80–100°C until liquid chromatography–mass spectrometry (LC/MS) indicated the reaction was complete or conversion of **4** ceased. Each substrate followed individual work-up procedures to isolate guanidine **5** as the HCl salt or freebase.

1-(5-(3-(Dimethylamino)propyl)-2-methylpyridin-3-yl)guanidine tris-hydrochloride (2). To a 50 mL round-bottom flask was added 5-(3-(dimethylamino)propyl)-2-methylpyridin-3-amine 2HCl **1** (4.35 mmol, 1.00 g), chloroformamidine HCl (5.22 mmol, 0.600 g), and acetonitrile (12.0 mL). The flask was then flushed with nitrogen. Acetic acid (1.20 mL) was

added, and the mixture was left to stir at room temperature for an addition 15 min. The reaction was heated to 80°C and monitored by LC/MS until complete. The reaction was then cooled to room temperature, and the solids isolated by filtration under nitrogen. The solids were washed with acetonitrile (2.00 mL) and dried in vacuo to give the tris-HCl salt as an off-white solid (1.32 g, 88.0% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.88 (s, 1H), 10.67 (s, 1H), 8.70 (d, J = 1.7 Hz, 1H), 8.37 (d, J = 1.7 Hz, 1H), 7.97 (s, 3H), 3.03 (dt, J = 9.9, 5.7 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 2.68 (d, J = 4.7 Hz, 6H), 2.65 (s, 3H), 2.05 (dq, J = 14.5, 7.2 Hz, 2H). ^{13}C NMR (75 MHz, DMSO) δ 157.0, 149.9, 143.8, 139.7, 139.2, 134.1, 55.6, 42.3, 28.3, 24.5, 16.4. HRMS: *m/z* for $C_{12}H_{24}Cl_3N_5$ (M^+ + H) 236.1870, found 236.1865.

1-(Pyridin-3-yl)guanidine dihydrochloride (5a). 3-Aminopyridine (26.6 mmol, 2.50 g), sulfolane (25.0 mL), and chloroformamidine HCl (31.9 mmol, 3.66 g) were added to a 40 mL scintillation vial. The vial was flushed with nitrogen and heated to 100°C until LC/MS showed full conversion of starting material. Once complete, the mixture was transferred to a 100 mL round-bottom flask with acetonitrile (25 mL). The resulting solids were isolated by filtration under nitrogen and washed with a portion of acetonitrile (20 mL). To remove the residual chloroformamidine, the material was then taken up in MeOH (35 mL), heated to 60°C for 2 h and then cooled to room temperature for an additional 2 h. The suspension was filtered and dried in vacuo to give the di-HCl salt as an off-white solid (5.30 g, 95.4% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.74 (dd, J = 5.5, 1.2 Hz, 1H), 8.34 (ddd, J = 8.4, 2.5, 1.3 Hz, 1H), 8.15 (s, 4H), 8.00 (dd, J = 8.4, 5.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 156.1, 139.7, 139.1, 138.8, 135.5, 127.3. HRMS: *m/z* for $C_6H_8N_4$ (M^+ + H) 137.0822, found 137.0818.

1-(6-(Trifluoromethyl)pyridin-3-yl)guanidine (5b). 3-Amino-6-(trifluoromethyl)pyridine (3.08 mmol, 0.500 g), acetonitrile (12.5 mL), and chloroformamidine HCl (4.32 mmol, 0.496 g) were added to a 20 mL scintillation vial and flushed with nitrogen. The reaction mixture was heated to 80°C until all starting material was consumed as indicated by LC/MS. The reaction mixture was cooled to ambient, the unreacted chloroformamidine filtered, and the filtrate concentrated. The filtrate was freebased using saturated sodium bicarbonate solution and water (1 mL) added to dissolve any salts. The slurry was filtered and clean freebase product was isolated as an off-white solid (0.429 g, 68.1% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.5 Hz, 1H), 7.69 (d, J = 8.3 Hz, 0H)? int of 0.22, 7.58 (dd, J = 8.5, 0.7 Hz, 1H), 7.28 (dd, J = 8.5, 2.4 Hz, 1H), 5.65 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 155.0, 151.4, 145.6, 129.6, 124.8, 121.3, 110.0. HRMS: *m/z* for $C_7H_7F_3N_4$ (M^+ + H) 205.0696, found 205.0690.

1-(Quinolin-3-yl)guanidine (5c). 3-Aminoquinoline (1.39 mmol, 0.200 g), acetonitrile (5.00 mL), and chloro formamidine HCl (1.94 mmol, 0.233 g) were added to a 2-dram vial. The vial was flushed with nitrogen and heated to 80°C for 70 h. The reaction was then cooled to room temperature. Unreacted chloroformamidine was removed by filtration and washed with minimal acetonitrile. The filtrate was concentrated, dissolved in minimal water, and then freebased with saturated sodium bicarbonate solution. The mixture was left to stir at room temperature for 30 min, and a fine white precipitate formed. The solids were then filtered, washed with another portion of water, and dried in vacuo to give the freebase as a white solid (0.236 g, 91% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (d, J = 2.5 Hz, 1H), 7.88–7.80 (m, 1H), 7.75–7.68 (m, 1H), 7.54–7.51 (m, 1H), 7.49–7.39 (m, 2H), 5.69 (s, 4H). ^{13}C NMR (75 MHz, DMSO) δ 154.6, 150.8, 144.3, 143.4, 129.6, 128.8, 127.2, 126.5, 126.2, 124.2. HRMS: *m/z* for $C_{10}H_{10}N_4$ (M^+ + H) 187.0978, found 187.0973.

1-(4-(Trifluoromethyl)phenyl)guanidine (5e). 4-(Trifluoro methyl)aniline (3.10 mmol, 1.00 g), 1,4-dioxane (15.0 mL), and chloroformamidine HCl (4.34 mmol, 1.00 g) were added to a 20 mL scintillation vial. The vial was flushed with nitrogen and then heated to 80°C for 24 h. Once complete, the reaction was cooled to room temperature and concentrated. The mixture was purified via column chromatography with a 40 g silica column using a 0–10% MeOH/0.05% triethylamine in EtOAc system. The product fractions were concentrated and dried in vacuo to yield the freebase as an off-white solid (1.05 g, 83.3% yield). ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.78–7.67 (m, 2H), 7.47–7.36 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 156.2, 140.8, 127.8, 127.4, 125.9, 122.3. HRMS: *m/z* for $C_8H_8F_3N_3$ (M^+ + H) 204.0743, found 204.0742.

1-(2-Nitro-4-(trifluoromethyl)phenyl)guanidine (5f). 4-Amino -3-nitrobenzotrifluoride (2.42 mmol, 0.500 g), 1,4-dioxane (5.00 mL), and chloroformamidine HCl (3.40 mmol, 0.390 g) was added to a 20 mL scintillation vial. The vial was flushed with nitrogen and then heated to 100°C until all starting material was consumed as indicated by LC/MS. A second portion of chloroformamidine HCl (3.40 mmol, 0.390 g) was then added to push the reaction to completion. Once complete, unreacted chloroformamidine was removed by filtration and washed with minimal dioxane. The crude solution was concentrated, dissolved in minimal water, and freebased with saturated sodium bicarbonate solution. The mixture was concentrated and run down a 24 g silica column using 0.05% triethylamine in EtOAc to remove salts and then another 24 g column using 50–80% EtOAc in hexanes to purify. The tubes containing product were concentrated and dried in vacuo to produce the freebase as an orange solid (0.330 g, 54.8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (dd, J = 2.3, 1.0 Hz, 1H), 7.61 (dd, J = 8.8, 2.3 Hz, 1H), 7.15 (dd, J = 8.7, 1.0 Hz, 1H), 5.90 (s, 4H). ^{13}C NMR (75 MHz, DMSO) δ 155.8, 149.8, 143.2, 129.1 (d, J = 3.8 Hz),

126.8, 122.1 (d, $J = 4.5$ Hz), 118.3, 117.9. HRMS: *m/z* for $C_8H_7F_3N_4O_2$ ($M^+ + H$) 249.0594, found 249.0586.

1-(2-Hydroxyphenyl)guanidine (5g). To a 20 mL scintillation vial was added 2-aminophenol (9.16 mmol, 1.00 g), chloro formamidine HCl (12.3 mmol, 1.47 g), and a co-solvent system of acetonitrile (10.0 mL) and acetic acid (1.00 mL). The vial was flushed with nitrogen and then heated to 80°C for 24 h. Once complete, unreacted chloroformamidine was removed by filtration and washed with minimal acetonitrile. The filtrate was concentrated and freebased using saturated sodium bicarbonate solution. The mixture was concentrated, dissolved in methanol, and passed through a silica plug (Whatman C18 ODS-3 Partisil, Clifton, NJ) to remove salts. The material was concentrated and further purified by prep HPLC to yield the freebase product as an off-white solid (1.02 g, 58.5% yield). ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.26–7.14 (m, 2H), 7.01–6.83 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 157.1, 152.8, 129.2, 127.6, 121.2, 119.8, 116.3. HRMS: *m/z* for $C_7H_9N_3O$ ($M^+ + H$) 152.0818, found 152.0813.

1-(Benzo[d]oxazol-4-yl)guanidine (5i). 1,3-Benzoxazol-4-amine (3.73 mmol, 0.500 g), sulfolane (2.50 mL), and chloroformamidine HCl (5.22 mmol, 0.600 g) were added to a 20 mL scintillation vial. The vial was flushed with nitrogen and heated to 60°C for 2 h. The reaction was then cooled to room temperature. A small portion of water was added to the vial to dissolve solids, and the solution was transferred to a separatory funnel. The aqueous layer was washed three times with DCM and then concentrated. Saturated sodium bicarbonate solution was added to freebase the material, and the mixture is concentrated once again. The product was isolated via prep HPLC and dried in vacuo to give the freebase as an off-white solid (0.314 g, 48% yield). ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.03 (s, 1H), 7.12–6.99 (m, 2H), 6.63 (dd, $J = 6.3$, 2.3 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 163.1, 147.9, 141.1, 140.2, 128.9, 124.7, 108.2, 107.0. HRMS: *m/z* for $C_8H_8N_4O$ ($M^+ + H$) 177.0771, found 135.0549 (consistent with **4i**). HRMS data for the product could not be obtained, likely because of the instability of this compound. All other data support the formation of the desired guanidine **5i**.

1-(Dibenzo[b,d]furan-3-yl)guanidine hydrochloride (5j). Dibenzo[b,d]furan-3-amine (0.546 mmol, 0.100 g), acetonitrile (2.50 mL), and chloroformamidine HCl (0.764 mmol, 0.0878 g) were added to a 20 mL scintillation vial. The vial was flushed with nitrogen and heated to 80°C for 36 h. The reaction was then cooled to room temperature. The mixture was filtered and washed with minimal acetonitrile to obtain crude product. The solids were slurried in water (10 mL) at 0°C for 30 min. The slurry was filtered; the solids washed with a small portion of cold water and dried in vacuo to obtain the mono-HCl salt as an off-white solid (0.418 g, 59% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.22–8.10 (m, 2H), 7.74–7.65 (m, 4H), 7.61 (d, $J = 1.8$ Hz, 1H), 7.55–7.48 (m, 1H), 7.40 (td, $J = 7.5$, 1.0 Hz, 1H), 7.25 (dd, $J = 8.3$, 1.9 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 156.8, 156.4, 156.2, 135.1, 128.1, 123.8, 123.5, 122.4, 122.3, 121.6, 120.4, 112.1, 108.7. HRMS: *m/z* for $C_{13}H_{11}N_3O$ ($M^+ + H$) 226.0975, found 226.0939.

1-(1-Methyl-1H-indazol-3-yl)guanidine (5m). 1-Methyl-1H-indazol-3-amine (0.652 mmol, 0.100 g), acetonitrile (2.50 mL), and chloroformamidine HCl (0.754 mmol, 0.0867 g) were added to a reaction vial. The vial was flushed with nitrogen and heated to 80°C for 24 h. The reaction was then cooled to room temperature. Solids were collected by filtration and washed with minimal acetonitrile. The material was dissolved in minimal water and then freebased with saturated sodium bicarbonate solution. The mixture was left to stir at room temperature overnight, filtered, and washed with a small amount of water. The solids were dried in vacuo to give the freebase as a pale yellow solid (0.0583 g, 47.2% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58 (dt, $J = 8.0$, 1.0 Hz, 1H), 7.35 (dt, $J = 8.4$, 1.0 Hz, 1H), 7.32–7.23 (m, 1H), 6.92 (ddd, $J = 7.8$, 6.7, 1.0 Hz, 1H), 6.29 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 155.5, 150.5, 140.2, 126.4, 120.6, 119.0, 118.0, 108.5, 34.8. HRMS: *m/z* for $C_9H_{11}N_5$ ($M^+ + H$) 190.1087, found 190.1084.

1-(Benzo[b]thiophen-3-yl)guanidine (5n). 1-Benzothiophen-3-amine hydrochloride (0.517 mmol, 0.100 g), sulfolane (0.50 mL), and chloroformamidine HCl (0.724 mmol, 0.0832 g) were added to a reaction vial. The vial was flushed with nitrogen and heated to 80°C for 36 h. The reaction was then cooled to room temperature. A small portion of water was added to the vial to dissolve solids, and then the solution was transferred to a separatory funnel. The aqueous layer was washed three times with DCM and then concentrated. Saturated sodium bicarbonate solution was added slowly resulting in a precipitate. The slurry was stirred at room temperature for 2 h and then filtered under nitrogen. The solids were washed with minimal water and dried in vacuo to give the freebase as a white solid (0.0413 g, 41.8% yield). ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.89–7.81 (m, 1H), 7.73–7.66 (m, 1H), 7.44–7.34 (m, 2H), 7.22 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 155.3, 139.1, 135.4, 124.6, 123.8, 122.6, 120.8, 117.3, 110.0. HRMS: *m/z* for $C_9H_9N_3S$ ($M^+ + H$) 192.0590, found 192.0586.

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[8] Before any work could be performed, an analysis method for the determination of chloroformamidine quality was necessary. To date, the only assessment of quality was elemental analysis and this was not considered sufficient for our purposes. See supporting information for full chloroformamidine hydrochloride analysis method development, synthesis, and stability details.

[9] See Supporting Information for data from full condition screen.

[10] See Supporting Information for data from the full chloroformamidine hydrochloride equivalent screen.