Comprehensive and Facile Entry into Substituted Amidines via the Condensation of N-Pmc-Substituted Thioamides with Amines Using Mukaiyama Reagent as a Thiophile

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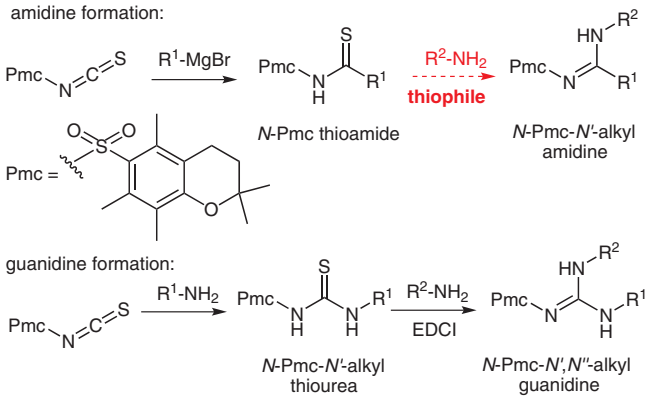
Abstract: A convenient approach is presented for the preparation of substituted amidines through the fusion of N-Pmc-substituted thioamides with amines, facilitated by a variety of thiophilic reagents. Assorted thiophiles were evaluated for their effectiveness as condensation reagents between the two partners, with the Mukaiyama reagent emerging as the optimal candidate for this process. The scope and limitations of this method were explored, revealing interesting synthetic challenges and constraints. Many of these limitations were overcome through the application of alternative reaction pathways in the construction of troublesome products. Treatment of the resultant Pmc-amidines with trifluoroacetic acid and trimethylsilyl trifluoromethanesulfonate cleanly afforded the deprotected substituted amidines.

Key words: amidine, thioamide, Mukaiyama reagent, thiophile, N-sulfonyl

The amidine functionality, whether as a discrete unit or a substructure within a larger molecular framework, represents a noteworthy template of connectivity in a variety of important compounds. Many bioactive molecules,[1] natural products,[2] and drug leads[3] contain the amidine functionality as a central or peripheral moiety within their architecture. As a discrete structure, the amidine connectivity can be thought of as either a nitrogenous analogue of a carboxylic acid or a carbon-substituted isoform of guanidine. This latter structural relationship is significant because the amidine functionality may be used as an isosteric replacement of the guanidine group in arginine-containing peptides.[4]

Because of the relevance of the amidine architecture in naturally occurring organic compounds, new and more globally applicable methods toward the synthesis of the amidine core are desired. The vast majority of approaches described in the literature toward the synthesis of amidines involves the functionalization of nitriles through either variations on the Pinner reaction,[5] the organometallic insertion strategy,[6] or the reaction of thioalkylated intermediates with amines.[7] Activation of amides with Et_3OBF_4, Tf_2O, PyBrop, etc., followed by reaction with amines has also provided a practical approach toward more substituted amidines,[8] as has nucleophilic addition to carbodiimides[9] and ketenimines[10] by alkyl lithiates and primary amines, respectively. The one-pot, multicomponent reactions developed by Chang[11] and Jin[12] represent some of the more novel entries into (*N*-sulfonyl) amidines described in the literature.

The present approach makes use of a masked electrophile in the form of an electron-deficient thioamide that is activated toward an incoming amine through treatment with an appropriate thiophile (Scheme 1). Although amidine formation by reaction of *N*-alkoxycarbonyl thioamides with amines has been reported,[13] the transformation is carried out in ethanol at reflux and does not have the benefit of a gentle desulfurization reagent to allow the introduction of a high degree of architectural diversity. An analogous transformation has been thoroughly explored by our research group in previously published accounts[14] in which substituted guanidines are generated through the *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDCI) mediated desulfurization of *N*-Pmc-*N*′-alkyl thioureas in the presence of amines (Scheme 1). While it was envisioned that an analogous entry into substituted amidines could be achieved by EDCI activation of an N-Pmc-thioamide followed by reaction of an amine, initial efforts toward this end were unsuccessful.



Scheme 1

The basis of the present research effort was to first survey potential thiophiles and reaction conditions that would result in the development of a viable route into N-Pmc-substituted amidines from the corresponding thioamides, a transformation that has, until now, remained elusive. Once optimized, the scope and limitations of the general

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reaction were carefully mapped with regard to steric and electronic constraints.

Given the unsuccessful results of our initial attempts at amidine formation through reaction of an N-Pmc-substituted thioamide and an amine under EDCI-mediated desulfurization conditions, we wanted to identify conditions that might effect this transformation. We hypothesized that the transformation might be achievable through the use of alternative thiophiles. As such, the primary variable in this assay became the identity of the most effective thiophile for amidinylation.

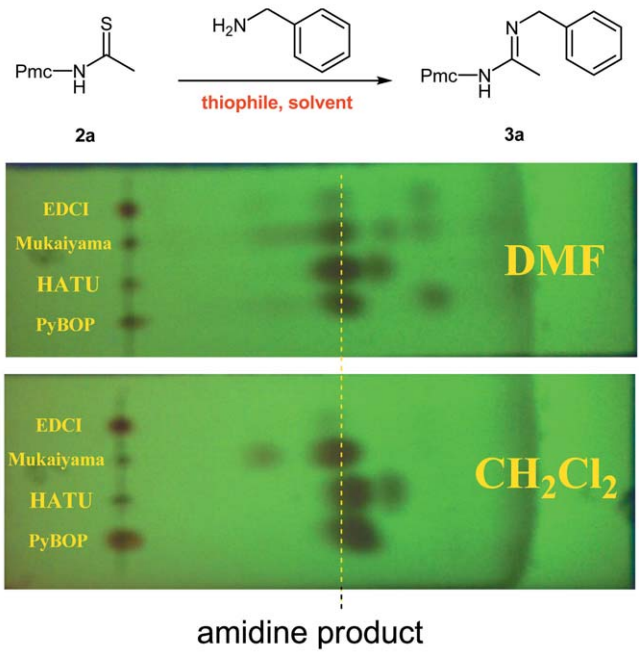
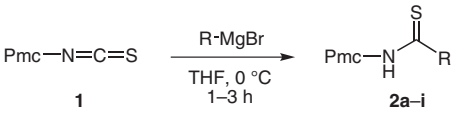
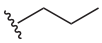
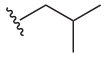
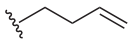
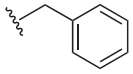
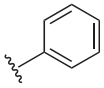
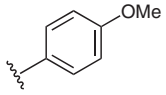
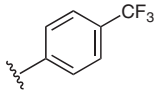


Figure 1 Crude TLC reaction profile of the thiophile assay, showing condensation efficiency between N-Pmc thioamide **2a** with benzylamine in DMF and CH_2Cl_2 solvent systems; the amidine **3a** product R_f value is highlighted for clarity

Four common thiophiles were assayed for their ability to mediate the amidinylation between *N*-Pmc-thioacetamide (**2a**) and benzylamine to yield *N*-Pmc-*N*′-benzylacetamidine (**3a**; Figure 1). A variation on the method developed by Walter was used to construct the *N*-Pmc-thioacetamide (**2a**) test system, through addition of methylmagnesium bromide to *N*-Pmc-isothiocyanate **1**.[15] In addition to the EDCI thiophile, diisopropylcarbodiimide (DIC), 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HATU), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), and 2-chloro-1-methylpyridinium iodide (Mukaiyama reagent) were each evaluated under identical conditions for their ability to promote the desired reaction in both *N*,*N*-dimethylformamide and dichloromethane. DIC was immediately excluded because it failed to yield any desired product. A comparative analysis of the remaining four thiophiles was undertaken, and the results can be compared in the TLC image shown in Figure 1. As expected, there was very little amidine product evident when EDCI was used as the thiophile, although complete reaction was apparent from the reactions mediated by HATU, PyBOP, and the Mukaiyama reagent, with PyBOP yielding the least by-products following reaction workup. Furthermore, the reactions carried out in dichloromethane appeared to be much cleaner than those using *N*,*N*-dimethylformamide as a solvent. Thus, three candidates were initially identified as optimal thiophiles for amidinylation on the test system using dichloromethane as solvent.

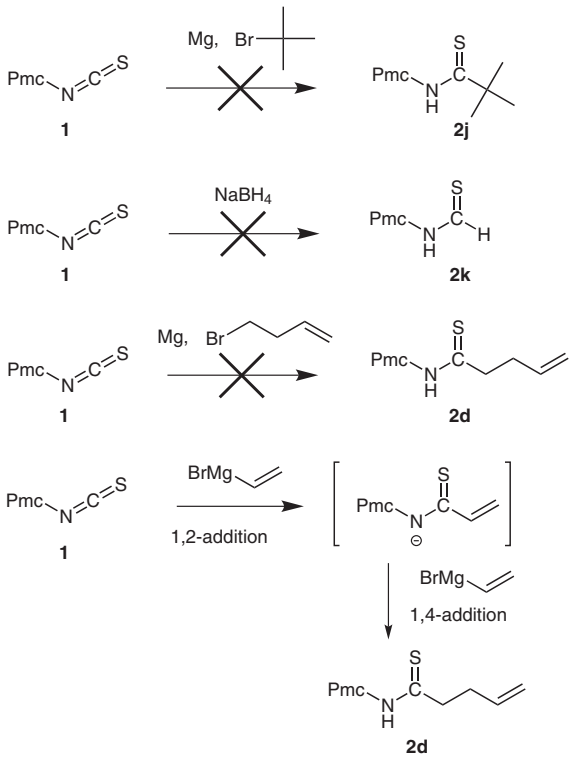
Table 1 Synthesis of Thioamides **2a–i**



Entry	2	R	Yield (%)
1	**2a**		74
2	**2b**		89
3	**2c**		90
4	**2d**		48
5	**2e**		62
6	**2f**		80
7	**2g**		58
8	**2h**		52
9	**2i**		77

To fully investigate the scope and limitations of the now-viable amidinylation process, a series of *N*-Pmc-thioamides was synthesized that allowed a full exploration of steric and electronic effects on the reactivity of thioamide and amine partners. The methodology developed by Walter and Röhr[15] was again used to synthesize a series of *N*-Pmc-thioamides **2**, which were obtained from addition of a series of Grignard reagents to *N*-Pmc-isothiocyanate **1**. Table 1 illustrates the range of aryl and alkyl architecture achievable from this process, comprising a spectrum of steric, functional, and electronic properties. Although the above conditions were satisfactory for the addition of methylmagnesium bromide to *N*-Pmc-isothiocyanate **1** to form *N*-Pmc-thioacetamide **2a**, a significant number of *N*-Pmc-thioamides **2** failed to form in acceptable yields. This was especially apparent when classic Grignard conditions were used in the attempted synthesis of thioamide **2h**,

bearing an electron-deficient aryl group. To gain access to reasonable amounts of these intermediates, augmented reaction conditions were applied. A LiCl-mediated 'turbo-Grignard' approach (Mg/RBr, LiCl, THF, 0 °C) was initiated[16] for the synthesis of the remaining *N*-Pmc-thioamides, which allowed access to the remaining alkyl- and aryl-substituted thioamides in moderate to good yields (Table 1).



Scheme 2

Although most of the desired thioamides were accessible by the Grignard approach, some thioamides resisted all efforts toward their synthesis (Scheme 2). Desiring a thioamide that bore functionality of high steric bulk, we attempted to gain access to the *tert*-butyl-substituted variant **2j**. Using the previously mentioned standard and 'turbo-Grignard' methodology both resulted in the formation of a complex mixture of products, as evidenced by ^{1}H NMR analysis of the crude reaction mixtures. This unexpected result could be due to the known propensity of *tert*-butyl anions to undergo unusual reaction pathways, primarily as potential hydride donors.[17] Attempted hydride addition to Pmc-isothiocyanate to afford the thioformamide **2k**, through the use of sodium borohydride as the hydride source, resulted in a colorless precipitate that was only sparingly soluble and could not be identified. A review of the literature revealed that hydride reductions of isothiocyanates[18] do not afford thioformamides.

One unexpected result was the synthetic route by which thioamide **2d** was achieved. One of the functionalities we wanted to be represented in the collection of thioamides was an alkene. Toward this end, we wanted to synthesize an alkenyl architecture, and homoallylic thioamide **2d** was chosen for this representation due to the ready commercial availability of a suitable halide (CH_2=$CHCH_2CH_2Br$) from which to derive the corresponding Grignard reagent. However, all attempts to synthesize thioamide **2d** through Grignard addition to *N*-Pmc-isothiocyanate **1** were unsuccessful (Scheme 2). In contrast, when the synthesis of *N*-Pmc-thioacrylamide was attempted through addition of vinylmagnesium bromide to *N*-Pmc-isothiocyanate **1**, to our surprise we recovered thioamide **2d** as the sole isolable product. A review of the literature revealed a similar reaction as noted by Lubell and co-workers,[19] and was likely the result of addition of the vinyl nucleophile to isothiocyanate **1**, followed by addition of a second equivalent of vinyl nucleophile in a conjugate fashion.

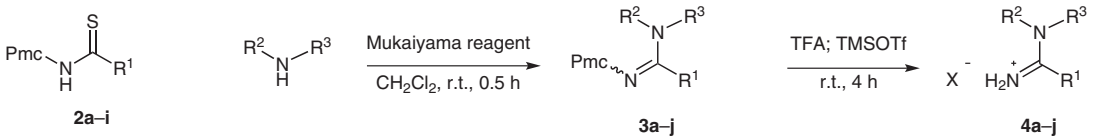
Having a series of *N*-Pmc-thioamides to work with, we next focused on optimizing the three thiophiles initially identified as having the ability to mediate an amidinylation reaction. Further investigations revealed that PyBOP was not able to mediate the reaction of aryl-substituted thioamides with amines and was thus not chosen for further studies. In contrast, HATU performed well on all solution-based reactions investigated, but was not as efficient in solid-phase amidinylations (data not shown), while the Mukaiyama reagent was easily able to carry out both solution-based and resin-bound amidinylations. As a result of these findings, the Mukaiyama reagent emerged as the optimal overall thiophile to advance in this study.

With the synthesis of *N*-Pmc-thioamides **2a–i** accomplished and an optimal thiophile identified, we explored the scope and limitations of the amidinylation reaction. Table 2 illustrates the wide functional and electronic tolerance this mild methodology allows. Through judicious selection of alkyl and aryl amine partners in the syntheses of these amidines, we are able to show the broad scope of this methodology, which allowed access to amidines with high steric bulk (**3b**), secondary and cyclic amidines (**3b** and **3c**), functionalized amidines (**3f**), and bis-amidines (**3j**). The reaction sequence for all amidines represented in Table 2 was facile, rapid, and straightforward. It could be carried out without the requirement for an inert atmosphere and was forgiving of excess thiophile and/or amine, with any excess reagents and by-products being easily removed during aqueous workup. Yields of amidines **3** were somewhat variable, depending upon the starting substrates, but generally ranged between 70–85%. Purification of the crude isolates was similarly straightforward, requiring only standard silica gel chromatography to afford the pure *N*-Pmc-amidine products.

In our efforts to demonstrate the utility of this methodology, we explored the scope and limitations of the amidinylation reaction. Accordingly, some amidinylation reactions failed to afford the desired product. For example, the electron-deficient *p*-nitroaniline failed to react with *N*-Pmc-thioamide **2c** to afford amidine **3k** (Scheme 3, a).

The majority of the *p*-nitroaniline was recovered unreacted, implying that it was not a strong enough nucleophile. Fortunately, the lack of reactivity of this type of substituted aniline nucleophile seemed to be constrained only to the electron-deficient variety, since amidine **3d** was readily prepared using ordinary aniline as the nucleophile. Another limitation arose when we attempted to condense benzyl-substituted thioamide **2e** with a variety of amines under the standard amidinylation conditions. Regardless of which amine was used in these condensation attempts, analysis of the reaction mixtures gave evidence of an identical intractable mixture of products. Furthermore, although in other cases the reaction solution remained colorless throughout the course of the reaction, in this instance, the solution took on a deep purple color over a period of ten minutes. We noted that this color change occurred regardless of whether an amine was added to the reaction mixture or not. The components of this reaction mixture were not readily separable over silica gel to obtain a product profile, so the reasons for this coloring phenomenon can only be theorized (see below).

Table 2 Scope of the Amidinylation Reaction



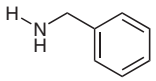
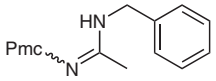
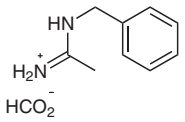
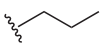
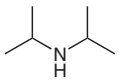
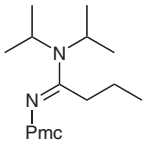
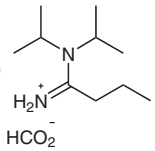
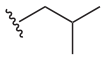
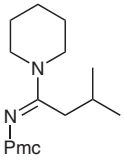
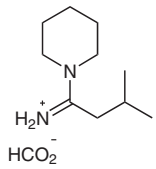
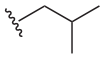
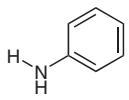
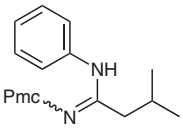
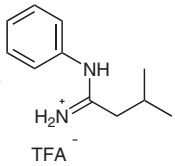
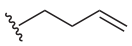
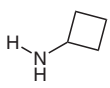
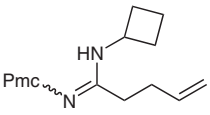
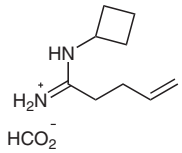
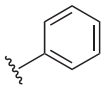
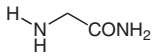
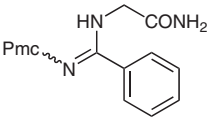
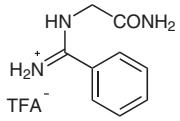
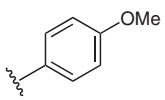
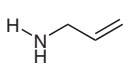
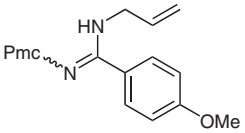
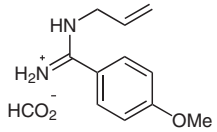
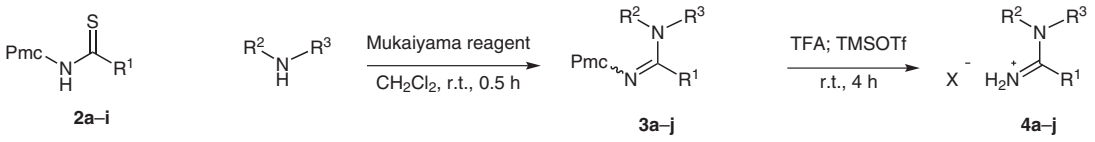
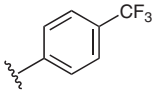
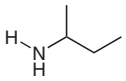
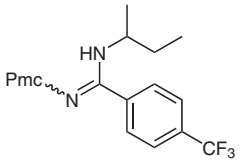
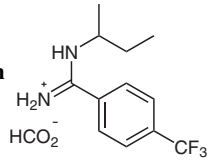
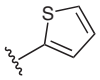
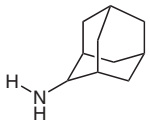
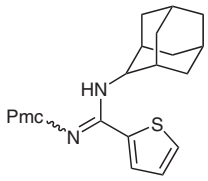
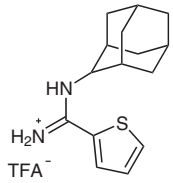
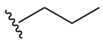
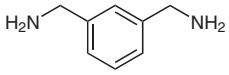
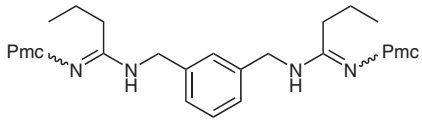
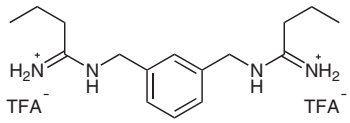
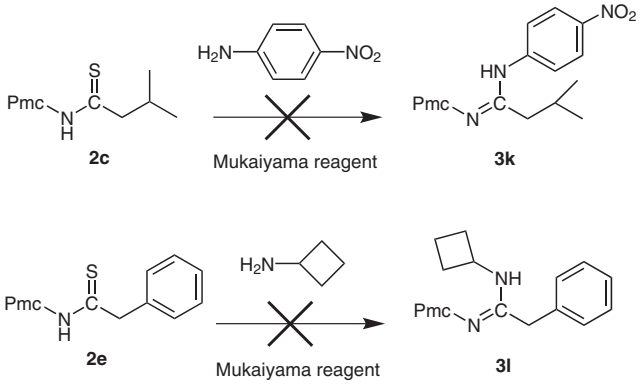
R[1]	Amine	3 Protected amidine product	Yld (%)	4 Amidine product	Yld (%)
Me		**3a** 	73	**4a** 	91
		**3b** 	87	**4b** 	80
		**3c** 	82	**4c** 	45
		**3d** 	72	**4d** 	66
		**3e** 	80	**4e** 	53
		**3f** 	52	**4f** 	48
		**3g** 	78	**4g** 	41

Table 2 Scope of the Amidinylation Reaction (continued)



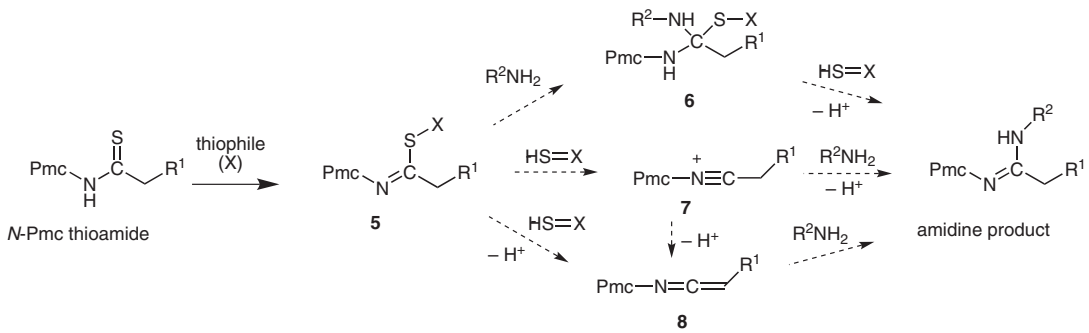
2a–i 3a–j 4a–j

R^1	Amine	3 Protected amidine product	Yld (%)	4 Amidine product	Yld (%)
		**3h** 	74	**4h** 	54
		**3i** 	85	**4i** 	71
		**3j** 	70	**4j** 	66



Scheme 3

To effectively generate the deprotected amidine core, the Pmc-protecting group that facilitated thioamide/amine condensation had to be removed as the final step in the sequence. This sulfonyl-based blocking group for the guanidine head-group in arginine-containing peptides is traditionally removed by standard acidolysis using trifluoroacetic acid (TFA) and suitable scavengers.[20] It was used very successfully as a protecting/activating group in our methodology for the synthesis of substituted guanidines.[15] However, when the Pmc-deprotection of the amidines **3** was attempted, NMR analysis of the crude product mixtures showed only partial Pmc-deprotection took place, even in the presence of scavengers such as $HSCH_2CH_2SH$, thioanisole, phenol, etc., and after long reaction times (data not shown). After some optimization, we found that a 95:5 (v/v) mixture of trifluoroacetic acid and trimethylsilyl trifluoromethanesulfonate allowed complete Pmc-deprotection in all cases. Standard workup involved trituration with cold diethyl ether to yield the crude amidines **4a–j** as either colorless crystalline solids or brown gums. The majority of the deprotected amidines were pure enough to undergo NMR characterization in their crude form, further illustrating the utility of this method for producing substituted amidines without requiring arduous purification procedures.



Scheme 4

The mechanism of the amidine-forming step warrants some discussion. With all thiophiles, we envision activation of the thioamide with the thiophile to form an intermediate **5** (Scheme 4). This intermediate may eliminate the sulfur–thiophile adduct to afford either the nitrilium ion **7** or the keteneimine **8**; addition of amine to either of these intermediates would afford the amidine product, however, evidence that the reaction does not proceed through the keteneimine intermediate **8** comes from the failure of thioamide **2e** to afford the product. While thioamide **2e** is the most likely candidate to form ketenimine **8**, due to conjugation with the phenyl ring, the aforementioned deep-blue color of the solution it produces upon treatment with Mukaiyama reagent and its resistance to reaction with added amine, suggests that if the ketenimine forms, it leads to products other than the desired amidine. Although the reaction of *N*-sulfonyl keteneimines with amines has been proposed in the literature,[21] these findings would support a reaction intermediate other than **8**. Furthermore, although the arene-substituted thioamides **2f–i** cannot possibly proceed through a keteneimine intermediate **8**, they nevertheless do afford the corresponding amidine products; these results suggest that, at least in these cases, amidine formation proceeds through either intermediate **6** or **7**.

Interestingly, the ^{1}H and ^{13}C NMR spectra of the aryl-substituted *N*-Pmc-thioamides **2f–h**, as well as the majority of *N*-Pmc-amidines **3**, exhibited a doubling of some resonances. After careful chromatographic purification of these compounds, certain regions of each of their corresponding ^{1}H and ^{13}C NMR spectra exhibited fully resolved peaks corresponding to at least two apparent species. In the case of aryl-substituted *N*-Pmc-thioamides **2f–h**, this phenomenon was most evident in the aromatic region of the ^{1}H NMR spectra (Figure 2, a). In the case of thioamides **2f** and **2g**, there were clear major and minor components; however, in the case of thioamide **2h**, the sets of peaks were approximately equal in integration. That there are two sets of signals particular to aryl-substituted thioamides has some literature precedent,[22] and can be explained by the presence of s-*cis*/s-*trans* isomers resulting from slow rotation about the C–N thioamide bond on the NMR timescale.

As illustrated in Figure 2 (b), it was believed that the cause of the NMR peak doubling of the amidines was due to the presence of *cis*/*trans* isomers about the imino C=N bond. Evidence that supports this observation comes from the NMR spectra of amidines **3b** and **3c**, which do not show doubling of resonances because it is expected that the A(1,3)-strain in **3b** and **3c** would favor the *trans* isomer (Pmc-group is *trans* to NR_2) as shown in Table 2. Further evidence of *cis*/*trans* isomerism about the imino bond also comes from the Pmc-deprotected samples, because loss of the Pmc group would be expected to eliminate *cis*/*trans* isomerism. Indeed, Figure 3 shows a comparison of representative ^{1}H NMR peak regions before and after Pmc-deprotection. As expected, in these (and all) cases, conversion of Pmc-amidines **3** into the deprotected amidines **4** results in NMR spectra that do not exhibit resonance doubling.

In conclusion, a new and versatile methodology has been presented for the facile synthesis of substituted amidines. The Mukaiyama-mediated condensation between an amine and an *N*-Pmc-thioamide cleanly affords *N*-Pmc-amidines in good yield, which can then be deprotected to afford the native substituted amidine system. The scope and limitations of this synthetic process have been carefully explored and optimized, resulting in a methodology that allows installment of the greatest diversity of substitution of the native amidine core. This procedure is well positioned for use in the synthesis of compounds containing an amidine functional group. Current efforts focus on the use of this chemistry on solid support in the synthesis of peptidomimetic systems.

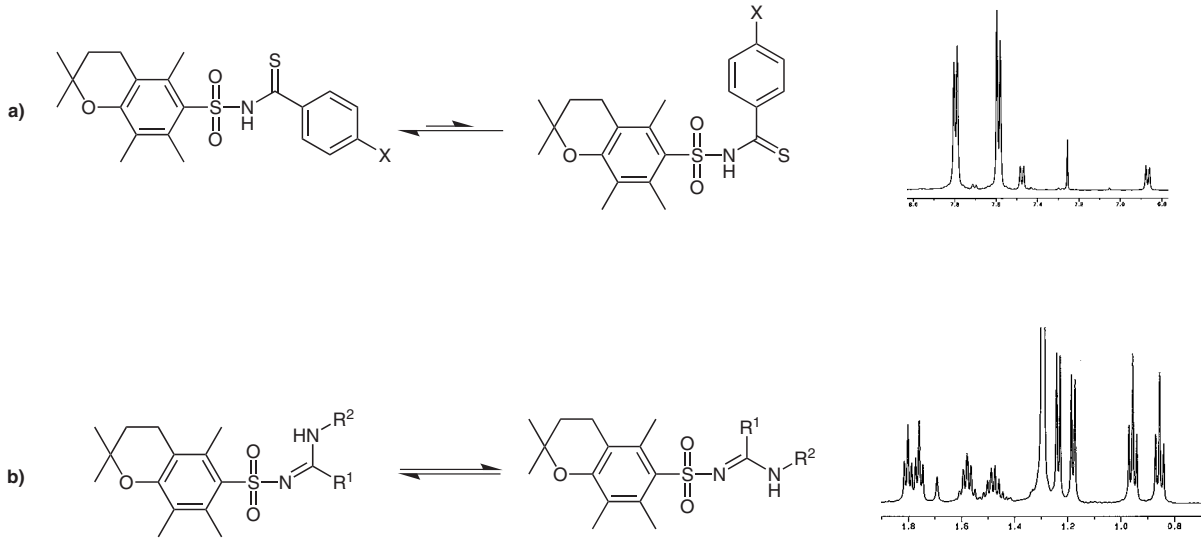


Figure 2 (a) Putative dual conformations of aryl-substituted *N*-Pmc thioamides **2**, showing the aromatic ^{1}H NMR region of *N*-Pmc thioamide **2h** as a representative example. (b) Theorized dual conformations of *N*-Pmc amidines **3**, showing the upfield ^{1}H NMR region of *N*-Pmc amidine **3h** as a representative example.

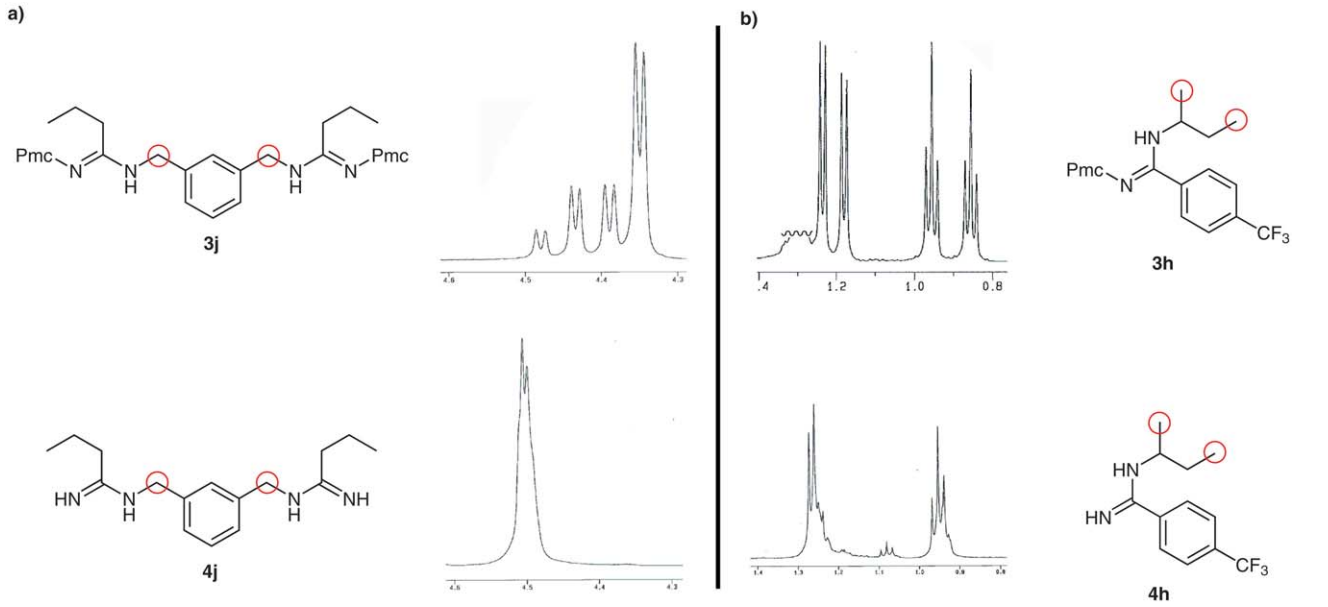


Figure 3 (a) Benzylic ^{1}H NMR peak coalescence of amidine **3j** and **4j** following removal of the Pmc group. (b) Upfield ^{1}H NMR peak coalescence of amidine **3h** and **4h** following removal of the Pmc group.

All solvents were purchased from Fisher Scientific (Pittsburgh, PA). Unless otherwise specified, all reagents were purchased from Sigma–Aldrich (St. Louis, MO) and were used without further purification. Flash chromatography was carried out on Sorbent Technologies silica gel (230–400 mesh). Melting points were recorded with an Electrothermal MelTemp capillary melting point apparatus and are uncorrected. Infrared spectra were obtained with a Shimadzu IR Affinity-1 FT-IR spectrophotometer. 1D NMR spectra (500 and 125 MHz) were collected using standard pulse sequences provided by Bruker. High-resolution mass spectra (HRMS) were acquired by John Greaves at the Mass Spectrometry Resource of UC-Irvine.

Preparation of *N*-Pmc-Substituted Thioamides 2a–i from Thiocyanate 1; General Procedure

A variation on the method developed by Walter and Röhr[15] was used to prepare all thioamides in this series. Magnesium turnings (140 mg, 5.75 mmol) and LiCl (214 mg, 5.06 mmol) were suspended in anhydrous THF (4 mL) under an N_2 atmosphere. Alkyl or aryl halide (4.60 mmol, 2 equiv) was added in one portion and the mixture was stirred until heat began to evolve. Additional THF (8 mL) was then added and the reaction was allowed to progress until no more heat evolution was evident (0.5–2 h, depending on the halide used). The Grignard solution was then cooled to 0 °C in an ice–water bath, and thiocyanate **1** (0.75 g, 2.30 mmol) dissolved in THF (10 mL) was then added dropwise over 20 min. The mixture was allowed to stir at 0 °C for an additional 30 min. The reaction was quenched by careful, slow addition of 1% aq HCl (25 mL). The mixture was partitioned between 1% HCl (50 mL) and EtOAc (50 mL) and the aqueous layer was further extracted with additional EtOAc (2 × 25 mL). The organic portions were combined, dried over $MgSO_4$, and concentrated in vacuo to yield the crude *N*-Pmc thioamide, which was then purified over silica gel by flash chromatography (EtOAc–hexane, 10–20%).

N-Pmc-Ethanethioamide (2a)

Yield: 0.58 g (74%); light-yellow friable foam; mp 135–137 °C.

IR (film): 1448, 3214 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.67 (t, *J* = 6.8 Hz, 2 H), 2.58 (s, 3 H), 2.57 (s, 3 H), 2.14 (s, 3 H), 1.84 (t, *J* = 6.9 Hz, 2 H), 1.33 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 137.4, 137.3, 126.3, 125.1, 118.7, 74.37, 32.27, 26.56, 21.29, 17.95, 17.06, 12.16, 12.1.

HRMS: *m/z* [M + Na] calcd for $C_{16}H_{23}NNaO_3S_2$: 364.1017; found: 364.1010.

N-Pmc-Butanethioamide (2b)

Yield: 0.76 g (89%); light-yellow friable foam; mp 153–155 °C.

IR (film): 3207, 1450 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.67 (t, *J* = 6.8 Hz, 2 H), 2.56–2.65 (m, 8 H), 2.13 (s, 3 H), 1.83 (t, *J* = 6.8 Hz, 2 H), 1.64–1.72 (m, 2 H), 1.33 (s, 6 H), 0.86 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 138.7, 138.2, 126.8, 125.8, 119.3, 75.1, 33.2, 27.4, 23.2, 22.2, 18.8, 17.9, 13.9, 12.9.

HRMS: *m/z* [M + Na] calcd for $C_{18}H_{27}NNaO_3S_2$: 392.1330; found: 392.1334.

N-Pmc-(3-Methyl)butanethioamide (2c)

Yield: 0.80 g (90%); light-yellow friable foam; mp 107–110 °C.

IR (film): 2928, 1549 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.66 (t, *J* = 6.8 Hz, 2 H), 2.58 (s, 6 H), 2.49 (d, *J* = 7.2 Hz, 2 H), 2.15–2.23 (m, 1 H), 2.13 (s, 3 H), 1.84 (t, *J* = 6.9 Hz, 2 H), 1.33 (s, 6 H), 0.85 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 138.0, 137.5, 126.6, 125.1, 118.6, 74.4, 32.5, 29.1, 26.7, 21.9, 21.5, 18.2, 17.2, 12.2.

HRMS: *m/z* [M + Na] calcd for $C_{19}H_{29}NNaO_3S_2$: 406.1487; found: 406.1489.

N-Pmc-Pent-4-enethioamide (2d)

Yield: 0.42 g (48%); yellow amorphous solid; mp 134–136 °C.

IR (film): 3204, 1549 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.98 (br s, 1 H), 5.64–5.73 (m, 1 H), 4.91–5.00 (m, 2 H), 2.71 (t, *J* = 7.4 Hz, 2 H), 2.67 (t,

J = 6.8 Hz, 2 H), 2.59 (s, 3 H), 2.58 (s, 3 H), 2.35–2.43 (m, 2 H), 2.13 (s, 3 H), 1.83 (t, J = 6.8 Hz, 2 H), 1.33 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 138.1, 137.5, 136.0, 126.4, 125.1, 118.6, 115.9, 74.4, 32.7, 32.5, 26.7, 21.4, 18.1, 17.2, 12.2.

HRMS: m/z [M + Na] calcd for $C_{18}H_{25}NNaO_3S_2$: 404.1330; found: 404.1338.

***N*-Pmc-(2-Phenyl)ethanethioamide (2e)**
Yield: 0.79 g (62%); light-yellow friable foam; mp 142–143 °C.

IR (film): 3208, 1667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.24 (br s, 1 H), 7.29–7.35 (m, 3 H), 7.18–7.23 (m, 2 H), 4.01 (s, 2 H), 2.60 (t, J = 6.8 Hz, 2 H), 2.39 (s, 3 H), 2.35 (s, 3 H), 2.08 (s, 3 H), 1.82 (t, J = 6.8 Hz, 2 H), 1.32 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 138.7, 137.7, 134.6, 129.1, 128.0, 124.9, 118.4, 74.4, 32.5, 26.7, 21.4, 17.8, 17.0, 12.2.

HRMS: m/z [M + Na] calcd for $C_{22}H_{27}NNaO_3S_2$: 440.1330; found: 440.1337.

***N*-Pmc-Thiobenzamide (2f)**
Yield: 0.74 g (80%); dark-yellow amorphous solid; mp 131–132 °C.

IR (film): 3214, 1448 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.4 Hz, 0.4 H), 7.73 (d, J = 7.4 Hz, 1.6 H), 7.51 (t, J = 7.5 Hz, 1 H), 7.47 (t, J = 7.9 Hz, 2 H), 7.38 (t, J = 7.9 Hz, 2 H), 2.67 (t, J = 6.9 Hz, 2 H), 2.61 (s, 2.5 H), 2.60 (s, 2.5 H), 2.34 (s, 0.5 H), 2.31 (s, 0.5 H), 2.18 (s, 0.5 H), 2.12 (s, 2.5 H), 1.83 (t, J = 6.8 Hz, 2 H), 1.33 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.3, 156.6, 154.9, 141.8, 141.3, 140.8, 139.1, 138.4, 132.8, 132.0, 129.2, 127.6, 127.5, 126.7, 125.5, 125.2, 119.4, 119.1, 75.0, 74.5, 33.2, 27.4, 22.2, 18.9, 18.0, 13.0, 12.9.

***N*-Pmc-(4-Methoxy)thiobenzamide (2g)**
Yield: 0.58 g (58%); dark-yellow amorphous solid; mp 101–103 °C.

IR (film): 2974, 1601 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.9 Hz, 0.3 H), 7.83 (d, J = 8.9 Hz, 1.7 H), 7.01 (d, J = 8.9 Hz, 0.3 H), 6.84 (d, J = 8.9 Hz, 1.7 H), 3.88 (s, 0.4 H), 3.82 (s, 2.6 H), 2.65 (t, J = 6.8 Hz, 2 H), 2.62 (s, 5.2 H), 2.34 (s, 0.4 H), 2.32 (s, 0.4 H), 2.15 (s, 0.4 H), 2.11 (s, 2.6 H), 1.81 (t, J = 6.8 Hz, 2 H), 1.31 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 155.7, 138.3, 137.7, 134.0, 132.5, 131.8, 130.3, 129.0, 128.2, 126.4, 124.7, 118.3, 114.5, 113.7, 74.2, 60.0, 55.5, 32.5, 26.7, 21.5, 21.1, 18.2, 17.4, 17.3, 14.2, 12.6, 12.2.

HRMS: m/z [M + Na] calcd for $C_{22}H_{27}NNaO_4S_2$: 456.1279; found: 456.1279.

***N*-Pmc-(4-Trifluoromethyl)thiobenzamide (2h)**
Yield: 0.56 g (52%); dark-yellow amorphous solid; mp 158–160 °C.

IR (film): 3196, 1323 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.1 Hz, 1.7 H), 7.58 (d, J = 8.1 Hz, 1.7 H), 7.47 (d, J = 8.1 Hz, 0.3 H), 6.87 (d, J = 8.1 Hz, 0.3 H), 2.65 (t, J = 6.8 Hz, 2 H), 2.58 (s, 2.9 H), 2.56 (s, 2.9 H), 2.34 (s, 0.1 H), 2.31 (s, 0.1 H), 2.17 (s, 0.1 H), 2.12 (s, 2.9 H), 1.83 (t, J = 6.8 Hz, 2 H), 1.32 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2, 142.9, 138.6, 137.8, 133.4, 133.1, 132.8, 127.3, 125.6, 125.4, 125.1, 124.5, 122.5, 118.6, 115.5, 74.5, 32.5, 26.7, 21.5, 18.2, 17.2, 12.2.

HRMS: m/z [M + Na] calcd for $C_{22}H_{24}F_3NNaO_3S_2$: 494.1047; found: 494.1046.

***N*-Pmc-2-Thiophenecarbothioamide (2i)**
Yield: 0.58 g (58%); dark-yellow friable foam; mp 126–128 °C.

IR (film): 3184, 1551 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (dd, J = 3.9, 1.5 Hz, 1 H), 7.55 (dd, J = 5.1, 1.0 Hz, 1 H), 7.07 (dd, J = 5.1, 4.0 Hz, 1 H), 2.67 (t, J = 6.8 Hz, 2 H), 2.64 (s, 3 H), 2.63 (s, 3 H), 2.12 (s, 3 H), 1.82 (t, J = 6.8 Hz, 2 H), 1.32 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.3, 156.0, 146.7, 138.5, 137.8, 135.4, 128.6, 126.1, 125.5, 124.9, 118.5, 74.4, 32.5, 26.7, 21.5, 18.2, 17.3, 12.3.

HRMS: m/z [M + Na] calcd for $C_{19}H_{23}NNaO_3S_3$: 432.0738; found: 432.0750.

Preparation of N-Pmc-Substituted Amidines 3a–j; General Procedure
In a 50 mL round-bottom flask, *N*-Pmc thioamide (**2a–i**; 1.30 mmol) was dissolved in CH_2Cl_2 (10 mL). To this stirred solution was sequentially added DIPEA (450 μL, 2.60 mmol, 2 equiv) and 2-chloro-*N*-methylpyridinium iodide (Mukaiyama reagent; 400 mg, 1.56 mmol, 1.2 equiv). This solution was incubated with stirring for 5 min, then the required amine nucleophile (1.95 mmol, 1.5 equiv) was added. The reaction was stirred for an additional 30 min. At the end of this time, the contents of the reaction vessel were poured into a 125 mL separating funnel containing EtOAc (150 mL) and 2% HCl (150 mL). The phases were separated and the organic layer was washed with 2% HCl (100 mL). The organic layer was then separated, dried over $MgSO_4$, and evaporated in vacuo to afford the crude *N*-Pmc amidine product. Purification over silica gel (EtOAc–hexane, 20–40%) afforded the amidine products.

***N*-Pmc-*N′*-Benzylacetamidine (3a)**
Yield: 0.39 g (73%); light-yellow semisolid.

IR (film): 3294, 1585 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12–7.23 (m, 5 H), 6.85 (br s, 1 H), 4.41 (d, J = 5.8 Hz, 0.3 H), 4.37 (d, J = 5.2 Hz, 1.7 H), 2.57 (t, J = 6.3 Hz, 2 H), 2.52 (s, 0.4 H), 2.51 (s, 0.4 H), 2.45 (s, 2.6 H), 2.43 (s, 2.6 H), 2.19 (s, 3 H), 2.10 (s, 0.4 H), 2.07 (s, 2.6 H), 1.79 (t, J = 6.1 Hz, 2 H), 1.30 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 165.2, 154.2, 153.6, 137.0, 136.1, 136.0, 135.5, 135.4, 134.9, 132.7, 132.3, 131.4, 130.8, 129.0, 128.7, 128.3, 127.9, 127.3, 126.6, 124.3, 123.9, 118.1, 117.8, 73.7, 73.6, 68.1, 47.8, 45.4, 38.6, 32.7, 30.8, 30.2, 28.8, 26.6, 25.3, 23.6, 22.9, 21.2, 20.3, 18.3, 17.3, 17.2, 14.0, 12.0, 10.9.

HRMS: m/z [M + Na] calcd for $C_{23}H_{30}N_2NaO_3S$: 437.1875; found: 437.1874.

***N*-Pmc-*N′*,*N′*-Diisopropylbutanamidine (3b)**
Yield: 0.49 g (87%); colorless amorphous solid; mp 165–167 °C.

IR (film): 2930, 1533 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.97–4.03 (m, 1 H), 3.43–3.55 (m, 1 H), 2.76–2.82 (m, 2 H), 2.63 (t, J = 6.8 Hz, 2 H), 2.57 (s, 3 H), 2.55 (s, 3 H), 2.11 (s, 3 H), 1.81 (t, J = 6.8 Hz, 2 H), 1.44–1.58 (m, 2 H), 1.34 (d, J = 6.7 Hz, 6 H), 1.31 (s, 6 H), 1.22 (d, J = 6.6 Hz, 6 H), 0.93 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.1, 166.9, 153.8, 136.2, 135.2, 135.1, 133.3, 124.3, 117.5, 74.7, 50.5, 48.6, 39.6, 35.3, 33.7, 30.9,

30.3, 29.5, 27.4, 24.4, 23.7, 22.0, 21.3, 21.2, 20.9, 19.2, 17.6, 14.9, 14.7, 13.6, 11.9.

HRMS: *m/z* [M + Na] calcd for $C_{24}H_{40}N_2NaO_3S$: 459.2657; found: 459.2657.

***N*-Pmc-3-Methyl-1-(piperidin-1-yl)butan-1-imine (3c)**
Yield: 0.46 g (82%); colorless gum.

IR (film): 2936, 1520 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.61–3.70 (m, 2 H), 3.40–3.50 (m, 2 H), 2.87 (d, *J* = 7.7 Hz, 2 H), 2.63 (t, *J* = 6.8 Hz, 2 H), 2.58 (s, 3 H), 2.57 (s, 3 H), 2.11 (s, 3 H), 1.80 (t, *J* = 6.7 Hz, 2 H), 1.43–1.69 (m, 7 H), 1.30 (s, 6 H), 0.98 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 153.1, 135.3, 134.5, 134.3, 123.6, 117.6, 73.4, 48.1, 45.8, 38.1, 32.8, 27.6, 26.6, 25.5, 24.1, 22.2, 21.3, 18.3, 17.2, 11.9.

HRMS: *m/z* [M + Na] calcd for $C_{24}H_{38}N_2NaO_3S$: 457.2501; found: 457.2500.

***N*-Pmc-*N*′-Phenyl-3-methylbutanamidine (3d)**
Yield: 0.41 g (72%); colorless friable foam; mp 148–150 °C.

IR (film): 3308, 1537 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.82 (br s, 1 H), 7.43–7.60 (m, 1 H), 7.27–7.41 (m, 2 H), 6.90–7.24 (m, 2 H), 2.45–2.68 (m, 8 H), 1.99–2.20 (m, 5 H), 1.82 (t, *J* = 6.5 Hz, 2 H), 1.32 (s, 6 H), 0.90–0.96 (m, 1 H), 0.71–0.89 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 154.1, 136.9, 136.0, 135.6, 130.9, 129.4, 127.7, 126.9, 124.2, 120.5, 118.0, 73.7, 41.8, 32.7, 26.7, 22.1, 21.3, 18.5, 17.4, 12.0.

HRMS: *m/z* [M + Na] calcd for $C_{25}H_{34}N_2NaO_3S$: 465.2188; found: 465.2192.

***N*-Pmc-*N*′-Cyclobutyl-4-pentenamidine (3e)**
Yield: 0.44 g (80%); light-yellow gum.

IR (film): 2976, 2531 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.11 (br s), 5.67–5.82 (m, 1 H), 4.94–5.06 (m, 2 H), 4.32–4.40 (m, 0.4 H), 3.97–4.08 (m, 0.6 H), 2.76 (t, *J* = 7.8 Hz, 1 H), 2.64 (t, *J* = 6.8 Hz, 2 H), 2.57 (s, 3 H), 2.56 (s, 3 H), 2.25–2.41 (m, 5 H), 2.11 (s, 3 H), 1.97–2.06 (m, 1 H), 1.77–1.87 (m, 4 H), 1.62–1.77 (m, 2 H), 1.31 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.5, 165.3, 154.0, 153.2, 136.5, 136.4, 136.0, 135.7, 135.4, 134.9, 133.3, 132.1, 124.1, 124.0, 118.0, 117.9, 116.4, 115.7, 73.7, 73.6, 48.3, 46.5, 32.8, 32.7, 32.6, 32.4, 31.4, 30.7, 30.0, 26.7, 21.3, 18.4, 17.4, 17.3, 15.2, 14.8, 12.0.

HRMS: *m/z* [M + Na] calcd for $C_{23}H_{34}N_2NaO_3S$: 441.2188; found: 441.2182.

***N*-Pmc-*N*′-(2-Acetamidyl)benzamide (3f)**
Yield: 0.30 g (52%); colorless dense solid; mp 193–195 °C.

IR (film): 3053, 1620 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.22 (t, *J* = 7.2 Hz, 1 H), 7.02–7.11 (m, 4 H), 6.76 (br s, 1 H), 6.13 (br s, 1 H), 4.24 (d, *J* = 4.4 Hz, 2 H), 2.44 (t, *J* = 6.4 Hz, 2 H), 2.30 (s, 3 H), 2.23 (s, 3 H), 1.96 (s, 3 H), 1.74 (t, *J* = 6.7 Hz, 2 H), 1.28 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 164.9, 153.6, 135.5, 135.0, 132.9, 132.1, 129.7, 127.3, 127.1, 123.8, 117.6, 73.5, 71.8, 70.5, 70.4, 58.9, 44.6, 32.7, 26.6, 21.1, 18.2, 16.9, 11.7.

HRMS: *m/z* [M + Na] calcd for $C_{23}H_{29}N_3NaO_4S$: 466.1776; found: 466.1758.

***N*-Pmc-*N*′-Allyl-4-methoxybenzamide (3g)**
Yield: 0.46 g (78%); colorless gum.

IR (film): 3296, 667 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.14 (br s, 1 H), 7.46 (d, *J* = 8.0 Hz, 1.3 H), 7.23 (d, *J* = 7.9 Hz, 0.7 H), 6.88 (d, *J* = 8.2 Hz, 1.3 H), 6.73 (d, *J* = 7.4 Hz, 0.7 H), 5.86–5.96 (m, 0.4 H), 5.74–5.84 (m, 0.6 H), 5.27–5.36 (m, 0.4 H), 5.18–5.27 (m, 0.6 H), 4.07–4.12 (m, 0.8 H), 3.88–3.93 (m, 1.2 H), 3.81 (s, 1.8 H), 3.78 (s, 1.2 H), 2.55–2.68 (m, 4.9 H), 2.48–2.54 (m, 0.9 H), 2.43 (s, 1.2 H), 2.37 (s, 1.2 H), 2.11 (s, 1.8 H), 2.03 (s, 1.2 H), 1.74–1.82 (m, 2 H), 1.58 (s, 1.3 H), 1.30 (s, 4.7 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.0, 161.7, 161.0, 154.2, 136.1, 135.6, 135.0, 133.5, 132.9, 131.9, 130.1, 129.0, 126.4, 125.3, 124.3, 123.7, 118.0, 117.9, 117.2, 113.8, 113.2, 73.7, 73.5, 55.4, 55.3, 48.2, 44.7, 32.8, 26.7, 21.4, 18.5, 17.4, 17.2, 12.0, 11.9.

HRMS: *m/z* [M + Na] calcd for $C_{25}H_{32}N_2NaO_4S$: 479.1980; found: 479.1971.

***N*-Pmc-*N*′-(1-Methylpropyl)-4-trifluoromethylbenzamide (3h)**
Yield: 0.49 g (74%); light-yellow gum.

IR (film): 3264, 1530 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.92 (br s, 1 H), 7.66 (d, *J* = 8.1 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 5.45 (d, *J* = 8.2 Hz, 0.5 H), 4.18–4.29 (m, 0.5 H), 3.94 (s, 0.5 H), 3.26–3.36 (m, 0.5 H), 2.63 (t, *J* = 6.8 Hz, 1 H), 2.59 (s, 1.5 H), 2.59 (s, 1.5 H), 2.45 (t, *J* = 6.8 Hz, 1 H), 2.35 (s, 1.5 H), 2.22 (s, 1.5 H), 2.11 (s, 1.5 H), 2.00 (s, 1.5 H), 1.80 (t, *J* = 6.8 Hz, 1 H), 1.76 (t, *J* = 6.8 Hz, 1 H), 1.53–1.62 (m, 1 H), 1.43–1.52 (m, 1 H), 1.29 (s, 6 H), 1.23 (d, *J* = 6.6 Hz, 1.5 H), 1.18 (d, *J* = 6.5 Hz, 1.5 H), 0.96 (t, *J* = 7.4 Hz, 1.5 H), 0.86 (t, *J* = 7.4 Hz, 1.5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 163.0, 154.3, 153.6, 140.8, 137.6, 137.4, 136.0, 135.9, 135.6, 135.5, 135.0, 133.9, 132.6, 132.2, 131.9, 131.5, 131.4, 131.3, 128.0, 127.6, 125.6, 124.6, 124.4, 123.9, 122.4, 118.1, 117.6, 113.3, 73.8, 73.5, 53.5, 49.4, 45.8, 32.7, 30.6, 28.9, 26.7, 26.6, 26.5, 21.7, 21.3, 21.1, 19.8, 18.4, 18.3, 17.3, 16.8, 12.0, 11.7, 10.3, 10.2.

HRMS: *m/z* [M + Na] calcd for $C_{26}H_{33}F_3N_2NaO_3S$: 533.2062; found: 533.2039.

***N*-Pmc-*N*′-(2-Adamantyl)-2-thiopheneamidine (3i)**
Yield: 0.58 g (85%); colorless friable foam; mp 177–179 °C.

IR (film): 2911, 1578 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.87 (br d, *J* = 9.6 Hz, 1 H), 7.49 (d, *J* = 4.8 Hz, 1 H), 7.44 (d, *J* = 3.1 Hz, 1 H), 7.06 (t, *J* = 4.0 Hz, 1 H), 4.08 (d, *J* = 8.7 Hz, 1 H), 2.58–2.69 (m, 7.6 H), 2.36 (s, 0.2 H), 2.31 (s, 0.2 H), 2.16 (s, 0.2 H), 2.10 (s, 2.8 H), 11.93–2.01 (m, 2 H), 1.82–1.92 (m, 3 H), 1.79 (t, *J* = 6.7 Hz, 2 H), 1.63–1.77 (m, 7 H), 1.29 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5, 153.9, 136.1, 135.5, 132.3, 130.9, 130.8, 127.4, 124.1, 118.0, 73.7, 59.1, 37.2, 36.9, 33.3, 32.7, 31.2, 26.9, 26.7, 21.3, 18.6, 17.5, 12.0.

HRMS: *m/z* [M + Na] calcd for $C_{29}H_{38}N_2NaO_3S_2$: 549.2222; found: 549.2210.

***N*,*N*′-[1,3-Phenylenebis(methylene)]bis(*N*′-Pmc-butanamidine) (3j)**
Yield: 0.74 g (70%); colorless friable foam; mp 118–120 °C.

IR (film): 3304, 1121 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.24–8.26 (m, 0.1 H), 8.16–8.22 (m, 0.3 H), 7.12–7.20 (m, 2.4 H), 7.08–7.11 (m, 0.4 H), 7.03–7.09 (m, 1.2 H), 6.46 (br s, 1.2 H), 6.11 (br s, 0.4 H), 4.48 (d, *J* = 6.1 Hz, 0.3 H), 4.43 (d, *J* = 5.4 Hz, 0.7 H), 4.39 (d, *J* = 6.0 Hz, 0.8 H), 4.35 (d, *J* = 5.4 Hz, 2.2 H), 2.69–2.74 (m, 0.8 H), 2.57–2.66 (m, 6.3 H),

2.56 (d, J = 4.6 Hz, 1 H), 2.53 (d, J = 4.4 Hz, 2.2 H), 2.51 (s, 2.1 H), 2.45–2.50 (m, 6.6 H), 2.23–2.31 (m, 0.9 H), 2.06–2.13 (m, 6 H), 1.75–1.84 (m, 4 H), 1.55–1.69 (m, 2 H), 1.47–1.57 (m, 2 H), 1.26–1.37 (m, 10.3 H), 1.26 (s, 1.7 H), 0.84–0.93 (m, 3 H), 0.81 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 168.1, 167.6, 153.6, 138.5, 137.4, 135.6, 134.9, 133.3, 131.9, 129.4, 128.8, 127.8, 127.7, 127.1, 126.5, 125.9, 124.0, 118.0, 117.9, 73.8, 73.6, 47.2, 45.4, 35.5, 35.4, 35.3, 32.8, 29.7, 26.7, 21.4, 20.8, 20.7, 19.6, 18.4, 17.3, 13.8, 12.0.

HRMS: m/z [M + Na] calcd for $C_{44}H_{62}N_4NaO_6S_2$: 829.4009; found: 829.4000.

Pmc-Deprotection of Substituted Amidines 4a–j

In a 25 mL round-bottom flask, *N*-Pmc-substituted amidine **3** (0.25 mmol) was dissolved in TFA (4 mL), and TMSOTf (50 μL) was added. The solution was stirred for 4 h at r.t., then reduced to approximately 1/4 of its volume under a stream of nitrogen, and the residue was then taken up in ice-cold anhydrous Et_2O (20 mL). In approximately half of the instances, the desired deprotected amidines precipitated directly from the ethereal solution and were isolated by centrifugation as their representative TFA salts. In the other instances, the amidine did not directly precipitate, necessitating the reduction of the ethereal solution in vacuo and purification of the resultant black gum over silica (EtOAc–MeOH–HCO_2H, 1:2:7) to yield the desired amidine products as their representative formate salts.

***N*-Benzylacetamidine (4a)**

Yield: 34 mg (91%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.31–7.44 (m, 5 H), 4.44 (d, J = 5.4 Hz, 1 H), 2.26 (s, 3 H).

MS (APCI): m/z = 149 [M + H].

***N*,*N*-Diisopropylbutanamidine (4b)**

Yield: 34 mg (80%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.80 (br s, 1 H), 7.52 (br s, 1 H), 4.21–4.30 (m, 1 H), 4.05–4.13 (m, 1 H), 2.58 (t, J = 7.8 Hz, 2 H), 1.64–1.76 (m, 2 H), 1.42 (d, J = 7.2 Hz, 6 H), 1.33 (d, J = 6.6 Hz, 6 H), 1.06 (t, J = 7.4 Hz, 3 H).

MS (APCI): m/z = 171 [M + H].

3-Methyl-1-(piperidin-1-yl)butan-1-imine (4c)

Yield: 19 mg (45%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.79 (br s, 1 H), 8.29 (br s, 1 H), 3.64 (t, J = 4.5 Hz, 2 H), 3.57 (t, J = 4.5 Hz, 2 H), 2.49 (d, J = 7.7 Hz, 2 H), 1.95–2.04 (m, 1 H), 1.66–1.80 (m, 8 H), 1.03 (d, J = 6.7 Hz, 6 H).

MS (APCI): m/z = 169 [M + H].

***N*-Phenyl-3-methylbutanamidine (4d)**

Yield: 29 mg (66%); isolated as its TFA salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.52–7.59 (m, 2 H), 7.44–7.50 (m, 1 H), 7.29–7.35 (m, 2 H), 2.50 (d, J = 7.6 Hz, 2 H), 2.13–2.24 (m, 1 H), 1.12 (d, J = 7.6 Hz, 6 H).

MS (APCI): m/z = 177 [M + H].

***N*-Cyclobutyl-4-pentenamidine (4e)**

Yield: 21 mg (53%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 5.76–5.85 (m, 1 H), 5.07–5.16 (m, 2 H), 4.00–4.10 (m, 1 H), 3.45–3.52 (m, 2 H), 2.48–2.58 (m, 2 H), 2.39–2.48 (m, 2 H), 2.03–2.16 (m, 2 H), 1.80–1.92 (m, 2 H).

MS (APCI): m/z = 153 [M + H].

***N*-(2-Acetamidyl)benzamide (4f)**

Yield: 21 mg (48%); isolated as its TFA salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.76–7.81 (m, 2 H), 7.70–7.75 (m, 1 H), 7.58–7.65 (m, 2 H), 4.26 (s, 2 H).

MS (APCI): m/z = 178 [M + H].

***N*-Allyl-4-methoxybenzamide (4g)**

Yield: 19 mg (41%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.72 (d, J = 8.9 Hz, 2 H), 7.13 (d, J = 8.9 Hz, 2 H), 5.92–6.02 (m, 1 H), 5.29–5.38 (m, 2 H), 4.06–4.12 (m, 2 H), 3.90 (s, 3 H).

MS (APCI): m/z = 191 [M + H].

***N*-(1-Methylpropyl)-4-trifluoromethylbenzamide (4h)**

Yield: 33 mg (54%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.79–7.84 (m, 4 H), 3.18–3.24 (m, 1 H), 1.57–1.69 (m, 2 H), 1.27 (d, J = 6.5 Hz, 3 H), 0.95 (t, J = 7.4 Hz, 3 H).

MS (APCI): m/z = 244 [M + H].

***N*-(2-Adamantyl)-2-thiopheneamidine (4i)**

Yield: 46 mg (71%); isolated as its TFA salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.53 (br s, 1 H), 7.93–7.97 (m, 1 H), 7.82–7.85 (m, 1 H), 7.27–7.31 (m, 1 H), 3.99 (br s, 1 H), 2.05–3.02 (m, 2 H), 1.90–2.00 (m, 7 H), 1.83–1.87 (m, 2 H), 1.72–1.78 (m, 2 H).

MS (APCI): m/z = 261 [M + H].

***N*,*N*′-[1,3-Phenylenebis(methylene)]bisbutanamidine (4j)**

Yield: 45 mg (66%); isolated as its TFA salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.44–7.50 (m, 1 H), 7.34–7.41 (m, 3 H), 4.50 (d, J = 3.2 Hz, 4 H), 4.49 (t, J = 7.7 Hz, 4 H), 1.69–1.80 (m, 4 H), 1.02 (t, J = 7.4 Hz, 6 H).

MS (APCI): m/z = 275 [M + H].

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