EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Solvent-free synthesis of cyanoformamides from carbamoyl imidazoles

Authors: Jeremy Nugent, Sarah G. Campbell, Yen Vo, and Brett D. Schwartz

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201700974

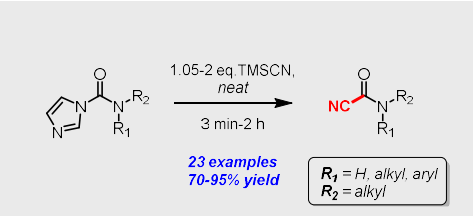
Link to VoR: http://dx.doi.org/10.1002/ejoc.201700974

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201700974

FULL PAPER



Secondary and tertiary cyanoformamides have been synthesised with a solvent-free approach from carbamoyl imidazoles and TMSCN. This method negates the need to use large excesses of toxic reagents and is ammenable to large-scale synthesis.

Cyanoformamide synthesis

Jeremy Nugent, Sarah G. Campbell, Yen Vo, and Brett D. Schwartz

Page No. – Page No.

Solvent-free synthesis of cyanoformamides from carbamoyl imidazoles

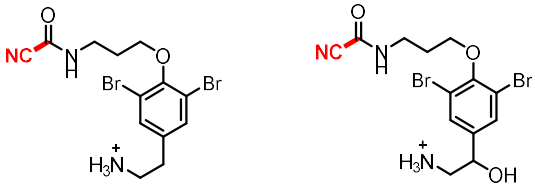
Solvent-free synthesis of cyanoformamides from carbamoyl imidazoles

Jeremy Nugent, [a] Sarah G. Campbell,[a] Yen Vo,[a] and Brett D. Schwartz*[a,b]

Abstract: A straightforward and solvent-free synthesis of various secondary and tertiary cyanoformamides from carbamoyl imidazoles and TMSCN has been developed. Both cyclic and acyclic carbamoyl imidazoles react smoothly to form the relevant cyanoformamides in excellent yields, often within minutes.

Introduction

The increasing number of recent synthetic applications of cyanoformamides have highlighted the need for more efficient synthetic routes to access these compounds. For example, cyanoformamides have been used for intramolecular alkene cyanoamidation,[1] enantioselective synthesis of disubstituted oxindoles,[2] the synthesis of *N*-hydroxy ureas,[3] lactams, tetrazoles[4] and various other heterocyclic compounds.[5] Furthermore, *N*-methoxy-*N*-methylcyanoformamide has recently been used as a carbonyl dication synthon in the synthesis of unsymmetrical ketones and as a means to install Weinreb amide functionality.[6] The discovery of two cyanoformamide natural products, ceratinamine and 7-hydroxyceratinamine,[7] further illustrates the importance of this motif; the former compound has been shown to possess antifouling properties.



ceratinamine 7-hydroxyceratinamine

Figure 1. Cyanoformamide-containing natural products.

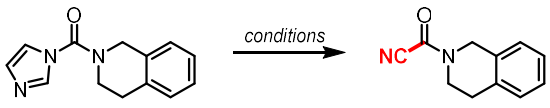
Currently, most routes to cyanoformamides suffer from numerous drawbacks. For example, traditional syntheses of cyanoformamides from an amine and carbonyl cyanide, or from carbamoyl chlorides and a cyanide ion, require the use of toxic and potentially explosive reagents.[8] More recent advances include the reaction of primary amines with carbon dioxide followed by a cyanophosphonate;[9] the reaction of 1-acyl-1-carbamoyl oximes with $POCl_3$,[10] and; the cyanocarbonylation of amines with *iso*-nitroso-Meldrum's acid.[11] All of these reactions require the use of exotic and commercially unavailable reagents. Similarly, the recently reported synthesis of cyanoformamides from 2-oxo-acetamides, ammonium acetate and a hypervalent iodine oxidant use starting materials which are not easily sourced, require extended reaction sequences to prepare and often result in difficult purifications.[12] The development of convenient and green methods for the synthesis of cyanoformamides is an outstanding challenge in synthetic chemistry. Herein we present a methodology that is a significant advancement towards achieving this goal.

Results and Discussion

Recently, our group reported a facile synthesis of *N*-methoxy-*N*-methylcyanoformamide through TMSCN-mediated cyanation of a carbamoyl imidazole precursor.[6] To extend our previous work we now report the synthesis of a range of secondary and tertiary cyanoformamides via a similar method.

Initial investigations utilised tertiary tetrahydroisoquinoline carbamoyl imidazole **1a** as a model substrate to optimise reaction conditions (Table 1). First, a range of solvents were screened. Neither THF nor toluene gave appreciable amounts of product (entries 1-2), however, when conducting the reaction neat with 2.00 eq. of TMSCN, the cyanoformamide **2a** was formed in good yield (entry 3). Further experimentation showed that a very high-yielding reaction proceeded when using only 1.05 eq. of TMSCN, with optimal conditions of 140 °C under microwave irradiation (entries 4-5).

Table 1. Optimisation studies.



1a **2a**

Entry	Conditions	Yield[a]
1	TMSCN (2 eq.), THF, reflux, 5 h	**N.R.**
2	TMSCN (2 eq.), toluene, reflux, 5 h	**trace**
3	TMSCN (2 eq.), *neat*, 100 °C, 7 h	**67%**
4	TMSCN (1.05 eq.), *neat*, 100 °C, 2 h, *mw*	**70%**
5	TMSCN (1.05 eq.), *neat*, 140 °C, 1 h, *mw*	**91%**

[a] Isolated yield.

With optimal conditions determined, we then evaluated reaction scope. Various tertiary carbamoyl imidazole compounds were reacted and the results are summarized in Table 2. Pyrrolidines (**2b-2d**), piperidines (**2e-2g**), morpholine (**2h**), pipera-

[a] Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia (current address)
E-mail: brett.schwartz@anu.edu.au
[b] Griffith Institute for Drug Discovery, Griffith University, Don Young Road, Nathan, QLD 4111, Australia

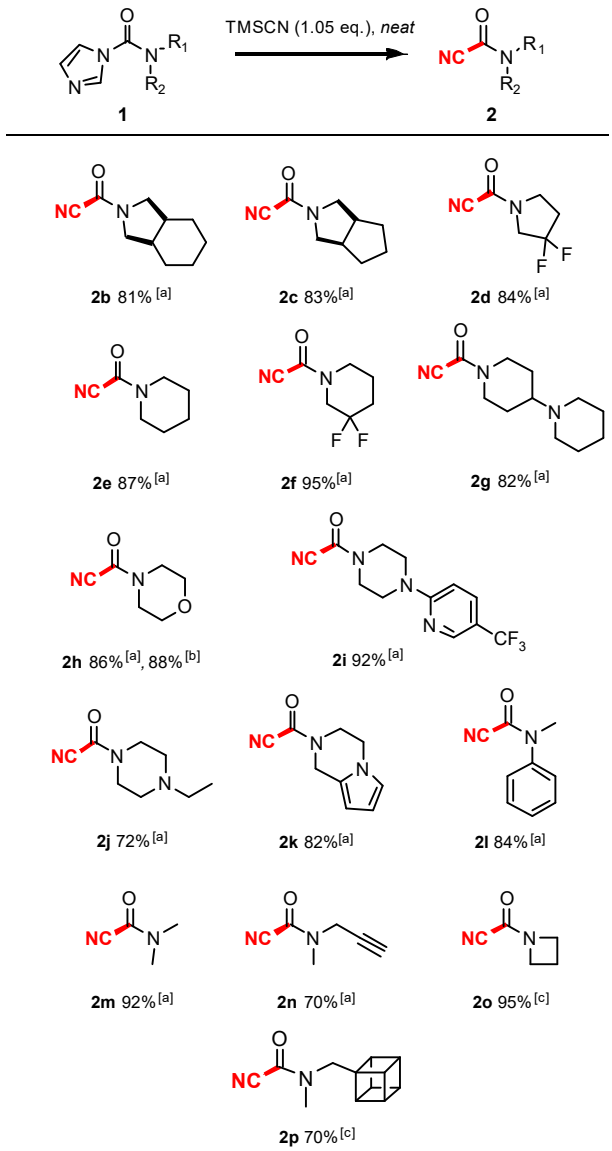
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

zines (**2i-2j**), tetrahydropyrrolopyrazine (**2k**), aniline (**2l**), dimethylamine (**2m**) and propargyl amine (**2n**) derived carbamoyl imidazoles readily underwent cyanation with TMSCN to form the product cyanoformamides, isolated in excellent yields (70-95%).[13] The azetidine (**2o**) and cubane carbamoyl imidazoles (**2p**) decomposed under standard conditions; however, excellent yields were achieved when conducting the reactions at lower temperatures. Furthermore, the large-scale synthesis of the synthetically-useful[5b,14] morpholine cyanoformamide was explored under conventional heating in a sealed tube. In this manner, **2h** was isolated in an excellent yield on exposure to 1.05 eq. of TMSCN at 100 °C.

The formation of secondary cyanoformamides was more challenging. Using *N*-benzyl carbamoyl imidazole (**1q**) as a model substrate, we optimized conditions for secondary cyanoformamide synthesis (Table 3). When using conventional heating at similar temperatures and stoichiometry to that of the tertiary system, the major product isolated was 5-iminoimidazolidine-2,4-dione **3**; only low yields of cyanoformamide (**2q**), along with a considerable amount of staring material, were isolated (entry 1). Performing the reaction at a lower temperature increased the yield of cyanoformamide **2q**, however, considerable amounts of starting material and dimer were still present (entry 2). Full conversion of starting material was observed when the stoichiometry was changed to 2.00 eq. of TMSCN, but considerable amounts of the 5-iminoimidazolidine-2,4-dione by-product were present (entries 3-4). The unwanted dimerization reaction has been shown, in the case of alkyl-substituted cyanoformamides, to only occur at elevated temperatures,[15] thus, we expected lower temperatures would facilitate an increase in yield of the cyanoformamide products. When the reaction was conducted at 70 °C a significant reduction in iminodione product was observed and excellent yields of *N*-benzylcyanoformamide (**2q**) were achieved after only 3 minutes at this temperature (entry 5).

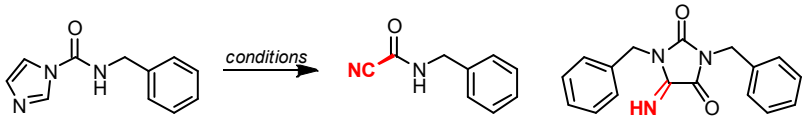
We could now apply these optimized conditions for the synthesis of various secondary cyanoformamides (Table 4). In all cases, the reaction was near complete within minutes at 70 °C. Electron rich 4-methoxybenzyl and 2,4-dimethoxybenzyl carbamoyl imidazoles both underwent a clean and high-yielding reaction to afford cyanoformamides with no trace of cyclisation products (**2r-s**).[16] Phenethylamine, cyclic and acyclic aliphatic carbamoyl imidazoles all readily afforded the expected products in excellent yields (**2t-w**). In all examples, only trace dimeric products were observed.

Table 2. Synthesis of tertiary cyanoformamides.



[a] 1 h, 140 °C, 200 W, μw. [b] 10 mmol scale: 18 h, 100 °C, sealed tube. [c] 2 h, 100 °C, 200 W, μw.

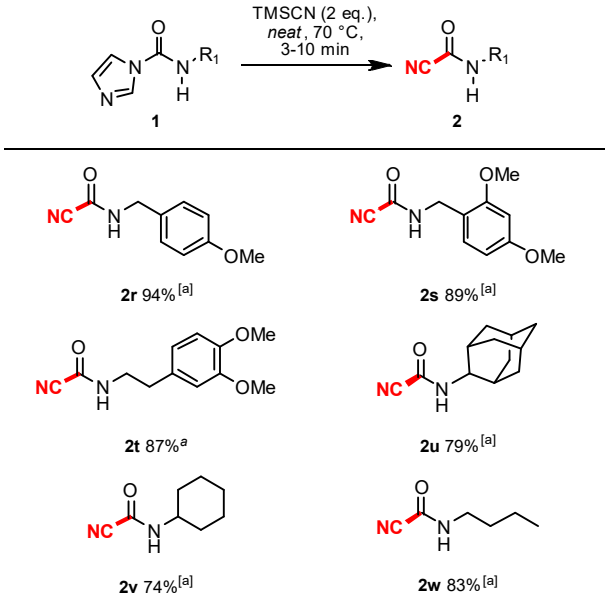
Table 3. Optimisation studies.



Entry	Conditions[a]	2q[b]	3[b]	1q[b]
1	TMSCN (1.05 eq.), *neat*, 100 °C, 10 min	24%	44%	15%
2	TMSCN (1.05 eq.), *neat*, 70 °C, 60 min	30%	36%	25%
3	TMSCN (2 eq.), *neat*, 100 °C, 10 min	26%	62%	trace
4	TMSCN (2 eq.), *neat*, 85 °C, 5 min	70%	15%	trace
5	TMSCN (2 eq.), *neat*, 70 °C, 3 min	83%	trace	trace

[a] Sealed tube. [b] Isolated yield.

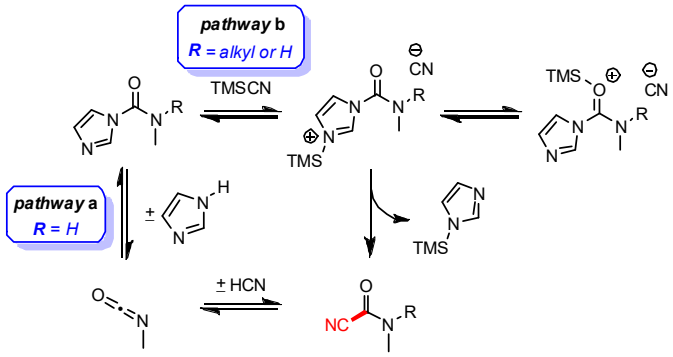
Table 4. Synthesis of secondary cyanoformamides.



[a] Isolated yield.

On the basis of our observations and literature reports, a plausible mechanism for the formation of the cyanoformamide products is shown in Scheme 1. Secondary carbamoyl imidazole compounds equilibrate with their isocyanate species (pathway a);[17] cyanation of this intermediate readily affords the product cyanoformamide. While fully substituted carbamoyl imidazoles are unlikely to equilibrate with their isocyanate species, a second possible mechanism exists that accommodates formation of both secondary and tertiary cyanoformamides. Activation of the carbonyl, via silylation of either the carbonyl or the imidazole nitrogen, followed by cyanation concomitant with the loss of TMS-imidazole, affords the tertiary cyanoformamide (pathway b). 5-Iminoimidazolidine-2,4-dione products form via reaction between an isocyanate and a secondary cyanoformamide, the mechanism of which has been proposed previously.**Error! Bookmark not defined.**

Scheme 1. *Reaction mechanism.*



Conclusions

In summary, we have reported a facile and operationally simple method for the synthesis of secondary and tertiary cyanoformamides. This methodology is attractive as the starting materials and reagents are easily sourced, no prolonged reaction sequences are needed and only a small excess of cyanide source is required.

Experimental Section

General Experimental Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 or 500 MHz for proton and 100 or 125 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; mc = centred multiplet; br = broad or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.16 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Where possible, major and minor rotamers have been indicated. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer (thin films on KBr plates) or Perkin–Elmer UATR Spectrum Two spectrometer (thin film or solid). A VG Fisons AutoSpec mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple-quadrupole MS instrument operating in positive ionization mode. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*[18] with silica gel 60 (40-63 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, AK Scientific Inc., Matrix Scientific Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol and dichloromethane (DCM) were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*[19] Triethylamine and DMSO were freshly distilled over calcium hydride before use. Where necessary, reactions were performed under a nitrogen atmosphere. Microwave facilitated reactions were carried out using a CEM Explorer system with conditions specified. Reactions with trimethylsilyl cyanide were conducted in a fully operational fumehood with appropriate personal protective equipment.

Specific Chemical Transformations

General Procedure A – *Padiya's 'In water' synthesis of carbamoyl imidazoles.*

Following a modified procedure.[20] A 250 mL conical flask in an ice-water bath was charged with crushed ice (10 g), a saturated aqueous solution of sodium hydrogen carbonate (10 mL), water (10 mL), free amine or hydrochloride (1 mmol) and vigorously stirred whilst treated, portion-wise, with the specified amount of *N*,*N*'-carbonyldiimidazole (CDI) (1-2 mmol) over a period of two minutes to avoid frothing. After 0.25 h the reaction was worked up by the indicated method. These methods were

either: ***i)*** collection of solids by vacuum filtration followed by washing with water (20 mL) and drying under high vacuum (1 mmHg); or, ***ii)*** the mixture was extracted with DCM (3 × 15 mL) followed by washing of the combined organic extracts with water (15 mL) then brine (10 mL). The combined layers were dried (Na_2SO_4), concentrated *in vacuo* and when necessary, the crude product purified by flash chromatography, eluting with the solvent system specified.

General Procedure B – *Batey's synthesis of carbamoyl imidazoles.*

Following a modified procedure.[21] A mixture of amine hydrochloride (3.0 mmol), DMF (1 mL) and acetonitrile (4 mL) under and atmosphere of nitrogen was treated with CDI (535 mg, 3.3 mmol) and stirred for 18 h. The mixture was concentrated *in vacuo* to afford a residue which after flash chromatography in the solvent specified afforded the carbamoyl imidazole.

General Procedure C – *Microwave-assisted synthesis of cyanoformamides.*

A 10 mL snap-cap microwave vessel fitted with a septum and magnetic stirring bar under an atmosphere of nitrogen was charged with carbamoyl imidazole (1.00 eq.) and trimethylsilyl cyanide (TMSCN, CAUTION!) (1.05 eq.). The septum was removed and replaced with a snap-cap then subjected to the microwave irradiation conditions specified (microwave reactor in fumehood). The mixture was quenched with an ice-cold aqueous solution of $NaHCO_3$ (5 mL) and extracted with DCM (2 × 10 mL) and the combined organic extracts washed with brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a residue which was purified by flash chromatography in the solvent system specified to afford the indicated cyanoformamide.

General Procedure D - *Synthesis of cyanoformamides under conventional heating.*

An oven-dried Ace Glass® pressure tube (100 × 25.4 mm, 15 mL) under an atmosphere of nitrogen fitted with a septum and stirrer bar, was charged with the specified amounts of carbamoyl imidazole and trimethylsilyl cyanide. The septum was removed and replaced with a screw-thread plug (front sealed with an FETFE O-ring) and heated with stirring in a silicon bath at the specified temperature behind a safety shield. After the specified time, the silicon oil bath was removed and the tube was then cooled in ice water and quenched with an ice-cold aqueous solution of $NaHCO_3$ (5 mL). The mixture was extracted with DCM (2 × 10 mL) and the combined organic extracts washed with brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a residue which was purified by flash chromatography in the solvent system specified to afford the indicated cyanoformamide.

(3,4-Dihydroisoquinolin-2(1*H*)-yl)(1*H*-imidazol-1-yl)methanone (1a): Prepared according to General Procedure A(i) from 1,2,3,4-tetrahydroisoquinoline (2.66 g, 20 mmol) and CDI (4.54 g, 28 mmol) to afford, after filtration, **1a** (3.11 g, 68%) as a beige powder: mp 91 – 94 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 – 7.77 (m, 1H), 7.27 (app. t, J = 1.4 Hz, 1H), 7.26 – 7.16 (m, 3H), 7.14 – 7.12 (m, 1H), 7.11 – 7.09 (m, 1H), 4.75 (s, 2H), 3.82 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 6.0 Hz, 2H). Spectral data were consistent with those reported.[22]

3,4-Dihydroisoquinoline-2(1*H*)-carbonyl cyanide (2a): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1a** (227 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford after flash chromatography (1:2, EtOAc:40-60 petroleum ether) **2a** (170 mg, 91%) as a colorless viscous oil: ^{1}H NMR ($CDCl_3$, 500 MHz) *0.7:1 mixture of rotamers* δ 7.30 – 7.15 (m, 4H), 4.92 (s, 2H$_{min}$), 4.77 (s, 2H$_{maj}$), 4.04 (t, J = 6.0 Hz, 2H$_{maj}$), 3.88 (t, J = 6.2 Hz, 2H$_{min}$), 3.04 (t, J = 6.0 Hz, 2H$_{maj}$), 2.96 (t, J = 6.2 Hz, 2H$_{min}$). ^{13}C NMR ($CDCl_3$, 125 MHz) *mixture of rotamers* δ 144.0, 143.7, 133.8, 133.0, 130.7, 130.5, 129.0, 128.9, 127.9, 127.5, 127.3, 127.2, 126.6, 126.3, 110.6, 110.5, 48.4, 44.9, 44.6, 40.8, 29.3, 27.9; MS (+)-LREI *m*/*z* (%) 186 (100, $M^{+\cdot}$), 171 (12), 130 (25), 117 (45), 116 (45), 104 (75), 77 (32); MS (+)-HRESI calcd. for $C_{11}H_{10}N_2NaO$ [M + Na]$^+$ 209.0685, found 209.0685; ν_{max} 2231, 1667, 1446, 721 cm^{-1}.

(1*H*-Imidazol-1-yl)(octahydro-2*H*-isoindol-2-yl)methanone (1b): Prepared according to General Procedure A(ii) from *cis*-hexahydroisoindoline (2.02 g, 16.1 mmol) and CDI (3.39 g, 20.9 mmol) to afford **1b** (2.70 g, 76%) as a pale-orange viscous oil which required no further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (app. t, J = 0.9 Hz, 1H), 7.35 (app. t, J = 1.4 Hz, 1H), 7.07 (dd, J = 1.4, 0.9 Hz, 1H), 3.62 (dd, J = 10.8, 7.1 Hz, 2H), 3.55 – 3.44 (m, 2H), 2.36 – 2.26 (m, 2H), 1.72 – 1.33 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) *mixture of rotamers* δ 150.3, 136.9, 129.6, 117.8, 77.2, 53.7, 51.7, 38.1, 35.9, 25.5, 22.5; MS (+)-LRESI *m*/*z* (%) 220 (35) [M + H]$^+$, 242 (100) [M + Na]$^+$, 152 (33); MS (+)-HRESI calcd. for $C_{12}H_{18}N_3O$ [M + H]$^+$ 220.1444 found 220.1451; ν_{max} 2926, 2855, 1682, 1406, 1210, 750 cm^{-1}.

Octahydro-2*H*-isoindole-2-carbonyl cyanide (2b): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1b** (219 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford after flash chromatography (1:2, EtOAc:40-60 petroleum ether) **2b** (144 mg, 81%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) *mixture of rotamers* δ 3.74 (dd, J = 10.6, 7.0 Hz, 1H), 3.62 (dd, J = 10.6, 5.7 Hz, 1H), 3.49 (dd, J = 12.8, 7.0 Hz, 1H), 3.39 (dd, J = 12.8, 5.7 Hz, 1H), 2.39 – 2.29 (m, 2H), 1.72 – 1.60 (m, 2H), 1.57 – 1.37 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.5, 111.3, 52.0, 49.9, 36.9, 36.3, 25.6, 25.5, 22.6, 22.4. (+)-LRESI *m*/*z* (%) 179 (100) [M + H]$^+$. MS (+)-HRESI calcd. for $C_{10}H_{15}N_2O$ [M + H]$^+$ 179.1179; found, 179.1181; ν_{max} 2929, 2859, 2231, 1669, 1406 cm^{-1}.

(Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)(1H-imidazol-1-yl)methanone (1c): Prepared according to General Procedure A(ii) from 3-azabicyclo[3.3.0]octane hydrochloride (2.08 g, 14.10 mmol) and CDI (2.86 g, 17.63 mmol) to afford **1c** (2.24 g, 77%) as a pale-yellow oil which required no further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (s, 1H), 7.31 (s, 1H), 7.05 (s, 1H), 3.81 (dd, J = 11.6, 7.0 Hz, 2H), 3.41 (dd, J = 11.4, 2.9 Hz, 2H), 2.78 – 2.66 (m, 2H), 1.92 – 1.80 (m, 2H), 1.80 – 1.73 (m, 1H), 1.70 – 1.59 (m, 1H), 1.53 – 1.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.6, 136.9, 129.5, 117.9, 54.4, 43.0, 31.8, 25.5; MS (+)-LRESI *m*/*z* (%) 228 (100) [M + Na]$^+$, 138 (20); MS (+)-HRESI calcd. for $C_{11}H_{15}N_3NaO$ [M + Na]$^+$ 228.1107, found 228.1113; ν_{max} 3121, 2946, 1663, 1420, 1243, 772 cm^{-1}.

Hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carbonyl cyanide (2c): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1c** (205 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford after flash chromatography (1:2, EtOAc:40-60 petroleum ether) **2c** (136 mg, 83%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (dd, J = 11.5, 7.9 Hz, 1H), 3.69 (dd, J = 13.4, 7.9 Hz, 1H), 3.54 (dd, J = 11.5, 4.3 Hz, 1H), 3.32 (dd, J = 13.4, 4.3 Hz, 1H), 2.83 – 2.72 (m, 2H), 1.96 – 1.85 (m, 2H), 1.82 – 1.69 (m, 1H), 1.71 – 1.61 (m, 1H), 1.54 – 1.42 (m, 2H).^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.4, 111.2, 54.1, 51.7, 42.7, 42.4, 32.2, 31.8, 25.6. MS (+)-LRESI *m*/*z* (%) 165 (100) [M + H]$^+$; MS (+)-HRESI calcd. for calcd. for $C_9H_{13}N_2O$ [M + H]$^+$: 165.1022; found, 165.1029; ν_{max} 2952, 2873, 2231, 1667, 1411 cm^{-1}.

(3,3-Difluoropyrrolidin-1-yl)(1H-imidazol-1-yl)methanone (1d): Prepared according to General Procedure B from 3,3-difluoropyrrolidine hydrochloride (431 mg, 3.0 mmol), CDI (535 mg, 3.3 mmol), DMF (1 mL) and acetonitrile (4 mL) to afford after flash chromatography (1:10, MeOH:DCM), **1d** (634 mg 90%) as white crystals: mp 76 – 80 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (s, 1H), 7.30 (s, 1H), 7.12 (s, 1H), 3.97 (t, J = 12.3 Hz, 2H), 3.90 (t, J = 7.4 Hz, 2H), 2.51 – 2.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.2, 149.4, 136.5, 129.6, 126.0 (t, $J_{C\text{-}F}$ = 248.6 Hz), 117.2, 54.1 (t, $J_{C\text{-}F}$ = 32.7 Hz), 46.0, 33.3 (t, $J_{C\text{-}F}$ = 23.8 Hz); MS (+)-LRESI *m*/*z* (%) 202 (72) [M + H]$^+$, 134 (100); MS (+)-HRESI calcd. for $C_8H_{10}F_2N_3O$ [M + H]$^+$ 202.0786, found 202.0788; ν_{max} 3149, 1675, 1262, 1122 cm^{-1}.

3,3-Difluoropyrrolidine-1-carbonyl cyanide (2d): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1d** (201 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:2, EtOAc:40-

60 petroleum ether), **2d** (134 mg, 84%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) *0.7:1 mixture of rotamers* δ 4.09 (t, J = 11.8 Hz, 1H$_{min}$), 4.02 (t, J = 7.4 Hz, 1H$_{maj}$), 3.85 (t, J = 12.3 Hz, 1H$_{maj}$), 3.78 (t, J = 7.6 Hz, 1H$_{min}$), 2.58 – 2.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.9, 142.8, 125.9 (t, $J_{C\text{-}F}$ = 249.0 Hz), 125.7 (t, $J_{C\text{-}F}$ = 250.3 Hz), 110.4, 110.2, 53.9 (t, $J_{C\text{-}F}$ = 33.5 Hz), 52.5 (t, $J_{C\text{-}F}$ = 33.6 Hz), 45.4 (t, $J_{C\text{-}F}$ = 3.1 Hz), 43.6 (t, $J_{C\text{-}F}$ = 3.1 Hz), 33.8 (t, $J_{C\text{-}F}$ = 24.7 Hz), 33.0 (t, $J_{C\text{-}F}$ = 24.2 Hz); GC/MS EI m/z (%) 160 (94, M$^{+\cdot}$), 141 (3), 131 (9), 111 (4), 96 (26), 77 (27), 68 (37), 54 (33), 42 (100); MS (+)-HRESI calcd. for $C_6H_6F_2N_2NaO$ [M + Na]$^+$ 183.0341, found 183.0340; ν_{max} 3396, 2916, 2849, 2237, 1688, 1686, 1450, 1423, 1369, 1131, 1116, 925 cm^{-1};

(1*H*-Imidazol-1-yl)(piperidin-1-yl)methanone (1e): Prepared according to General Procedure A(ii) from piperidine (2.78 mL, 28.0 mmol) and CDI (5.90 g, 36.6 mmol) to afford, after flash chromatography (1:10, MeOH:DCM), **1e** (3.62 g, 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 – 7.81 (m, 1H), 7.20 – 7.18 (m, 1H), 7.09 – 7.07 (m, 1H), 3.57 – 3.49 (m, 4H), 1.77 – 1.60 (m, 6H). Spectral data were consistent with those reported.[22]

Piperidine-1-carbonyl cyanide (2e): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1e** (179 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:2, EtOAc:40-60 petroleum ether), **2e** (120 mg, 87%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 – 3.67 (m, 2H), 3.62 – 3.53 (m, 2H), 1.78 – 1.66 (m, 4H), 1.64 – 1.58 (m, 2H). Spectral data were consistent with those reported.[10]

(3,3-Difluoropiperidin-1-yl)(1*H*-imidazol-1-yl)methanone (1f): Prepared according to General Procedure B from 3,3-difluoropiperidine hydrochloride (473 mg, 3.0 mmol), CDI (535 mg, 3.3 mmol), DMF (1 mL) and acetonitrile (4 mL) to afford, after flash chromatography (1:10, MeOH:DCM), **1f** (664 mg, 88 %) as white crystals: mp 98 – 101 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (s, 1H), 7.22 (s, 1H), 7.12 (s, 1H), 3.74 (t, J = 11.0 Hz, 1H), 3.60 (dd, J = 5.6, 5.6 Hz, 2H), 2.13 (tt, J = 13.3, 6.4 Hz, 2H), 1.97 – 1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.4, 137.1, 130.3, 118.6 (t, $J_{C\text{-}F}$ = 244.7 Hz), 118.0, 52.0 (t, $J_{C\text{-}F}$ = 32.8 Hz), 45.7, 32.5 (t, $J_{C\text{-}F}$ = 23.5 Hz), 21.8 (t, $J_{C\text{-}F}$ = 4.6 Hz); MS (+)-LRESI m/z (%) 216 (95) [M + H]$^+$, 134 (100); MS (+)-HRESI calcd. for $C_9H_{12}F_2N_3O$ [M + H]$^+$ 216.0943, found 216.0940; ν_{max} 3176, 1679, 1434, 1102 cm^{-1}.

3,3-Difluoropiperidine-1-carbonyl cyanide (2f): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1f** (215 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:2, EtOAc:40-60 petroleum ether), **2f** (165 mg, 95%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) *1:1 mixture of rotamers* δ 3.92 (t, J = 10.7 Hz, 1H), 3.84 (t, J = 11.2 Hz, 1H), 3.80 – 3.76 (m, 1H), 3.67 – 3.63 (m, 1H), 2.19 – 2.09 (m, 2H), 1.98 – 1.91 (m, 1H), 1.87 – 1.80 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) *mixture of rotamers* δ 143.9(0), 143.9(86), 118.2 (t, $J_{C\text{-}F}$ = 244.9 Hz), 118.0 (t, $J_{C\text{-}F}$ = 245.7 Hz), 110.0, 109.8, 52.4 (t, $J_{C\text{-}F}$ = 33.3 Hz), 47.3 (t, $J_{C\text{-}F}$ = 34.0 Hz), 46.4, 41.8, 32.5 (t, $J_{C\text{-}F}$ = 23.6 Hz), 32.3 (t, $J_{C\text{-}F}$ = 23.7 Hz), 22.5 (t, $J_{C\text{-}F}$ = 4.7 Hz), 21.2 (t, $J_{C\text{-}F}$ = 4.6 Hz); GC/MS EI m/z (%) 174 (100, M$^{+\cdot}$), 159 (9), 155 (7), 145 (18), 120 (52), 106 (10), 97 (34), 91 (18), 77 (19), 64 (41), 54 (40), 42 (52). MS (+)-HRESI calcd. for $C_7H_8F_2N_2NaO$ [M + Na]$^+$ 197.0497, found 197.0495; ν_{max} 2949, 2234, 1683, 1435, 1375, 1111 cm^{-1}.

[1,4'-Bipiperidin]-1'-yl(1*H*-imidazol-1-yl)methanone (1g): A solution of CDI (1.05 g, 6.51 mmol) in anhydrous THF (20 mL) was treated with 4-piperidinopiperidine (1.00 g, 5.96 mmol) under an atmosphere of nitrogen. The reaction mixture was then held at reflux for 18 h then cooled to 23 °C and quenched with $NaHCO_3$ (20 mL, saturated aqueous solution) and extracted with DCM (3 × 20 mL). The combined organic layers were then washed with water (2 × 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **1g** (1.21 g, 78%) as pale-yellow oil which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H), 7.18 (s, 1H), 7.08 (s, 1H), 4.21 – 4.08 (m, 2H), 3.08 – 2.96 (m, 2H), 2.57 – 2.44 (m, 5H), 1.96 – 1.88 (m, 2H), 1.65 – 1.52 (m, 6H), 1.49 – 1.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8, 136.9, 129.7, 118.0, 62.0, 50.4, 46.3, 28.3, 26.4, 24.8; MS (+)-LRESI m/z (%) 263 (100) [M + H]$^+$, 195 (48); MS (+)-HRESI calcd. for $C_{14}H_{23}N_4O$ [M + H]$^+$: 263.1866; found, 263.1872; ν_{max} 2930, 1688, 1426, 1275, 749 cm^{-1}.

4-Piperidinopiperidine-1-carbonyl cyanide (2g): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1g** (262 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:9, MeOH:DCM), **2g** (180 mg, 82%) as a yellow viscous oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.50 – 4.38 (m, 1H), 4.27 (m, 1H), 3.25 (ddd, J = 13.3, 12.0, 3.0 Hz, 1H), 2.88 – 2.75 (m, 1H), 2.62 – 2.44 (m, 5H), 2.06 – 1.82 (m, 2H), 1.67 – 1.37 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.1, 110.5, 61.7, 50.3, 46.8, 41.8, 28.6, 27.3, 26.4, 24.7. MS (+)-LRESI m/z (%) 222 (100) [M + H]$^+$. MS (+)-HRESI calcd. for $C_{12}H_{20}N_3NaO$ [M + H]$^+$: 222.1606; found, 222.1604; ν_{max} 2932, 2853, 2798, 2228, 1669, 1450, 1432 cm^{-1}.

4-(1*H*-Imidazol-1-ylcarbonyl)morpholine (1h): Prepared according to General Procedure B from morpholine hydrochloride (6.35 g, 49.0 mmol), CDI (7.95 g, 54.0 mmol), DMF (15 mL) and acetonitrile (50 mL) to afford, after flash chromatography (1:10, MeOH:DCM), **1h** (5.15 g, 58 %) as white crystals: mp 93 – 94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (t, J = 1.1 Hz, 1H), 7.19 (app. t, J = 1.1 Hz, 1H), 7.10 (t, J = 1.1 Hz, 1H), 3.78 – 3.74 (m, 4H), 3.65 – 3.61 (m, 4H). Spectral data were consistent with those reported.[22]

Morpholine-4-carbonyl cyanide (2h): Microwave method: Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1h** (181 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:1, EtOAc:40-60 petroleum ether), **2h** (120 mg, 86%) as a colourless solid. **Conventional heating method:** Prepared according to General Procedure D (100 °C, 18 h) from **1h** (1.81 g, 10.00 mmol) and TMSCN (1.31 mL, 10.5 mmol) to afford, after flash chromatography (1:1, EtOAc:40-60 petroleum ether), **2h** (1.23 g, 88%) as a colourless solid: mp 59 – 61 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 – 3.78 (m, 2H), 3.74 – 3.70 (m, 1H), 3.69 – 3.65 (m, 1H). Spectral data were consistent with those reported.[5b]

(1*H*-Imidazol-1-yl)(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)methanone (1i): Prepared according to General Procedure A(i) from 1-(5-(trifluoromethyl)pyridin-2-yl)piperazine (1.00 g, 4.32 mmol) and CDI (1.40 g, 8.65 mmol) to afford, after filtration, **1i** (0.98 g, 70 %) as a white powder: mp 141 – 145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43 (s, 1H), 7.92 (s, 1H), 7.70 (dd, J = 9.0, 2.5 Hz, 1H), 7.24 (s, 1H), 7.13 (s, 1H), 6.68 (d, J = 9.0 Hz, 1H), 3.80 – 3.73 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.0, 151.2, 145.9 (q, $J_{C\text{-}F}$ = 4.3 Hz), 137.0, 135.1 (q, $J_{C\text{-}F}$ = 3.2 Hz), 130.2, 124.5 (q, $J_{C\text{-}F}$ = 270.6 Hz), 118.0, 116.64 (q, $J_{C\text{-}F}$ = 33.1 Hz), 106.0, 46.1 (2C), 44.6 (2C). MS (+)-LRESI m/z (%) 348 (100) [M + Na]$^+$; MS (+)-HRESI calcd. for $C_{14}H_{15}F_3N_5O$ [M + H]$^+$ 326.1223, found 326.1229; ν_{max} 1679, 1611, 1323, 1239, 1099, 988 cm^{-1}.

4-(5-(Trifluoromethyl)pyridin-2-yl)piperazine-1-carbonyl cyanide (2i): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1i** (325 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:9, MeOH:DCM), **2i** (260 mg, 92%) as white crystals: mp 175 – 178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43 (s, 1H), 7.71 (dd, J = 9.0, 2.5 Hz, 1H), 6.70 (d, J = 8.9 Hz, 1H), 3.91 – 3.81 (m, 4H), 3.79 – 3.70 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.7, 146.0 (q, $J_{C\text{-}F}$ = 4.3 Hz) 143.5, 135.2 (q, $J_{C\text{-}F}$ = 3.3 Hz), 124.4 (d, $J_{C\text{-}F}$ = 270.5 Hz), 116.9 (q, J = 33.2 Hz), 110.2, 106.1, 46.5, 45.0, 44.2, 42.1;; MS (+)-LRESI m/z (%) 307 (75) [M + Na]$^+$; MS (+)-HRESI calcd. for $C_{12}H_{12}N_4OF_3$ [M + H]$^+$ 285.0958, found 285.0964; ν_{max} 2234, 1665, 1613, 1124 cm^{-1}.

(4-Ethylpiperazin-1-yl)(1*H*-imidazol-1-yl)methanone (1j). A solution of CDI (1.56 g, 9.59 mmol) in anhydrous THF (20 mL) was treated with 1-ethylpiperazine (1.10 mL, 8.70 mmol) under an atmosphere of nitrogen. The reaction mixture was then held at reflux for 18 h then cooled to 23 °C and quenched with $NaHCO_3$ (20 mL, saturated aqueous solution) and extracted with DCM (3 × 20 mL). The combined organic layers were then

washed with water (2 × 20 mL), dried (Na_2SO_4) and concentrated in vacuo to afford **1j** (0.98 g, 54%) as yellow oil which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.86 (s, 1H), 7.19 (br t, *J* = 1.4 Hz, 1H), 7.10 – 7.07 (m, 1H), 3.66 – 3.59 (m, 4H), 2.52 – 2.49 (m,4H), 2.46 (q, J = 7.3 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 150.9, 137.0, 129.9, 118.0, 52.5 (2C), 52.3, 46.6 (2C), 12.0; MS (+)-LRESI m/z (%) 209 (90) $[M + H]^+$, 141 (100); MS (+)-HRESI calcd. for $C_{10}H_{17}N_4O$ $[M + H]^+$ 209.1397, found 209.1400; ν_{max} 1693, 1429, 1243, 997 cm^{-1}.

4-Ethylpiperazine-1-carbonyl cyanide (2j): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1j** (194 mg, 0.93 mmol) and and TMSCN (122 µL, 0.98 mmol) to afford, after flash chromatography (1:2, EtOAc:40-60 petroleum ether), **2j** (120 mg, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 3.75 – 3.73 (m, 2H), 3.63 – 3.61 (m, 2H), 2.52 – 2.50 (m, 2H), 2.44 (q, *J* = 7.2 Hz, 2H), 2.43 – 2.42 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 143.2, 110.3, 52.6, 52.0, 51.6, 47.1, 42.4, 11.9; GC/MS EI m/z (%) 167 (27, $M^{+\cdot}$), 152 (100), 138 (13), 123 (8), 113 (22), 98 (12), 84 (10), 70 (7), 56 (33), 42 (40); MS (+)-HRESI calcd. for $C_8H_{14}N_3O$ $[M + H]^+$ 168.1131, found 168.1136; ν_{max} 2972, 2815, 2230, 1671, 1447, 1436, 1276, 1246, 1018 cm^{-1}.

(3,4-Dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)(1*H*-imidazol-1-yl)methanone (1k): Prepared according to General Procedure A(i) from 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (1.22 g, 10 mmol) to afford, after filtration, the **1k** (1.32 g, 61%) as a beige powder: mp 106 – 108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.95 (s, 1H), 7.28 – 7.27 (m, 1H), 7.15 (s, 1H), 6.67 (t, *J* = 2.1 Hz, 1H), 6.21 (t, *J* = 3.1 Hz, 1H), 5.97 – 5.95 (m, 1H), 4.83 (s, 2H), 4.19 – 4.15 (m, 2H), 4.03 – 3.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 151.2, 137.0, 130.2, 123.0, 119.8, 118.0, 109.0, 104.3, 45.4, 44.4, 44.0; MS (+)-LRESI *m*/*z* (%) 217 (15) $[M + H]^+$, 149 (100); MS (+)-HRESI calcd. for $C_{11}H_{13}N_4O$ $[M + H]^+$ 217.1084, found 217.1082; ν_{max} 3115, 1693, 1422, 1236 cm^{-1}.

3,4-Dihydropyrrolo[1,2-a]pyrazine-2(1*H*)-1-carbonyl cyanide (2k): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1k** (216 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:2, EtOAc:40-60 petroleum ether), **2k** (143 mg, 82%) as a tan powder: mp 110 – 111 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) *1:1 mixture of rotamers δ* 6.64 (dd, *J* = 4.0, 2.2 Hz, 2H), 6.20 (dd, *J* = 6.5, 3.6 Hz, 2H), 6.05 – 6.03 (m, 1H), 6.05 – 6.03 (m, 1H) 6.01 – 5.98 (m, 1H), 4.98 (s, 2H), 4.80 (s, 2H), 4.14 (s, 4H), 4.07 – 4.04 (m, 2H), 4.02 – 3.99 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) *mixture of rotamers δ* 143.8, 143.6, 121.9, 121.6, 120.1, 119.8, 110.2, 110.1, 109.3, 109.2, 104.9, 104.8, 45.1, 44.8, 44.6, 43.5, 41.1, 40.8; GC/MS EI *m*/*z* (%) 175 (100, $M^{+\cdot}$), 146 (4), 121 (38), 106 (32), 93 (39), 80 (9); MS (+)-HRESI calcd. for $C_9H_9N_3NaO$ $[M + Na]^+$ 198.0638, found 198.0640; ν_{max} 2232, 1664, 1078 cm^{-1}.

***N*-Methyl-*N*-phenyl-1*H*-imidazole-1-carboxamide (1l):** Prepared according to General Procedure A(ii) from *N*-methylaniline (2.00 g, 18.7 mmol) and CDI (3.94 g, 24.3 mmol) to afford, after flash chromatography (1:20, MeOH:DCM), **1l** (1.30 g, 35%) as a yellow powder: ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.57 – 7.52 (m, 1H), 7.41 – 7.27 (m, 3H), 7.13 – 7.09 (m, 2H) 6.84 – 6.82 (m, 1H), 6.79 – 6.78 (m, 1H), 3.47 (s, 3H). Spectral data were consistent with those reported.[23]

Methyl(phenyl)carbamoyl cyanide (2l): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1l** (201 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:2, EtOAc:40-60 petroleum ether) **2l** (135 mg, 84%) as a yellow powder: ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.35 – 7.18 (m, 3H), 7.19 – 6.97 (m, 2H), 3.13 (s, 3H). Spectral data were consistent with those reported.[12]

***N,N*-Dimethyl-1*H*-imidazole-1-carboxamide (1m):** Prepared according to General Procedure B from dimethylamine hydrochloride (1.50 g, 18.4 mmol), CDI (3.28 g, 20.2 mmol), DMF (4 mL) and acetonitrile (15 mL) to afford, after flash chromatography (1:20, MeOH:DCM), **1m** (2.18 g 85 %) as white crystals: mp 54 – 56 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 7.86 (s, 1H), 7.21 (t, *J* = 1.3 Hz, 1H), 7.07 – 7.03 (m, 1H), 3.08 (s, 7H); ^{13}C NMR ($CDCl_3$, 125MHz) *δ* 151.9, 137.0, 129.6, 118.1, 38.5; MS (+)-LRESI *m*/*z* (%) 140 (100) $[M + H]^+$; MS (+)-HRESI calcd. for $C_6H_{10}N_3O$ $[M + H]^+$ 140.0824 found 140.0826; ν_{max} 3397, 3119, 2937, 1692, 1396, 1221 cm^{-1}.

Dimethylcarbamoyl cyanide (2m): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1m** (139 mg, 1.00 mmol) and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:2 Et_2O:pentane) **2m** (90 mg, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 3.29 (s, 3H), 3.02 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 144.8, 110.6, 37.9, 34.4; MS (+)-LREI *m*/*z* (%) 98 ($M^{+\cdot}$, 6%), 83 (5), 58 (100); MS (+)-HREI calcd. for $C_3H_3N_2O_2$ $[M\text{-}CH_3]^{+\cdot}$: 83.0240; found, 83.0245; ν_{max} 2939, 2234, 1675, 1491,1439, 1398 cm^{-1}.

***N*-Methyl-*N*-(prop-2-yn-1-yl)-1*H*-imidazole-1-carboxamide (1n):** A vigorously stirring solution of CDI (3.73 g, 23.0 mmol) in DCM (60 mL) at 0 °C under an atmosphere of nitrogen was treated with *N*-methylpropargyl amine (1.66 mL, 20.0 mmol) portion-wise, followed by dropwise addition of triethylamine (2.79 mL, 20.0 mmol). The mixture was stirred for 1 h at 0 °C and then stirred for 18 h at 23 °C. The mixture was transferred to a separatory funnel, diluted with DCM (50 mL) and washed with water (3 × 30 mL) then brine (25 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford **1n** (2.15 g, 66%) as a tan solid that was used without further purification: mp 65 – 67 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.98 (app. t, *J* = 1.0 Hz, 1H), 7.32 (app. t, *J* = 1.6 Hz, 1H), 7.10 (dd, *J* = 1.6, 1.0 Hz, 1H), 4.18 (d, *J* = 2.5 Hz, 2H), 3.18 (s, 3H), 2.42 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 151.4, 137.1, 129.9, 118.0, 77.2, 74.1, 40.3, 36.1; MS (+)-LREI *m*/*z* (%) 163 (23, $M^{+\cdot}$), 106 (20), 96 (100), 68 (18), 55 (41); MS (+)-HRESI calcd. for $C_8H_{10}N_3O$ $[M + H]^+$ 164.0818, found 164.0819; ν_{max} 3197, 3140, 2113, 1685, 1274, 1015 cm^{-1}.

Methyl(prop-2-yn-1-yl)carbamoyl cyanide (2n): Prepared according to General Procedure C [140 °C, 1 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$) from **1n** (163 mg, 1.00 mmol)] and TMSCN (131 µL, 1.05 mmol) to afford, after flash chromatography (1:2, EtOAc:40-60 petroleum ether) **2n** (85 mg, 70%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) *0.6:1 mixture of rotamers δ* 4.36 (d, *J* = 2.5 Hz, $2H_{min}$), 4.21 (d, *J* = 2.5 Hz, $2H_{maj}$), 3.32 (s, $3H_{maj}$), 3.05 (s, $3H_{min}$), 2.45 (t, *J* = 2.5 Hz, $1H_{min}$), 2.34 (t, *J* = 2.5 Hz, $1H_{maj}$); ^{13}C NMR ($CDCl_3$, 125 MHz) *major rotamer δ* 144.7, 110.2, 75.6, 74.1, 35.9, 35.2; ^{13}C NMR ($CDCl_3$, 125 MHz) *minor rotamer δ* 144.3, 110.1, 75.5, 75.0, 40.5, 32.2; MS (+)-HRESI calcd. for $C_6H_6N_2NaO$ $[M + Na]^+$ 145.0372, found 145.0372; ν_{max} 3291, 2235, 2127, 1690, 1405, 1120 cm^{-1}.

Azetidin-1-yl(1*H*-imidazol-1-yl)methanone (1o): Prepared according to General Procedure B from azetidine hydrochloride (936 mg, 10.0 mmol), CDI (1.78 g, 11.0 mmol), DMF (3 mL) and acetonitrile (10 mL) to afford, after flash chromatography (1:20, MeOH:DCM), **1o** (845 mg 56 %) as a white crystals: mp 115 – 118 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 7.98 (s, 1H), 7.29 (app. t, *J* = 1.5 Hz, 1H), 7.09 – 7.05 (m, 1H), 4.34 (app. t, *J* = 7.9 Hz, 4H), 2.48 – 2.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 150.3, 136.3, 130.0, 116.7, 51.8 (br, 2C), 16.3; MS (+)-LREI *m*/*z* (%) 151 (50, $M^{+\cdot}$), 84 (81), 56 (100); MS (+)-HRESI calcd. for $C_7H_{10}N_3O$ $[M + Na]^+$ 152.0818, found 152.0824; ν_{max} 3152, 1668, 1460, 1440, 1224 cm^{-1}.

Azetidine-1-carbonyl cyanide (2o): Prepared according to General Procedure C [100 °C, 2h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1o** (300 mg, 2.00 mmol) and TMSCN (263 µL, 2.10 mmol) to afford, after flash chromatography (1:2 Et_2O:pentane) **2o** (210 mg, 95%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) 4.40 – 4.36 (m, 2H), 4.15 – 4.11 (m, 2H), 2.48 – 2.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 143.6, 109.8, 50.7, 49.2, 16.0; MS (+)-LREI *m*/*z* (%) 110 (90 $M^{+\cdot}$), 84 (45), 83 (46), 56 (68), 54 (100); MS (+)-HRESI calcd. for $C_5H_6N_2NaO$ $[M + Na]^+$ 133.0372, found 133.0374; ν_{max} 2958, 2231, 1686, 1440, 1298, 922 cm^{-1}.

***N*-(Cuban-1-ylmethyl)-1*H*-imidazole-1-carboxamide (1p):**. A solution of cubane carboxylic acid[24] (440 mg, 2.97 mmol) in THF (10 mL) was treated with CDI (578 mg, 3.56 mmol) and the resulting mixture was stirred at 20 °C for 2 h. The reaction mixture was cooled to 0 °C and treated dropwise with a solution of methylamine in THF (5.20 mL, 2M). The resulting mixture was maintained at to 0 °C for a further 0.25 h then stirred at 20 °C for 16 h. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica, 1:9, methanol saturated with $NH_{3(g)}$:DCM) to give, after concentration of the appropriate fractions *N*-methylcubane-1-carboxamide (400 mg, 84%) as a white solid: mp 162 − 163 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.57 (br s, H), 4.14 – 4.10 (m, 3H), 3.99 – 3.94 (m, 1H), 3.93 – 3.89 (m, 3H), 2.58 (d, J = 4.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.4, 56.9, 48.5, 46.9, 43.7, 25.3; MS (+)-LRESI m/z (%) 184 (100) [M + Na]$^+$, MS (+)-HRESI calcd. for $C_{10}H_{11}NNaO$ [M + Na]$^+$ 184.0733, found 184.0736; ν_{max} 3411, 2982, 1618, 1049, 1023, 1001, 823, 761 cm^{-1}. A portion of the *N*-methylamide generated above (250 mg, 1.55 mmol) was added to a suspension of $LiAlH_4$ (294 mg, 7.75 mmol, pellets ground under nitrogen) in THF (30 mL) at 0 °C. After warming to 20 °C the reaction mixture was heated at reflux for 16 h then cooled to 0 °C and $NaSO_4$.10 H_2O (5 g) was cautiously added portion-wise to quench excess $LiAlH_4$ then vigorously stirred for 0.5 h. The mixture was filtered and the solids were washed with DCM (40 mL). The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil which was then suspended in water (5 mL), vigorously stirred and treated portion-wise with CDI (302 mg, 1.86 mmol) at 0 °C. The suspension was then warmed to 20 °C followed by extraction with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a residue which was purified by flash chromatography (3:97, MeOH saturated with $NH_{3(g)}$:DCM) to afford *N*-(cuban-1-ylmethyl)-1*H*-imidazole-1-carboxamide (**1p**) (200 mg, 53%) as a white powder: mp 77 − 79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 – 7.84 (m, 1H), 7.20 – 7.18 (m, 1H), 7.06 – 7.05 (m, 1H), 4.05 – 3.99 (m, 1H), 3.96 – 3.91 (m, 3H), 3.89 – 3.85 (m, 3H), 3.67 (s, 2H), 3.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.9, 137.0, 129.6, 118.2, 57.0, 52.3, 48.4, 48.3, 44.5, 37.2; MS (+)-LRESI m/z (%) 264 (100) [M + Na]$^+$; MS (+)-HRESI calcd. for $C_{14}H_{16}N_3O$ [M + H]$^+$ 242.1288, found 242.1295; ν_{max} 2973, 1683, 1476, 1216, cm^{-1}.

***N*-(Cuban-1-ylmethyl)-1*H*-imidazole-1-cyanoformamide (2p):** Prepared according to General Procedure C [(100 °C, 2 h, ramp time 5 minutes, 200 W, PowerMax (cooling with $N_{2(g)}$)] from **1p** (60 mg, 0.25 mmol) and TMSCN (33 µL, 0.26 mmol) to afford, after flash chromatography (1:2, Et_2O:pentane), **2p** (42 mg, 70%) as a pale-yellow oil: ^{1}H NMR (C_6D_6, 400 MHz) *2:3 mixture of rotamers* δ 3.80 – 3.74 (m, 1H$_{min}$), 3.74 – 3.69 (m, 1H$_{maj}$), 3.65 – 3.61 (m, 3H$_{min}$), 3.59 – 3.55 (m, 3H$_{maj}$), 3.52 – 3.47 (m, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 145.2, 145.0, 111.7, 111.4, 56.8, 56.5, 52.2, 48.6, 48.5, 48.4, 47.9, 44.6, 44.4, 35.9, 33.1; MS (+)-LRESI m/z (%) 223 (52) [M + Na]$^+$, 413 (100); MS (+)-HRESI calcd. for $C_{12}H_{12}N_2NaO$ [M + Na]$^+$ 223.0842, found 223.0846; ν_{max} 2975, 2231, 1666, 1405, 721 cm^{-1}.

***N*-Benzyl-1*H*-imidazole-1-carboxamide (1q):** Prepared according to General Procedure A(i) from benzylamine (1.00 g, 9.33 mmol) and CDI (1.66 g, 10.3 mmol) to afford, after filtration, **1q** (0.91 g, 48%) as a white powder: mp 66 – 68 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 – 8.13 (m, 1H), 7.41 – 7.39 (m, 1H), 7.37 – 7.29 (m, 5H), 7.07 (br s, 1H), 7.00 – 6.97 (m, 1H), 4.58 (d, J = 5.7 Hz, 2H). Spectral data were consistent with those reported.[20]

Benzylcarbamoyl cyanide (2q): Prepared according to General Procedure D (3 mins, 70 °C) from **1q** (201 mg, 1.00 mmol) and TMSCN (251 µL, 2.00 mmol). Crude product was purified by flash chromatography (1:30, MeOH:DCM) to afford benzyl cyanoformamide (**2q**) (133 mg, 83%) as a white powder: ^{1}H NMR ($CDCl_3$, 400 MHz) *5:95 mixture of rotamers* δ 7.43 – 7.33 (m, 3H), 7.31 – 7.27 (m, 1H), 6.39 (br s, 1H$_{maj}$), 6.18 (br s, 1H$_{min}$), 4.69 (d, J = 6.6 Hz, 2H$_{min}$), 4.52 (d, J = 5.8 Hz, 2H$_{maj}$). Spectral data were consistent with those reported.[9]

1,3-Dibenzyl-5-iminoimidazolidine-2,4-dione (3): Prepared according to General Procedure D (10 mins, 100 °C) from **1q** (201 mg, 1.00 mmol) and TMSCN (132 µL, 1.05 mmol). Crude product was purified by flash chromatography (1:30, MeOH:DCM) which afforded three fractions, A, B and C. Concentration of fraction A afforded 1,3-dibenzyl-5-iminoimidazolidine-2,4-dione (**3**) (63 mg, 44%) as a white powder: mp 141 – 144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90 (s, 1H), 7.43 – 7.37 (m, 4H), 7.36 – 7.29 (m, 6H), 4.86 (s, 2H), 4.74 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 154.3, 152.4, 135.5, 135.0, 129.0, 128.9, 128.9, 128.9, 128.5, 128.3, 43.3, 43.0; MS (+)-LRESI m/z (%) 316 (100) [M + Na]$^+$; MS (+)-HRESI calcd. for $C_{17}H_{16}N_3O_2$ [M + H]$^+$ 294.1237, found 294.1242; ν_{max} 3258, 1789, 1729, 1671, 1440, 1410, 1136 cm^{-1}. Concentration of fraction B afforded benzylcarbamoyl cyanide (**2q**) (38 mg, 24%) as a white powder. Spectral data were identical to those described above. Concentration of fraction C afforded *N*-benzyl-1*H*-imidazole-1-carboxamide (**1q**) (30 mg, 15%) as a white powder. Spectral data were identical to those described above.

***N*-(4-Methoxybenzyl)-1*H*-imidazole-1-carboxamide (1r):** Prepared according to General Procedure A(ii) from 4-methoxybenzyl amine (1.30 mL, 10 mmol) and CDI (2.20 g, 13.5 mmol) to afford, after flash chromatography (1:1, acetone:40-60 petroleum ether), **1r** (1.05 g, 44%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 – 8.05 (m, 1H), 7.40 – 7.39 (m, 1H), 7.35 (t, J = 5.5 Hz, 1H), 7.26 – 7.22 (m, 2H), 6.92 – 6.91 (m, 1H), 6.88 – 6.84 (m, 2H), 4.49 (d, J = 5.5 Hz, 2H), 3.78 (s, 3H). Spectral data were consistent with those reported.[21]

(4-Methoxybenzyl)carbmoyl cyanide (2r): Prepared according to General Procedure D (3 mins, 70 °C) from **1r** (261 mg, 1.00 mmol) and TMSCN (251 µL, 2.00 mmol). The crude product was purified by flash chromatography (1:20, MeOH:DCM) to afford **2r** (180 mg, 94%) as a pale-yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) *1:10 mixture of rotamers* δ 7.25 – 7.16 (m, 2H), 6.94 – 6.85 (m, 2H), 6.53 (br s, 1H$_{maj}$), 6.25 (br s, 1H$_{min}$), 4.60 (d, J = 6.5 Hz, 2H$_{min}$), 4.43 (d, J = 5.7 Hz, 2H$_{maj}$), 3.82 (s, 3H$_{min}$), 3.81 (s, 3H$_{maj}$). Spectral data were consistent with those reported.[9]

***N*-(2,4-Dimethoxybenzyl)-1*H*-imidazole-1-carboxamide (1s):** Prepared according to General Procedure A(i) from 2,4-dimethoxybenzyl amine (2.03 g, 10.0 mmol) and CDI (3.24 g, 20 mmol) to afford, after filtration, **1s** (2.29 g, 88%) as a white powder: mp 111 – 114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 – 8.02 (m, 1H), 7.32 – 7.29 (m, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.06 – 7.01 (m, 1H), 6.50 – 6.39 (m, 3H), 4.50 (d, J = 5.7 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 161.2, 158.7, 148.8, 136.0, 131.0, 130.6, 117.5, 115.9, 104.3, 99.0, 55.6, 55.6, 40.9; MS (+)-LRESI m/z (%) 284 (100) [M + Na]$^+$; MS (+)-HRESI calcd. for $C_{13}H_{15}N_3O_3Na$ [M + Na]$^+$ 284.1006, found 284.1010; ν_{max} 1718, 1509, 1286, 1130 cm^{-1}.

(2,4-Dimethoxybenzyl)carbamoyl cyanide (2s): Prepared according to General Procedure D (3 mins, 70 °C) from **1s** (261 mg, 1.00 mmol) and TMSCN (251 µL, 2.00 mmol). The crude product was purified by flash chromatography (1:20, MeOH:DCM) to afford **2s** (195 mg, 89%) as a viscous colourles oil: ^{1}H NMR ($CDCl_3$, 400 MHz) *1:9 mixture of rotamers* δ 7.14 (d, J = 8.2 Hz, 1H), 6.79 – 6.63 (m, NH$_{maj}$), 6.48 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.2, 2.4 Hz, 1H), 6.40 (br s, NH$_{min}$), 4.54 (d, J = 6.7 Hz, 2H$_{min}$), 4.42 (d, J = 5.9 Hz, 2H$_{maj}$), 3.86 (s, 3H$_{maj}$), 3.85 (s, 3H$_{min}$), 3.81 (s, 3H$_{min}$), 3.81 (s, 3H$_{maj}$);^{13}C NMR ($CDCl_3$,100 MHz) *mixture of rotamers* δ 161.8$_{min}$, 161.5$_{maj}$, 158.7$_{maj}$, 158.7$_{min}$, 145.7$_{maj}$, 142.8$_{min}$, 131.1$_{min}$, 130.4$_{min}$, 116.4$_{min}$, 116.1$_{maj}$, 111.8$_{maj}$, 110.5$_{min}$, 104.4$_{maj}$, 104.3$_{min}$, 99.0$_{min}$, 98.9$_{maj}$, 55.6$_{maj}$, 55.5$_{min}$, 43.8 $_{min}$, 40.4$_{maj}$; MS (+)-LRESI m/z (%) 243 (100) [M + Na]$^+$; MS (+)-HRESI calcd. for $C_{11}H_{12}N_2O_3Na$ [M + Na]$^+$ 243.0740, found 243.0747; ν_{max} 3267, 2234, 1667, 1616, 1544, 1508, 1212, 1037 cm^{-1}.

***N*-(3,4-Dimethoxyphenethyl)-1*H*-imidazole-1-carboxamide (1t):** Prepared according to General Procedure A(i) from 3,4-dimethoxyphenethylamine (1.81 g, 10 mmol) and CDI (2.43 g, 15 mmol) to afford, after filtration, **1t** (2.44 g, 88%) as a white powder: mp 135 – 138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (s, 1H), 7.27 (s, 1H), 7.05 – 6.99 (m, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.78 – 6.68 (m, 2H), 6.27 (t, J = 5.7 Hz, 1H), 3.86 (s,

3H), 3.83 (s, 3H), 3.69 – 3.62 (m, 2H), 2.89 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 149.2, 149.1, 147.9, 135.9, 131.0, 129.9, 120.9, 116.3, 112.0, 111.6, 56.0, 55.9, 42.4, 35.1; MS (+)-LRESI *m*/*z* (%) 298 (100) $[M + Na]^+$; MS (+)-HRESI calcd. for $C_{14}H_{18}N_3O_3$ $[M + H]^+$ 276.1343, found 276.1348; ν_{max} 3283, 2231, 1701, 1514, 1155, 1023 cm^{-1}.

(3,4-Dimethoxyphenethyl)carbamoyl cyanide (2t): Prepared according to General Procedure D (7 mins, 70 °C) from **1t** (275 mg, 1.00 mmol) and TMSCN (251 µL, 2.00 mmol). Crude product was purified by flash chromatography (1:10, MeOH:DCM) to afford **2t** (203 mg, 87%) as a cream-colored powder: mp 87 – 89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) *1:9 mixture of rotamers* *δ* 6.84 (d, *J* = 8.1 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.68 (d, *J* = 2.1 Hz, 1H), 6.19 (br s, 1H$_{maj}$), 5.94 (s, 1H$_{min}$), 3.88 (s, 3H), 3.87 (s, 3H), 3.71 (td, *J* = 6.7, 6.7 Hz, 2H$_{min}$), 3.60 (td, *J* = 6.9, 5.9 Hz, 2H$_{maj}$), 2.86 (t, *J* = 6.62 Hz, 1H$_{min}$) 2.82 (t, *J* = 6.9 Hz, 2H$_{maj}$). Spectral data were consistent with those reported.[9]

***N*-(Adamantan-2-yl)-1*H*-imidazole-1-carboxamide (1u):** Prepared according to General Procedure B from 2-adamantylamine hydrochloride (1.88 g, 10.0 mmol), CDI (1.78 g, 11.0 mmol), DMF (3 mL) and acetonitrile (10 mL) to afford, after flash chromatography (1:20, MeOH:DCM), **1u** (1.63 g, 66%) as colorless crystals: mp 145 – 147 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 8.11 – 8.07 (m, 1H), 7.33 – 7.30 (m, 1H), 7.11 – 7.10 (m, 1H), 5.82 (s, 1H), 4.12 (dt, *J* = 6.8, 3.0 Hz, 1H), 2.10 – 2.04 (m, 2H), 1.96 – 1.85 (m, 6H), 1.83 – 1.71 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 148.3, 136.0, 130.4, 116.0, 55.6, 37.4, 37.0, 31.9, 31.8, 27.1, 27.0; MS (+)-LRESI *m*/*z* (%) 246 (100) $[M + H]^+$; MS (+)-HRESI calcd. for $C_{14}H_{20}N_3O$ $[M + H]^+$ 246.1601, found 246.1601; ν_{max} 3389, 2906, 1683, 1534 cm^{-1}.

(Adamantan-2-yl)carbamoyl cyanide (2u): Prepared according to General Procedure D (5 mins, 70 °C) from **1u** (239 mg, 1.00 mmol) and TMSCN (251 µL, 2.00 mmol). The crude product was purified by flash chromatography (1:30, MeOH:DCM) to afford **2u** (161 mg, 79%) as colorless crystals: mp 140 – 144 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) *1:8 mixture of rotamers* *δ* 6.37 (s, 1H), 4.12 (dt, *J* = 8.0, 2.6 Hz, 1H$_{maj}$), 4.03 (dt, *J* = 9.2, 2.8 Hz, 1H$_{min}$), 2.05 – 1.70 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 142.5$_{maj}$, 112.0$_{maj}$, 111.4$_{min}$, 58.0$_{min}$, 55.5$_{maj}$, 37.3$_{maj}$, 37.2$_{min}$, 37.1$_{min}$, 36.9$_{maj}$, 33.4$_{min}$, 31.7$_{maj}$, 31.5$_{maj}$, 31.4, 27.0$_{maj}$, 26.9$_{maj}$, 26.9$_{min}$, 26.6$_{min}$; MS (+)-LREI *m*/*z* (%) 204 (31, $M^{+\bullet}$), 177 (33), 176 (33), 159 (24), 134 (75), 92 (100), 79 (74); MS (+)-HRESI calcd. for $C_{12}H_{16}N_2NaO$ $[M + Na]^+$ 227.1155, found 247.1164; ν_{max} 3293, 2911, 2232, 1664, 1548 cm^{-1}.

***N*-Cyclohexyl-1*H*-imidazole-1-carboxamide (1v).** Prepared according to General Procedure A(ii) from cyclohexylamine (1.10 mL, 10.0 mmol) and CDI (2.40 g, 15 mmol) to afford, after flash chromatography (1:1, acetone:40-60 petroleum ether), **1v** (1.40 g, 73%) as a pale-yellow solid: mp 82 – 83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.10 – 8.08 (m, 1H), 7.32 – 7.29 (m, 1H), 7.11 – 7.08 (m, 1H), 5.63 – 5.40 (m, 1H), 3.89 – 3.78 (m, 1H), 2.10 – 2.03 (m, 2H), 1.82 – 1.74 (m, 2H), 1.72 – 1.64 (m, 1H), 1.48 – 1.36 (m, 2H), 1.32 – 1.17 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 148.4, 136.1, 129.3, 129.3, 116.7, 50.7, 32.8, 25.3, 25.1; (+)-LRESI *m*/*z* (%) 216 (100) $[M + Na]^+$; MS (+)-HRESI calcd. for $C_{10}H_{15}N_3ONa$ $[M + Na]^+$ 216.1113 found 216.1107; ν_{max} 3223, 3124, 3029, 2931, 2856, 1697, 1541, 1235 cm^{-1}.

Cyclohexylcarbamoyl cyanide (2v): Prepared according to General Procedure D (3 mins, 70 °C) from **1v** (193 mg, 1.00 mmol) and TMSCN (251 µL, 2.00 mmol). Crude product was purified by flash chromatography (1:20, MeOH:DCM) to afford **2v** (113 mg, 74%) as a viscous colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) *1:10 mixture of rotamers* *δ* 6.13 (br s, 1H$_{maj}$), 6.01 (br s, 1H$_{min}$), 3.88 – 3.78 (m, 1H$_{maj}$), 3.78 – 3.69 (m, 1H$_{min}$), 2.00 – 1.90 (m, 2H), 1.82 – 1.70 (m, 2H), 1.68 – 1.60 (m, 1H), 1.44 – 1.31 (m, 2H), 1.30 – 1.14 (m, 3H). ν_{max} 3272, 2934, 2238, 1662, 1559 cm^{-1}. Spectral data were consistent with those reported.[9]

***n*-Butyl-1*H*-imidazole-1-carboxamide (1w):** Prepared according to General Procedure A(ii) from *n*-butylamine (496 µL, 5 mmol) and CDI (1.62 g, 28 mmol) to afford, after extraction, **1w** (784 mg, 94%) as a colourless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.09 – 8.07 (m, 1H), 7.47 – 7.41 (m, 1H), 7.38 – 7.35 (m, 1H), 6.92 – 6.88 (m, 1H), 3.28 (td, *J* = 7.2, 5.6 Hz, 2H), 1.52 – 1.44 (m, 2H), 1.32 – 1.22 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 149.3, 136.1, 129.5, 116.8, 40.9, 31.5, 20.1, 13.7; MS (+)-LREI *m*/*z* (%) 167 (5, $M^{+\bullet}$), 83 (100); MS (+)-HREI calcd. for $C_8H_{13}N_3O$ $[M]^{+\bullet}$ 167.1059, found 167.1057; ν_{max} 3288, 2236, 1674, 1544, 1255 cm^{-1}.

***n*-Butylcarbamoyl cyanide (2w):** Prepared according to General Procedure D (3 mins, 70 °C) from **1w** (167 mg, 1.00 mmol) and TMSCN (251 µL, 2.00 mmol). Crude product was purified by flash chromatography (1:30, MeOH:DCM) to afford **2w** (105 mg, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 6.35 (br s, 1H$_{maj}$), 6.12 (br s, 1H$_{min}$), 3.50 (app. q, *J* = 6.9 Hz, 2H$_{min}$), 3.35 (td, *J* = 7.2, 6.0 Hz, 2H$_{maj}$), 1.65 – 1.60 (m, 2H$_{min}$), 1.60 – 1.51 (m, 2H$_{maj}$), 1.42 – 1.32 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H$_{min}$), 0.94 (t, *J* = 7.3 Hz, 3H$_{maj}$); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 143.3$_{maj}$, 111.8$_{maj}$, 43.3$_{min}$, 40.5$_{maj}$, 32.5$_{min}$, 30.9$_{maj}$, 20.0$_{maj}$, 19.7$_{min}$, 13.7$_{maj}$, 13.6$_{min}$; MS (+)-LREI *m*/*z* (%) 111 (5, $M^{+\bullet}-CH_3^{\bullet}$), 100 (24, $M^{+\bullet}-CN^{\bullet}$), 83 (100, $M^{+\bullet}-C_3H_7^{\bullet}$); MS (+)-HREI calcd. for $C_5H_7N_2O$ $[M^{+\bullet}-CH_3^{\bullet}]$ 111.0558, found 111.0553; ν_{max} 2237, 1674, 1543, 1255 cm^{-1}.

Acknowledgements

The authors would like to acknowledge Dr Keats Nelms (Beta Therapeutics Pty Ltd), Prof. Martin Banwell (The Australian National University) and Assoc. Profs. Mark Coster and Rohan Davis (Griffith Institute for Drug Discovery), and Dr Andrew Piggott (Macquarie University) for their generosity. The authors thank Dr John Tsanaktsidis (CSIRO) and Dr Justine Walter (Boron Molecular) for provision of 1,4-cubanedicarboxylic acid and Ellen V. Cliff for assistance with manuscript preparation. BDS is indebted to The National Health and Medical Research Council for financial support (grant APP1024314) and JN is grateful to the Australian Government for an APA scholarship.

Keywords: cyanoformamide • carbamoyl imidazole • solvent-free • green chemistry

REFERENCES

[1] A. M. Dreis, S. C. Otte, M. S. Eastwood, E. R. Alonzi, J. T. Brethorst, C. J. Douglas, *Eur. J. Org. Chem.* **2017**, 45–48.

[2] Y. Yasui, H. Kamisaki, Y. Takemoto, *Org. Lett.* **2008**, *10*, 3303–3306.

[3] J. Paz, C. Pérez-Balado, B. Iglesias, L. Muñoz, *J. Org. Chem.* **2010**, *75*, 8039–8047.

[4] R. E. Ford, P. Knowles, E. Lunt, S. M. Marshall, A. J. Penrose, C. A. Ramsden, A. J. H. Summers, J. L. Walker, D. E. Wright, *J. Med. Chem.* **1986**, *29*, 538–549.

[5] (a) Y. Kobayashi, H. Kamisaki, R. Yanada, Y. Takemoto, *Org. Lett.* **2006**, *8*, 2711–2713. (b) X. Fu, J. Chen, G. Li, Y. Liu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5500–5504.

[6] J. Nugent, B. D. Schwartz, *Org. Lett.* **2016,** *18*, 3834–3837.

[7] (a) S. Tsukamoto, H. Kato, H. Hirota, N. Fusetani, *J. Org. Chem.* **1996**, *61*, 2936–2937. (b) X. Fu, F. J. Schmitz, *J. Nat. Prod.* **1999,** *62*, 1072–1073.

[8] (a) W. J. Linn, O. W. Webster, R. E. Benson, *J. Am. Chem. Soc.*, **1965**, 87, 3651–3656; (b) E. L. Martin, *Org. Synth.*, **1971,** *51,* 70–74; (c) Y. Kobayashi, H. Kamisaki, H. Takeda, Y. Yasui, R. Yanada and Y. Takemoto, *Tetrahedron*, **2007**, 63, 2978–2989.

[9] E. Garcia-Egido, J. Paz, B. Iglesias, L. Munoz, *Org. Biomol. Chem.* **2009**, *7*, 3991–3999.

[10] J. Yang, D. Xiang, R. Zhang, N. Zhang, Y. Liang, D. Dong, *Org. Lett.* **2015,** *17*, 809-811.

[11] N. Katagiri, Y. Morishita, C. Kaneko, *Heterocycles* **1997**, *46*, 503–508.

[12] Z. Zhan, X. Cheng, Y. Zheng X. Ma, X. Wang, L. Hai, Y. Wu, *RSC Adv.* **2015,** *5*, 82800–82803.

[13] Besides product, only small amounts of starting material, imidazole and TMS-imidazole were found in the reaction mixture and these could be removed by facile flash chromatography."

[14] Y. Hirata, A. Yada, E. Morita, Y. Nakao, T. Hiyama, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2010**, *132*, 10070–10077.

[15] S.-I. Inaba, I. Ojima, *J. Organomet. Chem.* **1979,** *169*, 171–184.

[16] Preliminary experiments on electron poor systems provided low yields of desired products under these conditions.

[17] H. A. Staab, *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351–367.

[18] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. **1978**, *43*, 2923–2925.

[19] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, **1996**, *15*, 1518.

[20] K. J. Padiya, S. Gavade, B. Kardile, M. Tiwari, S. Bajare, M. Mane, V. Gaware, S. Varghese, D. Harel, S. Kurhade, *Org. Lett.* **2012,** *14*, 2814–2817.

[21] P. A. Duspara, Md. S. Islam, A. J. Lough, R. A. Batey, *J. Org. Chem.* **2012**, *77*, 10362–10368.

[22] A. Velavan, S. Sumathi, K. K. Balasubramanian, *Org. Biomol. Chem.* **2012**, *10*, 6420–6431.

[23] J. A. Grzyb, M. Shen, C. Yoshina-Ishii, W. Chi, R. S. Brown, R. A. Batey, *Tetrahedron* **2005**, *61*, 7153–7175.

[24] S. M. Wilkinson, H. Gunosewoyo, M. L. Barron, A. Boucher, M. McDonnell, P. Turner, D. E. Morrison, M. R. Bennett, I. S. McGregor, L. M. Rendina, M. Kassiou, *ACS Chem. Neurosci.* **2014**, *5*, 335–339.