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Trimethylaluminium-Mediated Reaction of Primary Carboxamides with Amines and Indoles: A Convenient Synthesis of Amidines and Indole-3-acylimines

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A simple, convenient and general method, exhibiting good functional group tolerance, is described for the synthesis of *N*- and *N*,*N*-disubstituted amidines by the reaction of primary carboxamides with amines mediated by trimethylaluminium ($AlMe_3$). Subsequent reaction of the indole systems with primary carboxamides in the presence of $AlMe_3$ gives exclusively the C-3 substituted imine product.

Introduction

Amidines, as a class of compounds, find wide applications as superbases[1] and in the fixation of CO_2.[2,3] They also find use in material science,[4,5] in the design of catalysts,[6,7] in medicinal chemistry as biologically active molecules,[8–11] and as important intermediates for many chemical transformations.[12–17] Amidines are usually synthesised by reacting amines with common precursors such as nitriles,[18–26] secondary amides[27–30] or thioamides.[31] Often in the functional group transformation of nitriles into amidines, the nitrile functionality is activated by Lewis acid or is converted into the corresponding imidate ester.[19–21] Shen et al. reported the synthesis of amidines from nitriles catalysed by Ytterbium amide[32,33] that involves a solvent-free reaction. However, this reaction requires an extended time and it is accompanied by the formation of the unwanted side product triazine. Furthermore, 4-cyanopyridine, aliphatic nitriles, and aliphatic amines reacted sluggishly under these conditions. The latter methodology requires the use of excess amine (2.0 equiv.), and has been successfully applied only for aromatic primary amines. Palladium-catalysed amidine synthesis using cyanamide has been recently reported by Larhed et al. but this approach has the limitation of only employing aliphatic amines.[34]

Synthesis of amidines by electrophilic activation of aliphatic secondary or tertiary amides using triflic anhydride was reported by Charette et al.,[27] but this approach is found to be less effective in the case of both aliphatic and aromatic primary carboxamides. Subsequent to this report related to the synthesis of amidines from secondary carboxamides, many research groups including Katritzky et al.,[28] Thakur et al.,[29] Loughlin et al.,[30a] Shibasaki et al.,[30b] and Bihel et al.,[30c] contributed significantly in this area. Whereas these methodologies are suitable for secondary carboxamides, they are strictly not applicable for primary carboxamides. Indeed, activation of primary carboxamides for the synthesis of amidines has not been successful in any of the methods reported hitherto.

Results and Discussion

During the course of our research work on trimethylaluminium ($AlMe_3$) mediated organic transformations for the synthesis of tetrasubstituted ureas,[35] we encountered dehydration of the primary carboxamide (**1**) to nitrile (**3**), instead of the expected urea (**4**) (Scheme 1). In the direct synthesis of nitriles from esters or primary carboxamides using methylchloroaluminium amide developed by Weinreb et al., there was no indication for the formation of any amidine product.[36] Later, Gielen et al.[37] reported the preparation of unsubstituted amidines directly from esters by employing an excess of methylchloroaluminium amide. In this methodology, only ammonia (NH_3) could be used, giving unsubstituted amidines. Reaction of primary/secondary amines with esters in the presence of $AlMe_3$ furnished only the amide product.[38a] $AlMe_3$-mediated amidine synthesis by activation of nitriles was first reported by Garigipati[23] and later by many others.[24–26] Herein, we report the synthesis of N- and N,N-disubstituted amidines by dual activation of primary carboxamides and amines by $AlMe_3$. A direct synthesis of indole-3-acylimines is also described. Because amidines were prepared from nitriles, we envisioned a one-pot reaction whereby both the nucleophile (amine) and the electrophile (primary carboxamide) could be activated to form amidines.

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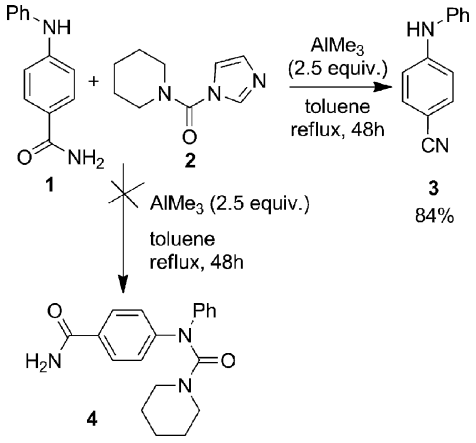
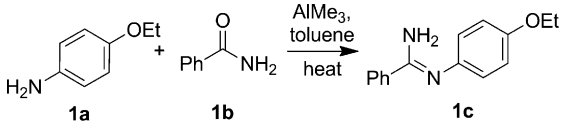


Scheme 1. Primary carboxamide dehydration using $AlMe_3$.

For this methodology, *p*-phenitidine (**1a**) and benzamide (**1b**) were chosen for optimization of the reaction conditions (Table 1). When a mixture of **1a** (1.1 mmol) and **1b** (1.0 mmol) were heated in anhydrous toluene with $AlMe_3$ (1.5 equiv.) under a nitrogen atmosphere for 4 h, only a very low conversion of the reactant into amidine **1c** (11–23%) was observed.

Table 1. $AlMe_3$-promoted direct coupling of *p*-phenitidine (**1a**) with benzamide (**1b**).

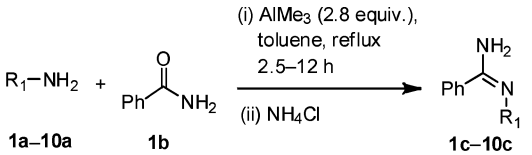


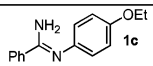
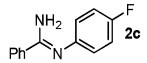
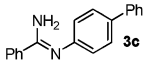
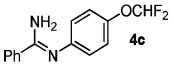
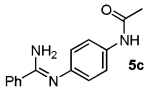
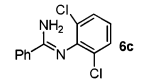
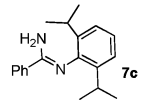
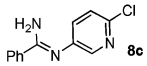
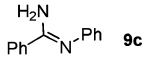
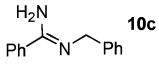
Entry	$AlMe_3$ [equiv.]	Conversion after 4 h [%][a] 80 °C	Reflux
1	1.5	11	23
2	2.2	59	72
3	2.8	89	99[b]

[a] Conversion based on **1b** by HPLC analysis. [b] After 2.5 h.

A better conversion was realised with an excess of $AlMe_3$ (2.2 equiv.), however, a considerable amount of benzamide **1b** remained unreacted. Although the stoichiometry of the reaction demands 2.0 equiv. $AlMe_3$ for the dehydration of primary carboxamide, the amidine reaction proceeded to completion with 2.8 equiv. of $AlMe_3$ (Table 1, entry 3). By employing the optimised conditions, the reaction of benzamide **1b** with a variety of amines (**1**–**10a**) of varying nucleophilicity was studied (Table 2). Both aromatic primary amines (Table 2, entries 1–9) as well as aliphatic primary amine **10a**, exhibited good reactivity under these conditions. Functional groups such as OEt, $OCHF_2$, and Cl (entries 1, 4, 6 and 8) were found to be compatible with this methodology. Even the less reactive 2,6-dichloroaniline (**6a**) reacted to afford amidine **6c**, although the maximum conversion was observed after 12 h reflux in toluene (entry 6). Thus, the $AlMe_3$-mediated reaction of benzamide **1b** with primary amines proved to be a useful method for the preparation of N-substituted amidines.

Table 2. Scope of the reaction with primary amines.[a]



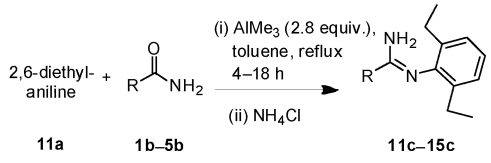
Entry	Amine	Time [h]	Amidine	Yield [%][b]
1	*p*-phenitidine **1a**	2.5	 **1c**	88
2	*p*-fluoroaniline **2a**	3	 **2c**	87
3	*p*-phenylaniline **3a**	2.5	 **3c**	81
4	*p*-(difluoromethoxy)-aniline **4a**	2.5	 **4c**	79
5	*p*-aminoacetanilide **5a**	4	 **5c**	71
6	2,6-dichloroaniline **6a**	12	 **6c**	85
7	2,6-diisopropyl-aniline **7a**	5	 **7c**	87
8	3-amino-6-chloro-pyridine **8a**	2.5	 **8c**	81
9	aniline **9a**	5	 **9c**	80
10	benzylamine **10a**	6	 **10c**	88[c]

[a] Reaction conditions: amine (1.1 mmol), primary carboxamide (1.0 mmol). [b] Isolated yield. [c] Amine (2.0 equiv.) was used.

We then studied the reactivity difference between the aliphatic and the aromatic primary carboxamides. 2,6-Diethylaniline (**11a**), a sterically hindered aromatic primary amine, was chosen as a standard and it was allowed to react with a selection of carboxamides (Table 3, **1**–**5b**). Aliphatic carboxamides **2b** and **4b** were found to be less reactive compared with the aromatic primary carboxamide **1b**. It is interesting to note that α,β-unsaturated carboxamide **3b** (entry 3) displayed a high reactivity and afforded amidine **13c** in very good yield, unlike phenylacetamide **2b**. The reaction of **3b** was clean and free from side products generated due to isomerisation of the double bond or Michael addition of the amine or methyl group.[39] The diminished reactivity of the aliphatic amides may be due to the lower acidity of the amide protons[40] compared with their aromatic counterparts, and consequent difficulty in forming the aluminium imidate (**A**, Scheme 4). The aliphatic carbox-

amide **4b**, derived from the anti-inflammatory drug, ibuprofen, was less reactive than **2b** (entry 4). Trimethylaluminium-mediated amidine formation from (*S*)-(4-isobutylphenyl)-2-methylpropionamide (**4b**) was observed with partial racemisation, and the product **14c** was isolated in 81% yield with 64% (*ee*) as revealed by chiral HPLC analysis. Pivalamide **5b** was found to be totally unreactive, and no amidine product was observed in this case (entry 5), which may be due to steric crowding around the amide functionality emanating from the amide **5b** as well as from 2,6-diethyaluminium amide.

Table 3. Reactivity of various carboxamides with aromatic primary amine **11a**.[a]

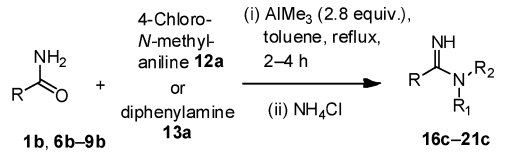


Entry	Amide	Time [h]	Amidine	Yield [%][b]
1	**1b**	5	**11c**	89
2	**2b**	9	**12c**	81
3	**3b**	4	**13c**	81
4	**4b**	18	**14c**	81
5	**5b**	8	**15c**	–[c]

[a] Reaction conditions: amine (1.1 mmol), primary carboxamide (1.0 mmol). [b] Isolated yield. [c] Not observed.

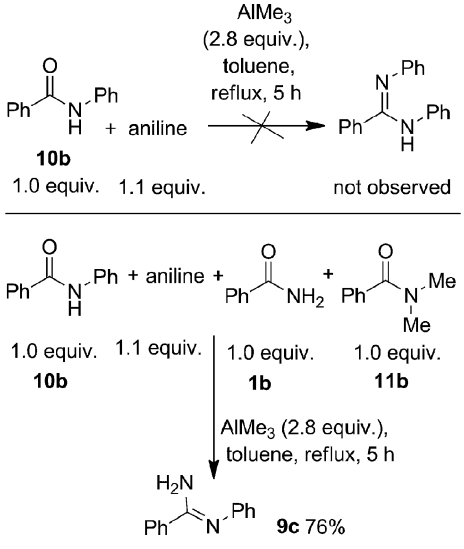
We then investigated the scope of this amidine synthesis by employing secondary amines with diphenylamine (**13a**) as a standard. Compound **13a** was treated with a selection of aromatic primary carboxamides **1b** and **6**–**9b** bearing different substituents (Table 4). All the amides reacted equally well except *p*-nitrobenzamide (**9b**). The reaction was complex in the case of **9b** (entry 6). The synthesis of amidines **18c** and **19c**, bearing halogen substituents from the corresponding halobenzoic acids, is more economical than from the corresponding halogenated benzonitriles. Secondary and the tertiary amides were prepared by the reaction of amines with carboxylic esters[38a] or acids[38b] in the presence of $AlMe_3$. In this connection, we wished to verify the scope of this $AlMe_3$-mediated transformation for the amidine formation from secondary amides. There was no reaction when secondary amide **10b** was subjected to the reaction conditions outlined in Scheme 2.

Table 4. Reactivity of carboxamides with aromatic secondary amines in amidine synthesis.[a]



Entry	Amide	Time [h]	Amidine	Yield [%][d]
1[b]	**1b**	2.5	**16c**	81
2[c]	**1b**	4	**17c**	84 48[e]
3[c]	**6b**	4	**18c**	80 64[e]
4[c]	**7b**	4	**19c**	78 51[e]
5[c]	**8b**	4	**20c**	81 50[e]
6[c]	**9b**	2	**21c**	–[f]

[a] Reaction conditions: amine (1.1 mmol), primary carboxamide (1.0 mmol). [b] 4-Chloro-*N*-methylaniline was used. [c] Diphenylamine was used. [d] Isolated yield. [e] HPLC conversion of carboxamide in 2 h at 80 °C. [f] Not observed.



Scheme 2. Reactivity comparison of primary and secondary carboxamides in the presence of $AlMe_3$.

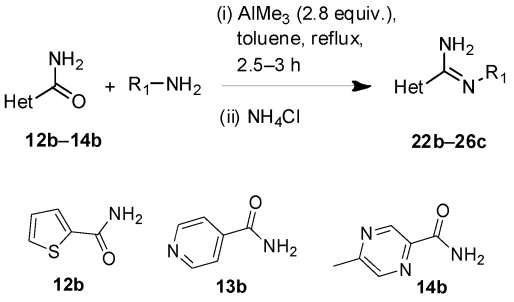
We also observed that when a mixture of benzamide (**1b**), benzanilide (**10b**) and *N*,*N*-dimethylbenzamide (**11b**) were treated with aniline in the presence of $AlMe_3$, amidine **9c** was formed as the sole product (Scheme 2). Furthermore, the $AlMe_3$-mediated reaction of *p*-aminoacetanilide (**5a**) with aniline afforded the amidine **5c** in 71% yield (Table 2, entry 5). The rest of the starting material remained unreacted. No polymeric product arising out of the self-condensation of **5a** could be detected. Thus, this transformation is found to display an exclusive chemoselectivity in favour of the primary carboxamide (Scheme 2).

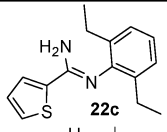
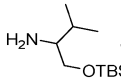
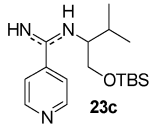
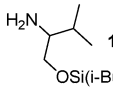
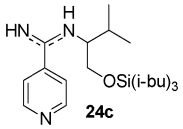
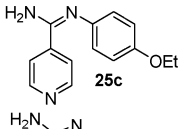
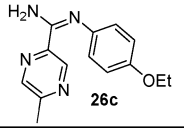
Aromatic secondary amines **12a** and **13a** (Table 4, entries 1–5) gave the respective amidines in good yields under these conditions. Sterically hindered 2,6-diisopropylaniline **7a** (Table 2, entry 7) and 2,6-diethylaniline **11a** (Table 3, entries 1–4) also underwent this transformation to afford the respective amidines in good yields. Heteroaromatic primary carboxamides **12**–**14b**, were also successfully transformed into the corresponding amidines **22**–**26c** (Table 5, entries 1–5). Silyl protecting groups OTBS (entry 2) and $OSi(iBu)_3$ (entry 3) showed good tolerance towards these conditions, with aliphatic primary amines derived from valine, **14a** and **15a** exhibiting good reactivity.

The success of this amidine formation seems to depend on the ease of formation of the aluminium-amide from the reaction of $AlMe_3$ with the amines. Aromatic amines are more readily deprotonated by $AlMe_3$ to form the more nucleophilic aluminium amide, whereas the more basic aliphatic amines form only the Lewis acid–base adduct with $AlMe_3$.[41] The reactions are also found to be faster in the cases of aromatic primary amine compared with that of aliphatic amines (Table 2, entry 10 and Table 5, entries 2 and 3), which may be due to the ease of formation of the aluminium amide in the case of aromatic amines (**B**, see Scheme 4 below).

Benzylamine is known to form a Lewis acid:base complex with trimethylaluminium. The formation of the aluminium amide from this complex is evidently a slow process. This is supported by the findings from the reaction of carboxamide **4b** with aliphatic secondary amines **16a**, **17a** and **18a**, and a hindered aromatic amine **11a** (see Table 6). Whereas no conversion was observed in the case of any of the aliphatic amines (entries 2–4), moderate conversion (42%) into amidine **14c** was observed in the case of 2,6-diethylaniline, despite it being a sterically hindered aromatic amine (entry 1).

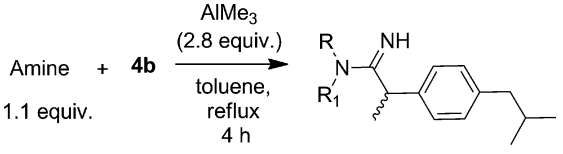
Table 5. Scope of the reaction with heterocyclic carboxamide and different amines.[a]



Entry	Amine	Amide	Time [h]	Amidine	Yield (%)[b]
1	2,6-diethylaniline **11a**	**12b**	3	 **22c**	81
2	 **14a**	**13b**	2.5	 **23c**	81[c]
3	 **15a**	**13b**	2.5	 **24c**	79[c]
4	**1a**	**13b**	3	 **25c**	81
5	**1a**	**14b**	3	 **26c**	80

[a] Reaction conditions: amine (1.1 mmol), primary carboxamide (1.0 mmol). [b] Isolated yield. [c] Amine (2.0 equiv.) was used.

Table 6. Nucleophilicity of amines with less reactive aliphatic carboxamide in the presence of $AlMe_3$.



Entry	Amine	Amidine (conversion, %)
1	2,6-diethylaniline (**11a**)	**14c** (42)[a]
2	dibenzylamine (**16a**)	**27c** (0)[b]
3	piperidine (**17a**)	**28c** (0)[b]
4	*N*-benzylpiperazine (**18a**)	**29c** (0)[b]

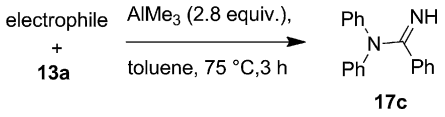
[a] By HPLC analysis. [b] Not observed by HPLC or LCMS analyses.

In addition to the above observation, we can compare the results from Table 2, in which 1.1 equiv. aniline **9a** (entry 9) was treated with **1b** to give amidine **9c** in good yield. When 1.1 equiv. benzylamine (**10a**, Table 2, entry 10) was used, the conversion by TLC was not attractive and excess benzylamine (2.0 equiv.) was required for complete conversion. Thus, it is clear that aliphatic amines are relatively poor substrates for the $AlMe_3$-mediated amidine synthesis. With such amines, the reaction could still be realised by employing the amine in excess (2.0–3.0 equiv.).[38b,42,43]

We also compared the reaction of benzonitrile and benzamide with diphenylamine under identical conditions (heating in toluene at 75 °C for 3 h using 2.8 equiv. $AlMe_3$; Table 7). HPLC analysis revealed the complete absence of benzonitrile after 3 h, with the maximum conversion of 89% into amidine (entry 1), whereas in the case of benz-

amide (entry 2) only 25% conversion into amidine **17c** was observed, with the major amount being the starting materials benzamide and diphenylamine. No benzonitrile intermediate was detected in this reaction (entry 2). In another reaction, conducted under the same conditions in the absence of diphenylamine, benzamide was completely dehydrated to benzonitrile (Scheme 3). Thus, it is evident that the reaction of the nitrile with amine is faster than the dehydration of the amide to nitrile.

Table 7. Reactivity comparison of benzonitrile and benzamide.

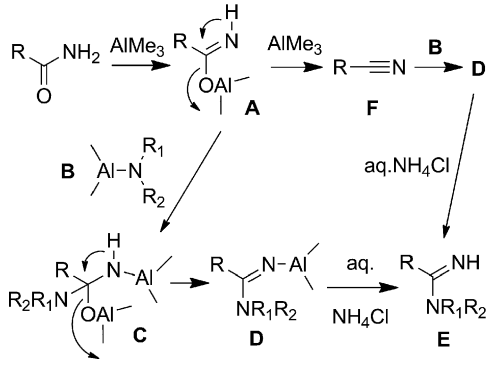


Entry	Electrophile	Conversion [%][a]
1	benzonitrile	89
2	benzamide	25

[a] Conversion based on HPLC analysis.

Scheme 3. Dehydration of benzamide mediated by $AlMe_3$.

We have not observed any transamidation[44] product or triazine[22,32,33] in any of our reactions. These observations suggest that amidine formation probably proceeds via nitrile intermediate **F**, as depicted in Scheme 4. An alternative mechanistic possibility, involving tetrahedral intermediate **C** formed by attack of aluminium amide **B** on imidate **A** (Scheme 4), seems to be less probable from the findings that the reaction takes place readily even in the case of hindered amines. Formation of tetrahedral intermediate **C** from imidate **A** would be sterically less favoured in the case of hindered amines such as 2,6-disubstituted anilines (Table 2, entry 7). Furthermore, nitriles have been isolated in some of these reactions (Scheme 3 and Scheme 1), and nitriles have been converted into the amidines by reacting with amines in the presence of Lewis acid catalysts.[23–26] Because indoles are ambident nucleophiles, it was of interest to investigate

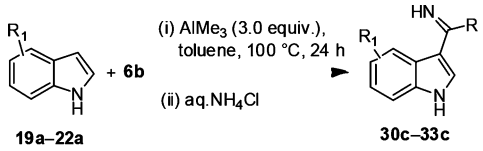


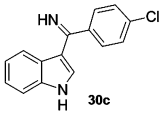
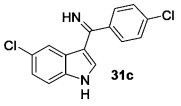
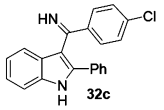
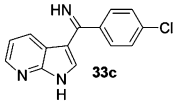
Scheme 4. Possible mechanistic pathways.

the behaviour of indoles towards primary carboxamide in the presence of $AlMe_3$.

When an equimolar mixture of indole, 4-chlorobenzamide and $AlMe_3$ (2.5 equiv.) were heated at 100 °C in toluene for 15 h, the reaction was incomplete as revealed by TLC. The reaction was driven to completion by employing 3.0 equiv. $AlMe_3$ and continuing the reaction for 24 h. We were pleased to observe the formation of indole-3-acylimine (**30c**; Table 8, entry 1) as the only product. We did not observe any amidine product arising from the attack of indole nitrogen. Indole C3, being a soft centre, preferentially reacted with the nitrile to give imines.

Table 8. Indole-3-acylimine synthesis.

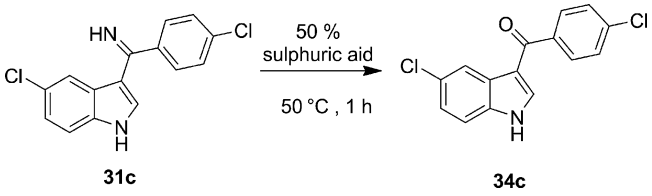


Entry	Indole	Imine	Yield[a]
1	indole **19a**	 **30c**	79
2	5-chloroindole **20a**	 **31c**	81
3	2-phenylindole **21a**	 **32c**	83
4	7-azaindole **22a**	 **33c**	–[b]

[a] Isolated yield. [b] Not observed.

Primary carboxamides have never been considered to be convenient candidates for Friedel–Crafts acylation reactions because of their weak electrophilic nature. It is worth mentioning here that this is the first report to demonstrate the use of primary carboxamides as electrophiles in the Friedel–Crafts acylation of indoles. There are only a few reports on Friedel–Crafts acylation reactions involving nitriles as electrophiles.[45] Indole C3-acyl imines are potential precursors for many transformations. All these imines are stable towards the aqueous work up conditions involving saturated ammonium chloride. Acylimine **31c** was hydrolysed to the corresponding ketone **34c** by using 50% sulfuric acid upon heating at 50 °C for 1 h (Scheme 5).

Unsymmetrical amidines are known to exist as tautomers in solution associated with proton transfer between the two nitrogen centres, and the existence of tautomerism was established by proton NMR spectroscopy.[46,47] It was observed that the predominant tautomer at equilibrium was



31c 34c

Scheme 5. Hydolysis of imine **31c**.

that with the more basic nitrogen atom bearing the hydrogen. The rotational isomerism was studied by using variable-temperature NMR spectroscopy. Tautomerism in amidines has also been studied by infrared spectroscopy.[48] In the IR spectrum ($CHCl_3$), primary amidines exhibit three bands in the N–H stretching region. The first is a weak band at 3400–3300 cm^{-1}, which corresponds to the asymmetric N–H stretching, and a second band in the region 3330–3250 cm^{-1}, corresponding to the symmetric N–H stretch. The third band occurs near 3450 cm^{-1}, and corresponds to the N–H stretch of a secondary amino group. In addition to these bands, a band due to N-H bending vibration is also observed near 1650–1580 cm^{-1}. *N*,*N*,*N*′-Trisubstituted amidines were found to be the least basic. With a view to gain some insight into the tautomerism of the amidines that we have synthesised, we analysed the proton NMR spectrum of amidine **1c**. The proton NMR spectrum of **1c** ($CDCl_3$) exhibited a signal due to the NH_2 protons (integrated for two protons) at δ = 4.58 ppm, which disappeared on D_2O exchange. No evidence could be found in the NMR spectrum for the presence of the second tautomer, i.e., the imino form. Indeed, no additional signals were seen in the ^1H NMR spectrum. Likewise, the ^{13}C NMR spectrum also suggested it to be homogeneous compound and did not contain any additional carbon signals. In contrast, amidines **23c** and **24c** were found to exist as a mixture of two tautomers, as revealed by their ^1H and ^{13}C NMR spectra (see NMR and IR spectra in the Supporting Information), although HPLC analysis indicated that amidine **24c** was 99% pure. Evidently, the mixture of tautomers could not be resolved by HPLC. HRMS of **24c** was consistent with the expected molecular formula. Although according to the literature reports, the amino and imino forms show distinguishable characteristic NH stretching bands in the IR spectrum, the IR spectrum of **24c** (neat) recorded in NaCl disc and in $CHCl_3$ did not clearly show =N-H and -NH_2 stretching vibrations. The region 3584–3012 cm^{-1} was broad and was not informative. A band of medium intensity was, however, seen at 1654 cm^{-1}, which corresponds to C=N stretching vibration. Amidines **23c** and **24c** exist as a mixture of tautomers in solution. The proton NMR spectrum of **24c** in [D_6]DMSO displayed two broad signals, with an appreciable chemical shift separation, one at δ = 6.22 ppm and one at δ = 5.11 ppm and both these signals disappeared upon D_2O exchange. The upfield exchangeable signal at δ = 5.11 ppm is due to the amino proton and the more downfield signal at δ = 6.22 ppm is due to the imino proton. This assignment is based on the integration as well as on the basis of previously reported data. The ^{13}C NMR spectrum of **24c** displayed more signals than can be accounted for on the basis of tautomers.

Conclusions

We have demonstrated a simple, general and high-yielding method for the synthesis of substituted amidines from the reaction of primary carboxamides and amines. This methodology is complementary to existing methodologies, which are restricted to secondary carboxamides. The present methodology is applicable for aliphatic primary amines and aromatic amines of diverse nucleophilicity. A variety of amines, including hindered aromatic amines, less nucleophilic amines and heterocyclic amines, undergo this reaction. Whereas aromatic and heterocyclic primary carboxamides are excellent substrates for this transformation, aliphatic carboxamides also exhibited reasonable reactivity. This methodology showed high functional group tolerance, with -OTBS, -OSi(*i*Bu)$_3$, -Cl, -I, -F, -$OCHF_2$, -OMe, -OEt, and -CONHR being stable under the conditions of the $AlMe_3$-mediated amidine formation. Primary carboxamides are chemoselectively transformed into amidines in the presence of secondary and tertiary carboxamides. This reaction is free from the formation of side products from transamidation or cyclotrimerisation (*s*-triazine). It is noteworthy that primary carboxamides, which have been useful only for transamidation,[49] or nitrile synthesis,[50] have been found to be a useful electrophile in Friedel–Crafts acylation of indoles. Because inexpensive halobenzoic acids could be preferred over the more expensive halogenated benzonitrile for amidine synthesis, this methodology provides convenient access to amidines directly from primary carboxamides and serves as an alternative to routes starting from nitriles.

Experimental Section

General Information: NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO with 300, 400 or 500 MHz spectrometers and resonances are reported relative to TMS. Melting points were recorded by the open capillary method and are uncorrected. All reagents were purchased from commercial suppliers and were used without further purification unless noted. $AlMe_3$ (2 M in toluene) was used. Toluene was dried with sodium, distilled and stored over molecular sieves. All reactions were conducted under an atmosphere of nitrogen. The products were purified with an automated flash chromatographer on silica gel (200–400 mesh). High-resolution mass spectroscopy was carried out in electron spray ionisation mode.

Typical Procedure for Amidine Synthesis: A solution of $AlMe_3$ (2 M in toluene, 5.6 mmol, 2.8 equiv.) was added dropwise to a mixture of aromatic amine (2.2 mmol, 1.1 equiv.) and primary carboxamide (2 mmol, 1.0 equiv.) in anhydrous toluene (3 mL) at 0 °C in a flame-dried two-necked flask, under nitrogen. The resulting mixture was stirred for 30 min at room temp. and heated to 110 °C (oil bath temperature) for the given time. The mixture was cooled to 0 °C and diluted with CH_2Cl_2 (20 vol) and then slowly poured into ice-cold saturated NH_4Cl solution (4 mL). THF (15 vol) was added

and the mixture was stirred for 30 min at room temp. then filtered through a Celite bed, dried with sodium sulphate, and concentrated to give the crude product.

Note: Different amounts of amine are necessary [aliphatic primary amine (2.0 equiv.) or aromatic amine (1.1 equiv.)] for maximum conversion where primary carboxamide is the limiting reagent.

***N′*-(4-Ethoxyphenyl)benzamidine (1c):** Yield 211 mg (88%); off-white solid; m.p. 106–108 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3446, 3144, 1633, 1568, 1502, 1477, 1386, 1277, 1240, 1225 cm^{-1}. ^1H NMR (400 MHz, TMS, $CDCl_3$): δ = 7.81 (d, J = 7.2 Hz, 2 H), 7.45–7.38 (m, 3 H), 6.94–6.85 (m, 4 H), 4.58 (br., 2 H), 4.00 (q, J = 6.8 Hz, 2 H), 1.40 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ = 155.2, 141.7, 136.3, 130.6, 128.7, 128.6, 126.9, 122.8, 115.6, 63.8, 15.0 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{17}N_2O$ [M + H]$^+$ 241.1335; found 241.1334.

***N′*-(4-Fluorophenyl)benzamidine (2c):** Yield 180 mg (87%); off-white solid; m.p. 126–128 °C (ref.[32] m.p. 127–129 °C). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3405, 1639, 1576, 1500, 1367 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.82 (d, J = 7.2 Hz, 2 H), 7.51–7.40 (m, 3 H), 7.07–7.01 (m, 2 H), 6.94–6.89 (m, 2 H), 4.87 (br., 2 H) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{12}FN_2$ [M + H]$^+$ 215.0979; found 215.0942.

***N*-Biphenyl-4-yl-benzamidine (3c):** Yield 292 mg (81%); white solid; m.p. 179–182 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3468, 3352, 1614, 1592, 1570, 1485, 1377 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$): δ = 7.89 (s, 2 H), 7.60 (d, J = 8.0 Hz, 4 H), 7.50–7.41 (m, 5 H), 7.33–7.30 (m, 1 H), 7.08 (d, J = 7.5 Hz, 2 H), 4.90 (br., 2 H) ppm. ^{13}C NMR (125 MHz, TMS, $CDCl_3$): δ = 155.5, 149.2, 141.0, 136.0, 135.9, 130.8, 128.8, 128.7, 128.3, 126.9, 126.8, 126.7, 122.2 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{17}N_2$ [M + H]$^+$ 273.1386; found 273.1392.

***N*-(4-Difluoromethoxyphenyl)benzamidine (4c):** Yield 210 mg (79%); brown solid; m.p. 74–77 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3467, 3332, 1618, 1572, 1499, 1383, 1213, 1126, 1046, 868 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$): δ = 7.81–7.79 (m, 2 H), 7.43–7.41 (m, 3 H), 7.10–6.94 (m, 4 H), 6.47 (t, $J_{H,F}$ = 58 Hz, 1 H), 5.30–4.50 (br., 2 H) ppm. ^{13}C NMR (125 MHz, TMS, $CDCl_3$): δ = 155.9, 146.9, 135.4, 130.9, 128.7, 126.9, 123.0, 121.2, 118.3 ($OCHF_2$), 116.3 ($OCHF_2$), 116.2, 114.2 ($J_{C,F}$ = 257.5 Hz, $OCHF_2$) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{13}F_2N_2O$ [M + H]$^+$ 263.0990; found 263.1007.

***N*-[4-(-Benzamido)phenyl]acetamide (5c):** The crude material was washed with 15% EtOAc in hexane to obtain a solid, and filtered; yield 71%; off-white solid; mp 179–181 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3295, 1655, 1630, 1597, 1562, 1539, 1502, 1384, 1370, 1315 cm^{-1}. ^1H NMR (300 MHz, TMS, [D$_6$]DMSO): δ = 9.79 (s, 1 H), 7.96–7.94 (m, 2 H), 7.53–7.44 (m, 5 H), 6.82–6.81 (m, 2 H), 6.35–6.20 (m, 2 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (75 MHz, TMS, [D$_6$]DMSO): δ = 167.5, 164.0, 136.7, 134.5, 132.4, 131.8, 128.8, 127.9, 126.8, 120.1, 119.0, 20.3 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{16}N_3O$ [M + H]$^+$ 254.1289; found 254.1287.

***N′*-(2,6-Dichlorophenyl)benzamidine (6c):** Purified by silica gel column chromatography using an automated flash column chromatographer, eluted at the flow rate of 20 mL/min, with column packing of 25 g silica gel. Silica gel (230–400 mesh) washed with 2% Et_3N in hexanes before elution. 2% Et_3N used as an additive in both solvents. Product eluted out in 40% EtOAc in hexanes to give **6c**; yield 230 mg (85%); white solid; m.p. 80–83 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3482, 3458, 3179, 1685, 1630, 1572, 1432, 1390, 1244, 1025 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.95 (d, J = 6.6 Hz, 2 H), 7.52–7.42 (m, 3 H), 7.34 (d, J = 7.8 Hz, 2 H), 6.94 (t, J = 7.8 Hz, 1 H), 4.88–4.72 (br., 2 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 155.4, 143.9, 134.8, 133.3, 131.0, 129.3, 128.6, 128.4, 127.6, 127.1, 123.9 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{11}Cl_2N_2$ [M + H]$^+$ 265.0294; found 265.0291.

***N*-(2,6-Diisopropylphenyl)benzamidine (7c):** Yield 90 mg (89%); white solid; m.p. 160–163 °C (ref.[32] m.p. 162–163 °C). ^1H NMR (300 MHz, TMS, [D$_6$]DMSO): δ = 8.0 (d, J = 6 Hz, 2 H), 7.54–7.44 (m, 3 H), 7.13–7.10 (m, 2 H), 7.04–6.90 (m, 1 H), 6.50–6.10 (br., 2 H), 2.98–2.89 (m, 2 H), 1.17–1.15 (m, 12 H) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{25}N_2$ [M + H]$^+$ 281.2012; found 281.2029.

***N′*-(6-Chloropyridin-3-yl)benzamidine (8c):** Yield 170 mg (81%); brown solid; m.p. 132–135 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3394, 3320, 3197, 1638, 1605, 1571, 1460, 1385, 1100, 855, 699 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$): δ = 8.05 (s, 1 H), 7.84–7.82 (m, 2 H), 7.51–7.43 (m, 3 H), 7.29 (m, 2 H), 5.12–4.98 (br., 2 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 156.7, 145.0, 144.9, 143.1, 134.8, 132.6, 131.1, 128.7, 126.9, 124.6 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{11}ClN_3$ [M + H]$^+$ 232.0636; found 232.0642.

***N*-Phenylbenzamidine (9c):** Yield 190 mg (80%); white solid; m.p. 111–113 °C (ref.[32] m.p. 114–115 °C). ^1H NMR (300 MHz, TMS, [D$_6$]DMSO): δ = 7.96–7.94 (m, 2 H), 7.45–7.43 (m, 3 H), 7.33–7.28 (m, 2 H), 6.97–6.88 (m, 3 H), 6.29–6.26 (br., 1.4 H) ppm.

***N*-Benzyl-benzamidine (10c):**[51] Yield 280 mg (88%); off-white solid; m.p. 228–230 °C. ^1H NMR (300 MHz, TMS, [D$_6$]DMSO): δ = 10.53–9.55 (br., 2 H), 7.82 (d, J = 7.5 Hz, 2 H), 7.73 (t, J = 7.5 Hz, 1 H), 7.61 (t, J = 7.8 Hz, 2 H), 7.48–7.32 (m, 5 H), 4.73 (s, 2 H) ppm. ^{13}C NMR (75 MHz, TMS, [D$_6$]DMSO): δ = 162.5, 135.8, 133.2, 128.7, 128.6, 128.3, 128.2, 127.7, 127.5, 45.0 ppm.

***N*-(2,6-Diethylphenyl)benzamidine (11c):** Yield 160 mg (89%); white solid; m.p. 97–99 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3456, 3326, 3181, 2962, 2925, 1626, 1575, 1449, 1380 cm^{-1}. ^1H NMR (400 MHz, TMS, $CDCl_3$): δ = 7.92 (dd, J = 8, 1.6 Hz, 2 H), 7.50–7.45 (m, 3 H), 7.11 (d, J = 7.6 Hz, 2 H), 7.01 (d, J = 7.6 Hz, 1 H), 4.62–4.40 (br., 2 H), 2.59–2.45 (m, 4 H), 1.19 (t, J = 7.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ = 153.2, 144.7, 135.8, 134.7, 130.6, 128.6, 126.7, 126.3, 123.1, 24.6, 14.4 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{21}N_2$ [M + H]$^+$ 253.1699; found 253.1686.

***N*-(2,6-Diethylphenyl)-2-phenyl-acetamidine (12c):** Yield 121 mg (81%); white solid; m.p. 148–150 °C. ^1H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.39–7.30 (m, 5 H), 7.06–6.95 (m, 3 H), 4.14–4.10 (br., 2 H), 3.75 (s, 2 H), 2.62–2.41 (m, 4 H), 1.22–1.12 (m, 6 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 155.0, 145.0, 136.7, 134.8, 129.0, 128.8, 127.1, 125.7, 123.0, 43.0, 24.4, 14.3 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{23}N_2$ [M + H]$^+$ 267.1855; found 267.1864.

***N′*-(2,6-Diethylphenyl)cinnamamidine (13c):** Yield 360 mg (81%); off-white solid; m.p. 146–148 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3436, 3289, 3116, 2960, 1634, 1579, 1571, 1442, 1391 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.53 (d, J = 6.6 Hz, 2 H), 7.38–7.32 (m, 3 H), 7.20 (d, J = 16.2 Hz, 1 H), 7.09 (d, J = 7.5 Hz, 2 H), 7.02–6.99 (m, 1 H), 6.75 (d, J = 16.8 Hz, 1 H), 4.39 (br., 2 H), 2.51–2.46 (m, 4 H), 1.17 (t, J = 7.5 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, TMS, [D$_6$]DMSO): δ = 152.4, 146.8, 136.1, 134.6, 134.2, 129.3, 129.1, 127.5, 126.9, 126.3, 125.5, 122.4, 24.6, 14.8 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{23}N_2$ [M + H]$^+$ 279.1855; found 279.1863.

(*S*)-*N′*-(2,6-Diethylphenyl)-2-(4-isobutylphenyl)propanamidine (14c): Purified by column chromatography. Silica gel (230–400 mesh) was washed with 2% Et_3N in hexanes before elution. 2% Et_3N used as an additive in both solvents. Product eluted out of column in 6–10% EtOAc in hexanes; yield 292 mg (81%); off-white solid; m.p. 70–72 °C. IR (KBr): ῡmax = 3434, 3282, 2963, 2930, 2867, 1634,

1586, 1514, 1449, 1390 cm^{-1}. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.34 (d, J = 7.8 Hz, 2 H), 7.15 (d, J = 8.1 Hz, 2 H), 7.04–7.02 (m, 2 H), 6.93 (t, J = 7.5 Hz, 1 H), 4.2–3.9 (br., 2 H), 3.82–3.75 (m, 1 H), 2.48–2.40 (m, 6 H), 1.88–1.84 (m, 1 H), 1.67 (d, J = 7.2 Hz, 3 H), 1.17–1.11 (m, 6 H), 0. 90 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 158.7, 144.9, 140.5, 139.5, 134.8, 129.4, 127.1, 126.2, 123.0, 45.4, 30.2, 24.4, 22.3, 18.6, 14.4 ppm. HRMS (ESI): m/z calcd. for $C_{23}H_{33}N_2$ $[M + H]^+$ 337.2638; found 337.2646.

***N*-(4-Chlorophenyl)-*N*-methylbenzamidine (16c):** Yield 188 mg (81%); white solid; m.p. 195–197 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2887 (br), 1601, 1571, 1491, 1132, 1090, 1017 cm^{-1}. ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ = 7.41 (d, J = 7.5 Hz, 2 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.28 (t, J = 7.5 Hz, 2 H), 7.21 (d, J = 9.0 Hz, 2 H), 7.01 (d, J = 8.5 Hz, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (125 MHz, TMS, $CDCl_3$): δ = 165.9, 142.0, 133.9, 132.0, 129.8, 129.4, 129.3, 128.7, 128.0, 43.5 ppm. HRMS (ESI): m/z calcd. for $C_{14}H_{14}ClN_2$ $[M + H]^+$ 245.0840; found 245.0847.

***N*,*N*-Diphenylbenzamidine (17c):** Purified by reverse-phase column chromatography using an automated flash column chromatographer, column size (50 g with C18 packing material; MeCN–H_2O); flow rate: 50 mL/min, eluted out of column using 30–40% of MeCN–H_2O; yield 163 mg (84%); off-white solid; m.p. 62–64 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3268, 3055, 1605, 1588, 1568, 1487, 1446, 1358 cm^{-1}. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.57–7.55 (m, 2 H), 7.27–7.22 (m, 7 H), 7.11–7.06 (m, 6 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 167.2, 145.3, 137.5, 129.5, 128.7, 128.3, 127.3, 127.2 ppm. HRMS (ESI): m/z calcd. for $C_{19}H_{17}N_2$ $[M + H]^+$ 273.1386; found 273.1397.

4-Chloro-*N*,*N*-diphenylbenzamidine (18c): Purified by silica gel column chromatography using an automated flash column chromatographer, eluted at the flow rate of 20 mL/min, with column packing of 25 g silica gel. Silica gel (230–400 mesh) washed with 2% Et_3N in hexane before elution. 2% Et_3N was used as an additive in both solvents. Product eluted out in 10% EtOAc in hexane; yield 177 mg (81%); brown solid; m.p. 118–120 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3436 (br), 3265, 3044, 1610, 1587, 1564, 1490, 1349 cm^{-1}. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.52 (d, J = 8.4 Hz, 2 H), 7.28–7.19 (m, 6 H), 7.13–7.04 (m, 6 H), 6.40–5.90 (br., 1 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 165.8, 144.9, 135.8, 135.5, 130.1, 129.3, 128.4, 126.9, 125.4 ppm. HRMS (ESI): m/z calcd. for $C_{19}H_{16}ClN_2$ $[M + H]^+$ 307.0997; found 307.0999.

2-Iodo-*N*,*N*-diphenylbenzamidine (19c): Purified by silica gel column chromatography using an automated flash column chromatographer, eluted at the flow rate of 20 mL/min, with column packing of 25 g silica gel. Silica gel (230–400 mesh) washed with 2% Et_3N in hexane before elution. 2% Et_3N used as an additive in both solvents. Product eluted out in 30% of EtOAc in hexane; yield 149 mg (78%); white solid; m.p. 105–109 °C; IR (KBr): $\tilde{\nu}_{max}$ = 3302, 3061, 3037, 1589, 1575, 1491, 1389, 1231 cm^{-1}. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.66 (dd, J = 8.1, 0.6 Hz, 1 H), 7.44 (dd, J = 7.8, 1.3 Hz, 1 H), 7.28–7.21 (m, 9 H), 7.14–7.06 (m, 2 H), 6.87 (td, J = 15.3, 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ = 167.0, 144.1, 142.5, 139.6, 130.5, 129.9, 128.9, 127.6, 125.7, 95.1 ppm. HRMS (ESI): m/z calcd. for $C_{19}H_{16}IN_2$ $[M + H]^+$ 399.0346; found 399.0352.

4-Methoxy-*N*,*N*-diphenylbenzamidine (20c): Yield 180 mg (81%); off-white solid; m.p. 106–108 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3057, 3034, 2967, 2932, 1607, 1587, 1573, 1508, 1487, 1356, 1247, 1232 cm^{-1}. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.52 (d, J = 8.7 Hz, 2 H), 7.27–7.22 (m, 4 H), 7.10–7.04 (m, 6 H), 6.74 (d, J = 8.7 Hz, 2 H), 3.75 (s, 3 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 166.8, 160.6, 145.6, 130.3, 129.7, 129.2, 126.8, 124.9, 113.4, 55.2 ppm. HRMS (ESI): m/z calcd. for $C_{20}H_{19}N_2O$ $[M + H]^+$ 303.1492; found 303.1493.

***N*′-(2,6-Diethylphenyl)thiophene-2-carboxamidine (22c):** Purified by silica gel column chromatography using an automated flash column chromatographer, eluted at the flow rate of 20 mL/min, 25 g silica gel. Silica gel (230–400 mesh) washed with 2% Et_3N in hexane before elution. 2% Et_3N used as an additive in both solvents. Product eluted out in 10% EtOAc in hexane to give **22**; yield 222 mg (81%); colourless sticky mass. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3396, 2969, 1636, 1583, 1030 cm^{-1}. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ = 7.41–7.35 (m, 2 H), 7.07–6.97 (m, 4 H), 4.56 (br., 2 H), 2.58–2.40 (m, 4 H), 1.19–1.14 (m, 6 H) ppm. ^{13}C NMR (75 MHz, TMS, [D_6]DMSO): δ = 148.6, 146.0, 142.1, 134.6, 129.5, 127.8, 126.7, 126.3, 126.0, 122.6, 24.8, 14.7 ppm. HRMS (ESI): m/z calcd. for $C_{15}H_{19}N_2S$ $[M + H]^+$ 259.1263; found 259.1271.

***N*-[1-(*tert*-Butyl-dimethylsilanyloxymethyl)-2-methylpropyl]isonicotinamidine (23c):** Mixture of tautomers; yield 370 mg (81%); yellow gum; HPLC purity: 92%. IR (KBr): $\tilde{\nu}_{max}$ = 2958, 2930, 2857, 1652, 1601, 1255 cm^{-1}. ^{1}H NMR (300 MHz, TMS, [D_6]-DMSO): δ = 8.63–8.57 (m, 2 H), 7.72–7.70 (m, 2 H), 6.4–6.3 (br., 1.4 H, NH), 3.69–3.64 (m, 1.2 H), 3.53–3.34 (m, 3 H), 1.94–1.83 (m, 1 H), 0.93–0.89 (m, 6 H), 0.88–0.83 (m, 10 H), 0.006–0.004 (m, 6 H) ppm. ^{13}C NMR (75 MHz, TMS, [D_6]DMSO): δ = 161.1, 150.8, 149.9, 145.1, 134.6, 122.0, 121.5, 72.5, 70.7, 64.9, 61.6, 32.6, 29.9, 26.2, 20.3, 19.0, 18.6, 18.4, 18.2, –2.7, –4.8, –4.98 ppm. HRMS (ESI): m/z calcd. for $C_{17}H_{32}N_3OSi$ $[M + H]^+$ 322.2309; found 322.2315.

Compound (24c): Mixture of tautomers; yield 360 mg (79%); yellow gum; HPLC purity: 99%. IR (KBr): $\tilde{\nu}_{max}$ = 2955, 2929, 2869, 1654, 1601, 1465, 1364 cm^{-1}. ^{1}H NMR (300 MHz, TMS, [D_6]DMSO): δ = 8.71 (d, J = 6 Hz, 1 H), 8.57 (d, J = 6 Hz, 1.92 H), 7.75 (d, J = 6 Hz, 1 H), 7.69 (d, J = 6 Hz, 1.92 H), 6.5–6.1 (br., 1.35 H), 5.3–5.18 (br., 0.42 H), 4.51–4.44 (m, 0.62 H, NH), 4.19–4.05 (m, 1.39 H, NH), 3.68–3.63 (m, 1.07 H), 3.53–3.48 (m, 1.4 H), 1.95–1.69 (m, 7 H), 0.96–0.86 (m, 37 H), 0.56–0.53 (m, 5.4 H), 0.48–0.46 (m, 3.8 H) ppm. ^{13}C NMR (75 MHz, TMS, [D_6]DMSO): δ = 161.0, 150.8, 149.8, 145.0, 135.1, 122.0, 121.4, 72.5, 70.7, 64.3, 32.6, 29.9, 27.5, 26.8, 26.6, 25.2, 24.3, 24.2, 20.2, 18.9, 18.6, 18.4 ppm. HRMS (ESI): m/z calcd. for $C_{23}H_{44}N_3OSi$ $[M + H]^+$ 406.3248; found 406.3221.

***N*′-(4-Ethoxyphenyl)isonicotinamidine (25c):** Crude material washed with 10% EtOAc in hexanes; yield 191 mg (81%); off-white solid; m.p. 123–125 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3307, 3161, 1636, 1503, 1549, 1503, 1377, 1238, 1046 cm^{-1}. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ = 8.61 (d, J = 4.8 Hz, 2 H), 7.66 (d, J = 4.2 Hz, 2 H), 6.86 (m, 4 H), 5.19 (br., 2 H), 3.99 (q, J = 6.9 Hz, 2 H), 1.39 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 155.4, 153.2, 150.1, 143.1, 141.7, 122.4, 121.1, 115.6, 63.7, 14.9 ppm. HRMS (ESI): m/z calcd. for $C_{14}H_{16}N_3O$ $[M + H]^+$ 242.1288; found 242.1286.

***N*′-(4-Ethoxyphenyl)-5-methylpyrazine-2-carboxamidine(26c):** Recystallised from IPA and hexane; yield 179 mg(80%); yellow solid; m.p. 125–127 °C. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ = 9.50 (s, 1 H), 8.38 (s, 1 H), 6.98–6.90 (m, 4 H), 5.73 (br., 2 H), 4.03 (q, J = 6.8 Hz, 2 H), 2.64 (s, 3 H), 1.42 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ = 155.2, 155.1, 151.4, 143.9, 142.9, 142.2, 141.7, 122.4, 115.5, 63.7, 21.6, 15.0 ppm. HRMS (ESI): m/z calcd. for $C_{14}H_{17}N_4O$ $[M + H]^+$ 257.1397; found 257.1402.

(4-Chlorophenyl)(1*H*-indol-1-yl)methanimine (30c): Crude material was washed with hexane; yield 282 mg (79%); light-pink solid; m.p.

192–194 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3390 (br), 1582, 1558, 1519, 1242, 1143, 1092 cm^{-1}. ^1H NMR (300 MHz, TMS, [D$_6$]DMSO): δ = 13.0–9.5 (br., 2 H), 8.07 (s, 1 H), 7.61–7.45 (m, 6 H), 7.22–7.10 (m, 2 H) ppm. ^{13}C NMR (75 MHz, TMS, [D$_6$]DMSO): δ = 170.3, 140.2, 137.1, 133.9, 130.9, 129.3, 128.8, 128.2, 125.6, 122.2, 121.3, 120.5, 114.3, 112.0 ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{12}ClN_2$ $[M + H]^+$ 255.0683; found 255.0686.

(5-Chloro-1*H*-indol-1-yl)(4-chlorophenyl)methanimine (31c): Crude material was washed with hexane; yield 290 mg (81%); light-pink solid; m.p. 189–191 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3110, 1583, 1556, 1436, 1236, 1092 cm^{-1}. ^1H NMR (300 MHz, TMS, [D$_6$]DMSO): δ = 11.77 (s, 1 H), 9.78 (s, 1 H), 8.24–8.23 (m, 1 H), 7.61–7.46 (m, 6 H), 7.20 (dd, J = 8.7, 1.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, TMS, $CDCl_3$, [D$_6$]DMSO): δ = 172.2, 139.9, 135.7, 135.5, 131.3, 129.1, 128.6, 127.0, 126.8, 123.2, 121.0, 115.2, 112.9 ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{11}Cl_2N_2$ $[M + H]^+$ 289.0293; found 289.0299.

(4-Chlorophenyl)(2-phenyl-1*H*-indol-1-yl)methanimine (32c): Crude material was washed with hexane to give **32c**; yield 321 mg (83%); yellow solid; m.p. 185–188 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3401 (br), 3062, 1589, 1557, 1486, 1454, 1435, 1236, 1087, 1012 cm^{-1}. ^1H NMR (300 MHz, TMS, [D$_6$]DMSO): δ = 11.87 (s, 1 H), 10.46 (s, 1 H), 7.62 (d, J = 8.1 Hz, 2 H), 7.50–7.48 (m, 3 H), 7.39–7.21 (m, 6 H), 7.18 (t, J = 7.8 Hz, 1 H), 7.03 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, TMS, [D$_6$]DMSO): δ = 171.0, 138.7, 137.3, 136.4, 135.3, 132.0, 130.1, 128.9, 128.5, 128.4, 128.1, 122.8, 120.6, 119.7, 112.4, 112.1 ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{16}ClN_2$ $[M + H]^+$ 331.0996; found 331.1003.

(5-Chloro-1*H*-indol-3-yl)-(4-chlorophenyl)methanone (34c): Yield 89%; pink solid; m.p. 233–236 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3159, 1590, 1559, 1511, 1438, 1211 cm^{-1}. ^1H NMR (300 MHz, TMS, [D$_6$]-DMSO): δ = 12.33 (br.,1 H), 8.24 (s, 1 H), 8.09 (s, 1 H), 7.83 (d, J = 8.4 Hz, 2 H), 7.20 (m, 3 H), 7.30 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, TMS, [D$_6$]DMSO): δ = 188.4, 138.6, 137.1, 136.0, 135.2, 130.2, 128.4, 127.3, 126.7, 123.2, 120.5, 114.3, 113.8 ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{10}Cl_2NO$ $[M + H]^+$ 290.0133; found 290.0139.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for all key intermediates and final products.

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