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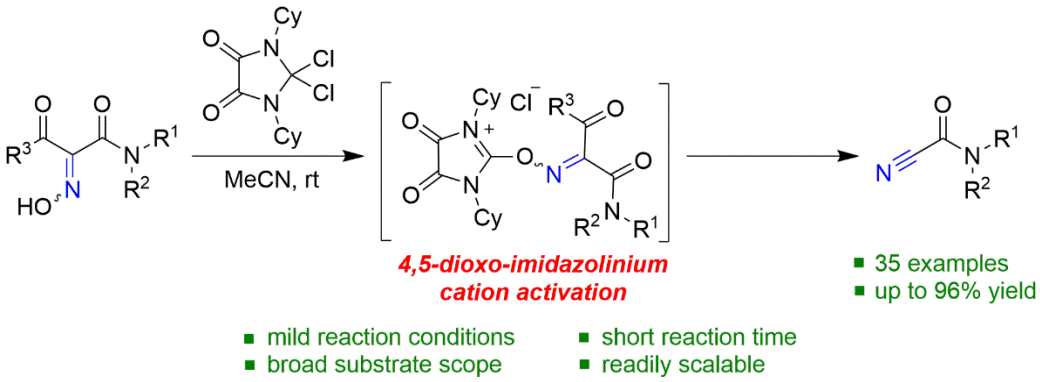
4,5-Dioxo-imidazolinium Cation Activation of 1-Acyl-1-carbamoyl Oximes: Access to Cyanoformamides Using Dichloroimidazolidinedione

Yu Gao,[†] Zhihao Zhang,[†] Zhenjiang Li,*[,†,‡] Tianfo Guo,[†] Yuejia Zhu,[†] Zhiwei Yao,[†] Bo Liu,[†] Yongqiang Li,[†] and Kai Guo*[,†,‡]

[†]College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, 30 Puzhu Road South, Nanjing 211816, P. R. China

[‡]State Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University, 30 Puzhu Road South, Nanjing 211816, P. R. China

ABSTRACT

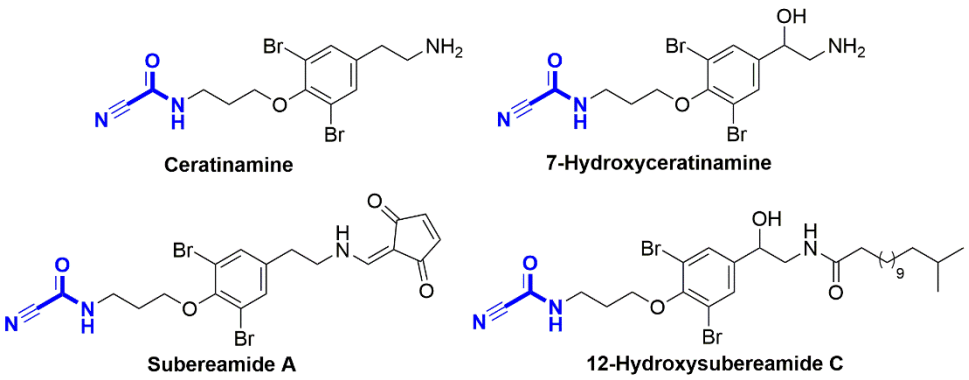


Cyanoformamides are prevalent as versatile building blocks for accessing synthetically useful intermediates and biologically active compounds. The development of a milder, simpler, and more efficient approach to cyanoformamides is nontrivial. Herein, we demonstrate the effectiveness of 4,5-dioxo-imidazolinium cation activation for transforming 1-acyl-1-carbamoyl oximes to cyanoformamides. By making use of the readily available and highly modifiable dichloroimidazolidinediones (DCIDs), this novel method of activation offers reactivity remarkably greater than that of other reported protocols, exhibits a high functional group compatibility with the mild conditions, and could be scaled up easily. More than 30 examples are demonstrated with good to excellent yields in short reaction times. This research not only provides a mild and efficient alternative approach to assembling a portfolio of cyanoformamides, but also extends the dichloroimidazolidinedione-mediated chemistry to encompass the C–C bond cleavage reaction.

INTRODUCTION

Cyanoformamides are a class of versatile building blocks for assembling synthetically useful intermediates[1] and biologically active compounds.[2] A prototype cyanoformamide ($NCCONH_2$) is a known interstellar molecular precursor to nucleic acids under prebiotic conditions.[3] In addition, such a prevalent motif also exists in natural products, including antifouling ceratinamine,[4] 7-hydroxyceratinamine,[5] subereamide A,[6] and 12-hydroxysubereamide C (Scheme 1).[6] Therefore, considerable efforts have been made to develop methods for preparing valuable cyanoformamides. Traditional methods focused on the cyanocarbonylation of amines with reagents such as carbonyl cyanide,[7] 4-chloro-5H-1,2,3-dithiazol-5-one,[8] triphosgene followed by substitution with a cyanide ion,[7b] and isonitroso Meldrum's acid[9] or its tosyl derivatives.[10] Yet, the use of highly toxic and structurally complex reagents hampered their synthetic applications. Until recently, sporadic examples of alternative approaches to cyanoformamides formation were reported.[11] While effective, most of these protocols called for elevated temperatures (60−140 °C)[11b,d–f] as well as long reaction times[11d,f] or suffered from limited product scope excluding secondary cyanoformamides.[11c,d,f] Worthy of note, Dong and co-workers reported a new pathway for the synthesis of cyanoformamides from readily accessible 1-acyl-1-carbamoyl oximes mediated by phosphoryltrichloride ($POCl_3$).[11b] However, the reagent employed ($POCl_3$) is hazardous and lacks the ability of structural modification for the goal of enhancing reactivity. For these reasons, the development of a novel alternative method aiming at mild reaction conditions, high efficiency, broad substrate scope, and avoiding the use of undesirable reagents is still in high demand.

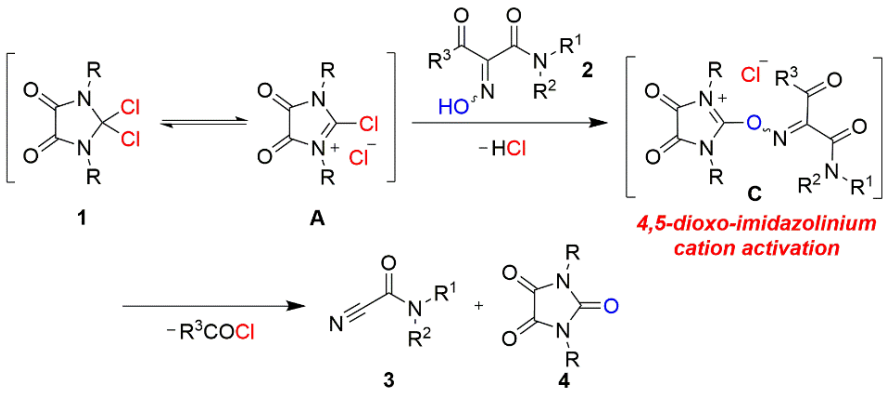
Scheme 1. Examples of Cyanoformamide-Containing Natural Products



Recently, we have successfully demonstrated the great potential of 4,5-dioxo-imidazolinium cation activation strategy in the Beckmann rearrangement using dichloroimidazolidinediones on a

substoichiometric scale.[12] 2,2-Dichloroimidazolidine-4,5-diones (DCIDs) (**1**),[13] a planar five-membered *N*-heterocycle, possess a unique combination of stability of the oxalamide framework and highly electrophilic reactivity of a quaternary germinal dichlorocarbon nucleus (Scheme 2).[14] Easy to prepare in nearly quantitative yield on a large scale,[15] DCIDs are also highly amenable to electronic and steric tunability. Besides, DCIDs bearing germinal halogens as good leaving groups can dissociate to form 4,5-dioxo-imidazolinium chloride salts (**A**) (Scheme 2).[16a] Despite having been known for over a half century, the synthetic value of DCIDs has only recently been explored in a limited context.[12,16] Particularly, DCIDs have rarely been utilized in mediating C–C bond cleavage reaction.[12]

Scheme 2. Proposed Design for 4,5-Dioxo-imidazolinium Cation Activation of 1-Acyl-1-carbamoyl Oximes to Form Cyanoformamides



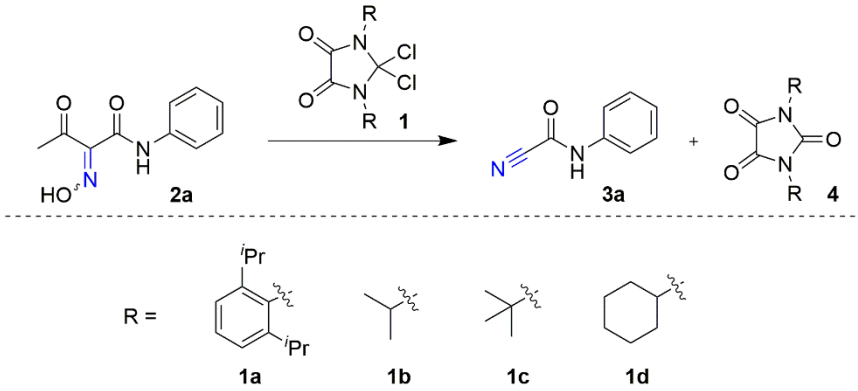
Inspired by the intriguing property of DCIDs, we envisioned that our recently developed 4,5-dioxo-imidazolinium cation system might also be capable of facilitating the conversion of 1-acyl-1-carbamoyl oximes to cyanoformamides (Scheme 2). Specifically, we assumed that treatment of a 1-acyl-1-carbamoyl oxime **2** with a dichloroimidazolidinedione **1** would produce a 4,5-dioxo-imidazolinium oxime intermediate **C**, which would then be highly activated to furnish the product cyanoformamide **3** along with imidazolidinetrione[17] **4**. As a result, we advanced the 4,5-dioxo-imidazolinium cation activation strategy to the context of rapid transformation of 1-acyl-1-carbamoyl oximes to cyanoformamides via a C–C bond cleavage, offering a powerful alternative method for accessing cyanoformamides with reactivity remarkably greater than that of established protocols. Herein, we would like to report the development of such a mild and highly efficient protocol.

RESUITS AND DISCUSSION

We set out to test the possibility of 4,5-dioxo-imidazolinium-activated transformation of 2-(hydroxyimino)-3-oxo-*N*-phenylbutanamide (**2a**) as a model substrate. Our initial trial on the conversion of **2a** using 1.05 equiv of readily available DCID **1a** in acetonitrile (MeCN) at room temperature was promising (Table 1, entry 1). The target product phenylcarbamoyl cyanide (**3a)** was obtained and imidazolidinetrione **4** was also observed. We next surveyed the effect of the dichloroimidazolidinedione structure on reaction efficiency. Yield was significantly improved by switching to *N*-alkyl substituents compared to that of DCID **1a** with sterically demanding aryl groups (entries 2–4). Remarkably, *N*-cyclohexyl substituted DCID **1d** showcased superior reactivity, affording cyanoformamide **3a** in 89% yield in 30 min at room temperature (entry 4). This is rationalized probably by the greater inclination for DCID **1d** to ionize to produce the more sable 4,5-dioxo-imidazolinium carbocation, thereby facilitating the formation of the key 4,5-dioxo-imidazolinium oxime intermediate. The basis for the reactivity difference between DCID **1b** and **1d** in comparison to DCID **1c** is unknown. This favorable result demonstrates that 4,5-dioxo-imidazolinium cation activation is a strategically viable means to promote this transformation.

A screening of the solvent effect revealed that other polar aprotic or nonpolar solvents, including dichloromethane (DCM), 1,2-dichloroethane (DCE), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), and toluene, were less effective than MeCN (Table 1, entry 4 vs entries 5–10). In the cases of entries 7–10, these media could only give the target product in negligible yields (<5%), indicating that MeCN might serve as a critical and effective medium for DCID **1d** to ionize. Whereas a potential equivalent of HCl was generated in the course of the reaction, treatment of **2a** with 1.05 equiv of HCl in MeCN did not give any desired product, excluding the possibility that the activation was owing to a background reaction (entry 11). On the other hand, elevating the temperature affected little on the outcome of reaction (entries 12–14). When using 1.5 equiv of DCID **1d**, the yield increased up to 96% within 15 min (entry 16). Notably, an essentially identical high yield (95%) was achieved after 15 min using only 1.2 equiv of DCID **1d** (entry 15). For comparison, $POCl_3$ (1.5 equiv) in DCE solvent has been reported to demand 80 °C and 2 h to reach 83% product yield with this substrate.[11b] The notable advantages of our protocol, with up to 8-fold decrease in the reaction duration, ambient temperature, and a higher yield, are more desirable for sustainable and green synthesis.

Table 1. Optimization of the Reaction Conditions[a]



entry	reagent (equiv)	solvent	T (°C)	time (min)	yield (%)[b]
1	1a (1.05)	MeCN	25	30	27
2	1b (1.05)	MeCN	25	30	63
3	1c (1.05)	MeCN	25	30	75
4	1d (1.05)	MeCN	25	30	89
5	1d (1.05)	DCM	25	30	69
6	1d (1.05)	DCE	25	30	71
7	1d (1.05)	DMF	25	30	<5
8	1d (1.05)	DMSO	25	30	trace
9	1d (1.05)	THF	25	30	trace
10	1d (1.05)	toluene	25	30	<5
11[c]	HCl (1.05)	MeCN	25	30	0
12	1d (1.05)	MeCN	40	30	88
13	1d (1.05)	MeCN	60	30	89
14	1d (1.05)	MeCN	80	30	89
15	1d (1.2)	MeCN	25	15	95
16	1d (1.5)	MeCN	25	15	96

[a]Reaction conditions: **2a** (0.5 mmol), reagent, dry solvent (2.5 mL) under argon atmosphere. [b]Yield based on the substrate **2a**. [c]HCl (36–38 wt%, 1.05 equiv, 0.525 mmol) was added.

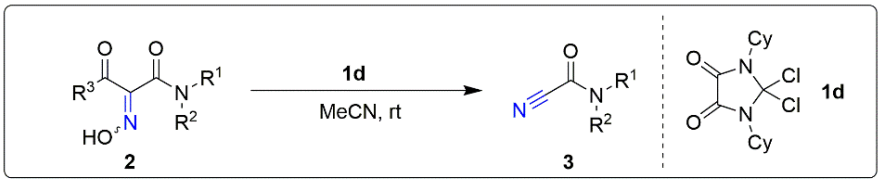
With the optimized reaction conditions in hand, the generality of this protocol was subsequently evaluated. In general, a variety of 1-acyl-1-carbamoyl oximes bearing either secondary or tertiary amide groups were converted to their corresponding cyanoformamides in a mild, rapid, and efficient fashion (Scheme 3). A gamut of functional groups, encompassing halides (**2f–2h**, and **2m**), ester (**2i**), ketone (**2j**), alkyne (**2p**), and boronic ester (**2q**), were well compatible under the mild reaction conditions (Scheme 3A). 1-Acyl-1-carbamoyl oximes **2b–2j** bearing either electron-donating (**2b–2d**) or -withdrawing (**2e–2j**) groups at the para-position of the *N*-aryl ring were accommodated, rapidly affording the desired cyanoformamides **3b–3j** in good to excellent

yields. In particular, it is noteworthy that 1-acyl-1-carbamoyl oxime **2e** bearing a strong electron-withdrawing group, namely, CF_3, produces cyanoformamide **3e** in 90% yield within 20 min at room temperature. For comparison, the reagent $POCl_3$ has been reported to require 80 °C to reach 67% yield with this substrate.[11b] The position of the substituents on the *N*-aryl ring had a minimal influence on the efficiency of this 4,5-dioxo-imidazolinium-activated transformation, as the substrates (**2l**, **2o**, and **2c**) with *ortho*-, *meta*-, or *para*-substitution furnished the corresponding cyanoformamides in comparably high yields. Also, steric hindrance did not restrain cyanoformamides formation under this protocol, with *ortho*-, di-, and tris-substituted arenes (**2l**, **2r**, and **2s**) also giving access to the desired products in high yields (92–93%) within a short time (10–30 min). Worthy of note, the presence of bromide and pinacol boronate in the cyanoformamides **3h** and **3q** are synthetically valuable, which offers a platform for late-stage elaboration of the products through cross-coupling reactions. Besides the *N*-phenyl-substituted 1-acyl-1-carbamoyl oximes, substrates bearing biphenyl, naphthyl, and indanyl groups (**2k**, **2t**, and **2u**) could similarly engage efficiently in the 4,5-dioxo-imidazolinium-activated transformation, yielding products **3k**, **3t**, and **3u** in good yields, respectively. In addition, *N*-alkyl-substituted 1-acyl-1-carbamoyl oximes **2v–2aa**, either *N*-benzyl, *N*-phenethyl, or *N*-phenylpropyl variations, also proved to be viable for the rapid and efficient assembly of **3v–3aa** by treatment of 1.5 equiv of **1d** in MeCN at room temperature. In the case of **2z** containing a thiophene core in the aliphatic chain, the resulting product **3z** was obtained in 90% yield after 15 min.

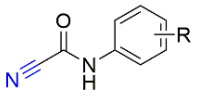
As expected, when the dioxime **2ab** was subjected to this reaction using 3 equiv of **1d**, the dicarbamoyl cyanide **3ab** was obtained in 95% yield (Scheme 3B). Furthermore, less active 1-acyl-1-carbamoyl oximes **2ac–2ae** bearing tertiary amide groups in this protocol were found to undergo efficient transformation, albeit a higher reaction temperature was entailed in these cases (Scheme 3C). Other than methyl, additional variations in the R^3 moiety of the 1-acyl-1-carbamoyl oximes, such as ethyl (**2ah)**, isopropyl (**2ai**), and phenyl (**2aj**), were surveyed (Scheme 3D). Whereas 1-acyl-1-carbamoyl oximes **2ah** and **2ai** afforded **3a** in similar high yields within a short time, substrate **2aj** furnished **3a** in only 33% yield. We hypothesize that this relatively poor result may be due to the larger conjugated system of **2aj**, which would make itself more stable and thus weaken its ability to form the key 4,5-dioxo-imidazolinium oxime intermediate.

Scheme 3. Substrate Scope Studies for Cyanoformamides Formation via 4,5-Dioxo-imidazolinium

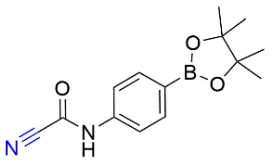
Cation Activation[a]



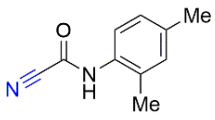
A R^3 = Me



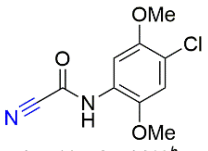
3a, R = 4-H (15 min, 95%)
3b, R = 4-Me (10 min, 96%)
3c, R = 4-MeO (10 min, 92%)
3d, R = 4-^{t}Bu (40 min, 93%)[b,c]
3e, R = 4-CF_3 (20 min, 90%)
3f, R = 4-F (30 min, 81%)
3g, R = 4-Cl (30 min, 93%)
3h, R = 4-Br (15 min, 96%)[b]
3i, R = 4-CO_2Et (10 min, 95%)[b]
3j, R = 4-C(O)Me (10 min, 90%)[b]
3k, R = 4-Ph (60 min, 81%)[b,c]
3l, R = 2-MeO (30 min, 93%)
3m, R = 3-Cl (10 min, 93%)
3n, R = 3-Et (15 min, 84%)
3o, R = 3-MeO (10 min, 94%)
3p, R = 3-alkynyl (15 min, 93%)



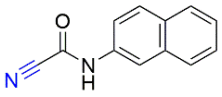
3q, 20 min, 80%



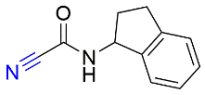
3r, 15 min, 92%



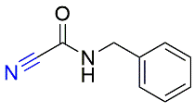
3s, 10 min, 92%[b]



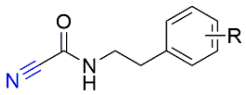
3t, 10 min, 91%[b]



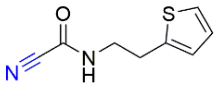
3u, 15 min, 89%



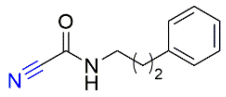
3v, 10 min, 89%[b]



3w, R = 4-F (15 min, 92%)[b]
3x, R = 4-Me (15 min, 93%)[b]
3y, R = 3,4-$(MeO)_2$ (15 min, 92%)[b]

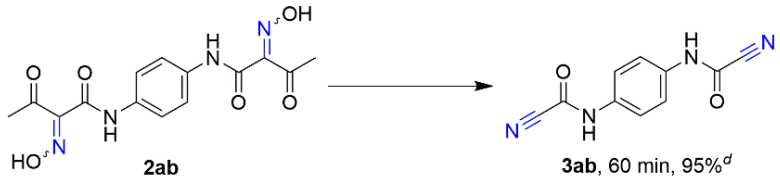


3z, 15 min, 90%[b]



3aa, 30 min, 88%[b]

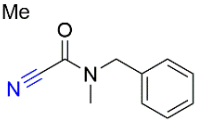
B



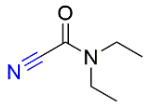
2ab

3ab, 60 min, 95%[d]

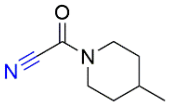
C R^3 = Me



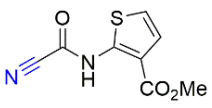
3ac, 30 min, 90%[e]



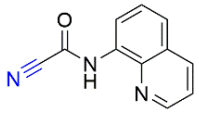
3ad, 30 min, 83%[e]



3ae, 30 min, 77%[e]

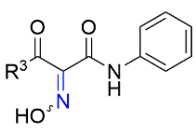


3af, 10 min, 87%[e]



3ag, trace

D



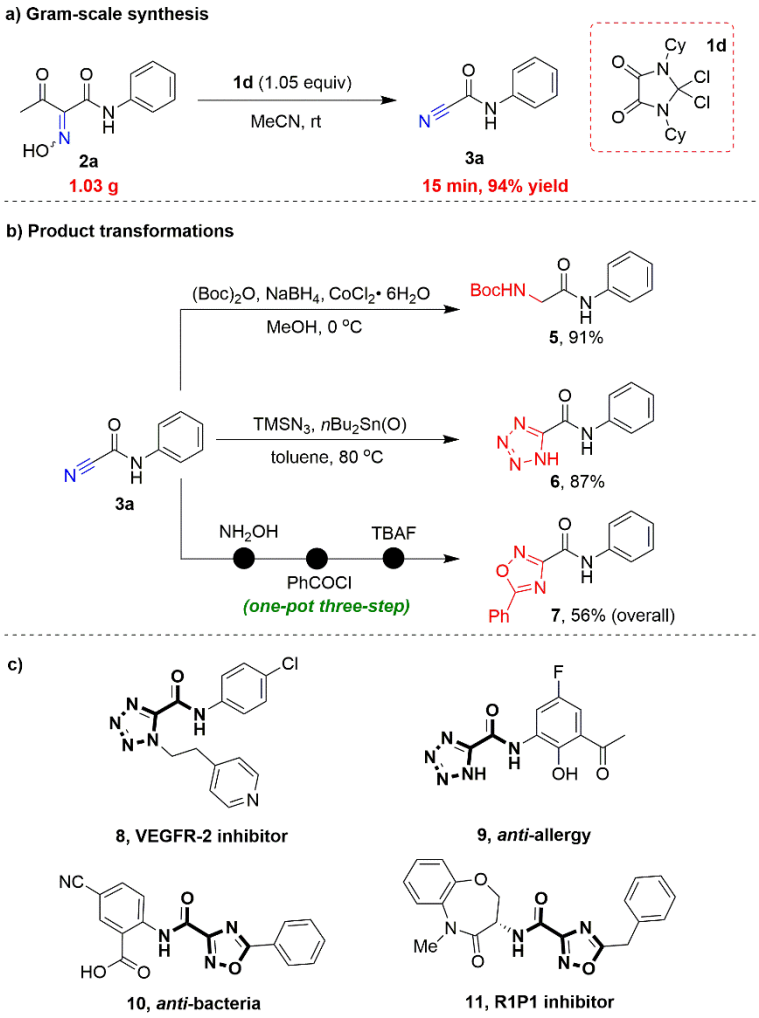
2ah, R^3 = Et
2ai, R^3 = ^{i}Pr
2aj, R^3 = Ph

3a, 15 min, 94%[b]
3a, 30 min, 93%[b]
3a, 30 min, 33%[b]

[a]Reaction conditions: substrate **2** (0.5 mmol), **1d** (1.2 equiv), and dry MeCN (2.5 mL) at 25 °C under Ar atmosphere. Yields based on **2** are given. [b]**1d** (1.5 equiv) was used. [c]Dry DCM (2.5 mL) was used as the solvent. [d]With 3 equiv of **1d** in dry MeCN (5.0 mL) for **2ab**. [e]Reaction performed at 80 °C with 1.2 equiv of **1d** in dry MeCN (2.5 mL).

The synthesis of 1-acyl-1-carbamoyl oximes bearing primary amide groups could not be achieved.[18] The corresponding product ($NCCONH_2$) was reported to be rather unstable at room temperature and atmospheric pressure.[3] *N*-heteroaryl-substituted 1-acyl-1-carbamoyl oximes **2af** and **2ag** were also investigated (Scheme 3C). Although 1-acyl-1-carbamoyl oxime **2af** bearing a thiophene core reacted efficiently at elevated temperature, substrate **2ag** with a basic quinoline ring was not compatible in this protocol.

Scheme 4. Scalability and Synthetic Applications[a]



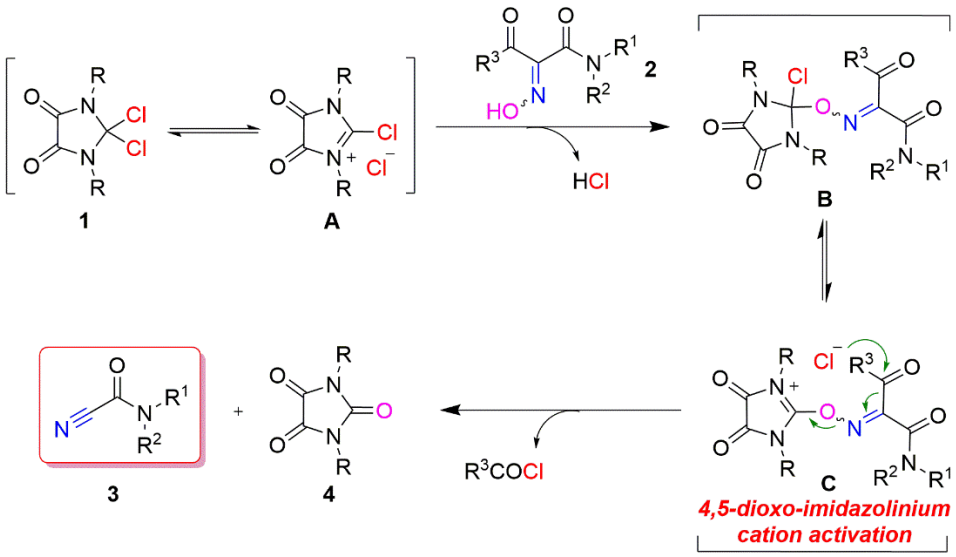
[a]See EXPERIMENTAL SECTION for detailed reaction conditions. TBAF=tetrabutylammonium fluoride.

To demonstrate the application potential of this method, the conversion of **1a** was performed on a one gram scale (Scheme 4a). An excellent product yield (94% yield) and a high efficiency (15 min) were still achieved. On the other hand, the thus obtained cyanoformamide product **3a** could

be further transformed into valuable building blocks (Scheme 4b). Treatment of **3a** with $(Boc)_2O$ in a $NaBH_4$–$CoCl_2{\cdot}6H_2O$ reductive system readily afforded *N*-Boc carbamate **5** in 91% yield.[19] Tetrazole-5-carboxamide **6** could be generated in 87% yield via dibutyltin oxide-mediated [3 + 2] cycloaddition of cyanoformamide **3a** with trimethylsilyl azide.[20] In addition, cyanoformamide **3a** was easily converted to 1,2,4-oxadiazole derivative **7** (56% overall yield) via a tandem process of amidoximation by hydroxylamine, acylation with benzoyl chloride, and cyclization with tetrabutylammonium fluoride (TBAF) in a facile one-pot procedure. It is important to note that the tetrazole skeleton **6** and 1,2,4-oxadiazole skeleton **7** are privileged motifs for a portfolio of biologically active compounds, such as VEGFR-2 receptor inhibitor (**8**),[21] anti-allergy compound (**9**),[2a] antibacterial compound (**10**),[22] and R1P1 kinase inhibitor (**11**)[23] (Scheme 4c).

Based on the above experimental results and our previous work,[12] a tentative mechanism for 4,5-dioxo-imidazolinium-promoted reaction of **2** is depicted in Scheme 5. DCID **1** may exist in equilibrium with 4,5-dioxo-imidazolinium chloride salt **A**,[16a] resulting in a rapid combination with oxime substrate **2** to afford intermediate **B**. Subsequently, the neutral intermediate **B** re-ionizes via dissociation of the second chlorine atom, giving the 4,5-dioxo-imidazolinium cation activated intermediate **C**. Finally, concomitant $C(sp^2)$-$C(sp^2)$ bond and N-O bond cleavages of intermediate **C**, enabled by the attack of a chloride ion on the C=O double bond of intermediate **C**,[11b] could furnish the cyanoformamide product **3** along with the imidazolidinetrione **4**. Compound **4** was isolated and characterized by NMR and HRMS. The formation of the acid chloride was also verified experimentally (See EXPERIMENTAL SECTION for details).[24]

Scheme 5. Tentative Mechanism for 4,5-Dioxo-imidazolinium-Activated Reaction of **2**



CONCLUSION

In conclusion, we have demonstrated the effectiveness of 4,5-dioxo-imidazolinium cation activation for converting an array of 1-acyl-1-carbamoyl oximes to cyanoformamides under very mild reaction conditions. Based on the readily accessible, electronically and sterically tunable DCIDs, this novel protocol of activation offers reactivity that far surpasses other reported methods, exhibits a broad functional group compatibility, and could be scaled up easily. This work not only provides a highly efficient alternative approach to assembling cyanoformamides, but also enriches and diversifies the dichloroimidazolidinedione-mediated chemistry that includes the C–C bond cleavage reaction.

EXPERIMENTAL SECTION

General Information. Reactions, unless otherwise noted, were performed with magnetic stirring in oven-dried glassware. All reagents were used as received without being further purified. Reaction solvents were distilled according to standard laboratory methods prior to use. Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel plates (HSGF 254) and visualized under UV irradiation (254 nm). Flash column chromatography was performed using silica gel (200–300 mesh).

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance 400 and 100 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peak (^{1}H δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-d_6; ^{13}C δ 77.16 for $CDCl_3$, δ 39.52 for DMSO-d_6). The following abbreviations were used to explain NMR peak multiplicities: brs = broad signal, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, and m = multiplet. High-resolution mass spectra (HRMS) were obtained on an Agilent Technologies 6520 Q-TOF LC/MS mass spectrometer with an electron spray ionization (ESI) probe or an Agilent Technologies 7250 GC/Q-TOF mass spectrometer with an electron impact ionization (EI) probe. Melting points were measured using a capillary melting point apparatus (Shanghai Precision & Scientific Instrument Co., LTD) in degrees Celsius (°C).

The starting material 1-acyl-1-carbamoyl oximes **2a**–**2aj** were prepared according to the reported procedures[18] on a 8 mmol scale. Dichloroimidazolidinediones **1a**–**1d** were prepared according to our previous work.[12]

New Starting Materials. *N-([1,1'-Biphenyl]-4-yl)-2-(hydroxyimino)-3-oxobutanamide* ***(2k)***. A yellow solid, 1.81 g, 80% yield. R_f = 0.47 (petroleum ether (PE)/ethyl acetate (EA), 2:1); mp 179.1−180.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 10.48 (s, 1H), 7.70−7.64 (m, 6H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.35−7.32 (m, 1H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.5, 160.0, 153.3, 139.6, 137.7, 135.5, 128.9, 127.2, 127.1, 126.3, 119.5, 25.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{14}N_2O_3Na$ 305.0897, found 305.0890.

2-(Hydroxyimino)-3-oxo-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanamide ***(2q)***. A colorless solid, 2.07 g, 78% yield. R_f = 0.46 (PE/EA, 2:1); mp 149.1−150.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (brs, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 2.58 (s, 3H), 1.35 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.3, 161.6, 143.6, 138.1, 136.0, 120.5, 84.1, 26.6, 25.0 (The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{21}BN_2O_5Na$ 355.1444, found 355.1446.

*N-(2,3-Dihydro-1H-inden-1-yl)-2-(hydroxyimino)-3-oxobutanamide (****2u****)*. A colorless solid, 1.64 g, 83% yield. R_f = 0.48 (PE/EA, 3:1); mp 134.2−135.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (brs, 1H), 7.23−7.14 (m, 4H), 5.44 (q, *J* = 7.6 Hz, 1H), 3.03−2.96 (m, 1H), 2.90−2.82 (m, 1H), 2.61−2.53 (m, 1H), 2.43 (s, 3H), 1.92−1.83 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.6, 163.5, 143.6, 143.4, 141.6, 128.6, 127.2, 125.1, 124.2, 54.3, 33.5, 30.5, 26.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{14}N_2O_3Na$ 269.0897, found 269.0901.

*2-(Hydroxyimino)-3-oxo-N-(2-(thiophen-2-yl)ethyl)butanamide (****2z****)*. A pale yellow solid, 1.52 g, 79% yield. R_f = 0.42 (PE/EA, 4:1); mp 69.0−71.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (brs, 1H), 7.19 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.89−6.88 (m, 1H), 3.67−3.62 (m, 2H), 3.12 (t, *J* = 6.8 Hz, 2H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.6, 163.8, 143.5, 140.2, 127.3, 125.8, 124.5, 40.4, 29.3, 26.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{10}H_{12}N_2O_3SNa$ 263.0461, found 263.0469.

*2-(Hydroxyimino)-3-oxo-N-(3-phenylpropyl)butanamide (****2aa****)*. A colorless solid, 1.25 g, 83% yield. R_f = 0.53 (PE/EA, 4:1); mp 124.0−124.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 8.27 (t, *J* = 5.4 Hz, 1H), 7.30−7.26 (m, 2H), 7.21−7.15 (m, 3H), 3.13 (q, *J* = 6.6 Hz, 2H), 2.62−2.59 (m, 2H), 2.31 (s, 3H), 1.74−1.67 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.4, 161.2, 154.0, 141.8, 128.4, 128.3, 125.7, 37.7, 32.2, 30.9, 25.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}N_2O_3Na$ 271.1053, found 271.1056.

*N,N'-(1,4-Phenylene)bis(2-(hydroxyimino)-3-oxobutanamide) (**2ab**)*. A yellow solid, 2.01 g, 75% yield. R_f = 0.45 (PE/EA, 1:2); mp 192.3−193.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 2H), 10.34 (s, 2H), 7.55 (s, 4H), 2.36 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.5, 159.7, 153.3, 134.2, 119.6, 25.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{14}N_4O_6Na$ 357.0806, found 357.0815.

*Methyl 2-(2-(Hydroxyimino)-3-oxobutanamido)thiophene-3-carboxylate (**2af**)*. A yellow solid, 1.10 g, 51% yield. R_f = 0.40 (DCM); mp 152.1−153.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.39 (brs, 1H), 7.33 (d, *J* = 5.7 Hz, 1H), 6.95 (d, *J* = 5.7 Hz, 1H), 3.98 (s, 3H), 2.59 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.7, 164.6, 159.3, 143.6, 142.8, 125.3, 119.4, 117.3, 52.4, 26.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{10}H_{10}N_2O_5SNa$ 293.0203, found 293.0209.

*2-(Hydroxyimino)-3-oxo-N-(quinolin-8-yl)butanamide (**2ag**)*. A light yellow solid, 0.86 g, 42% yield. R_f = 0.45 (DCM); mp 161.4−162.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.76 (brs, 1H), 8.92−8.91 (m, 1H), 8.62 (d, *J* = 7.6 Hz, 1H), 8.11−8.09 (m, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.48−7.41 (m, 2H), 2.54 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.3, 161.6, 149.6, 144.1, 139.6, 136.4, 133.1, 128.2, 127.0, 124.4, 122.1, 119.4, 26.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{12}N_3O_3$ 258.0873, found 258.0877.

*2-(Hydroxyimino)-3-oxo-N-phenylpentanamide (**2ah**)*. A colorless solid, 1.43 g, 81% yield. R_f = 0.50 (PE/EA, 3:1); mp 81.1−81.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.06 (brs, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 3.04 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.0, 161.6, 143.0, 135.6, 129.4, 126.4, 121.5, 31.7, 8.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{11}H_{12}N_2O_3Na$ 243.0740, found 243.0738.

*2-(Hydroxyimino)-4-methyl-3-oxo-N-phenylpentanamide (**2ai**)*. A colorless solid, 1.61 g, 86% yield. R_f = 0.59 (PE/EA, 3:1); mp 97.4−99.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (brs, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 3.84 (sept, *J* = 6.9 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 206.5, 161.9, 141.8, 135.5, 129.4, 126.3, 121.5, 35.2, 19.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{12}H_{14}N_2O_3Na$ 257.0897, found 257.0915.

*2-(Hydroxyimino)-3-oxo-N,3-diphenylpropanamide (**2aj**)*. A colorless solid, 1.70 g, 79% yield. R_f = 0.60 (PE/EA, 1:1); mp 179.2−180.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (brs, 1H), 10.36 (brs, 1H), 7.86 (d, *J* = 7.9 Hz, 2H), 7.75−7.76 (m, 3H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H); ^{13}C{^{1}H} (100 MHz, DMSO-d_6) δ 192.3, 160.0, 150.8, 137.9, 134.7, 134.4, 129.3, 128.74, 128.73, 124.3, 120.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{12}N_2O_3Na$ 291.0740, found 291.0741.

General Procedure for the Synthesis of Cyanoformamides 3. The substrates **2a**–**2ah** (0.5 mmol, 1.0 equiv), DCID **1d** (200.0 mg, 0.6 mmol, 1.2 equiv), and anhydrous MeCN (2.5 mL) were continuously added to a flame-dried Schlenk tube under an argon atmosphere. Then the reaction mixture was stirred at 25 °C for 10 to 60 min, depending on the substrate. Upon completion of the reaction (monitored by TLC), the organic solvent was evaporated under reduced pressure, and the residue was purified via flash column chromatography to furnish the desired products **3a**–**3af**.

*Phenylcarbamoyl Cyanide (**3a**)*.[11b] The compound was prepared from **2a** (103.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 40:1 to 20:1) furnished **3a** (69.4 mg, 95% yield) as a colorless solid: R_f = 0.54 (PE/EA, 3:1); mp 124.5–125.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (brs, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.24–7.19 (m, 1H); ^{13}C{^{1}H} (100 MHz, DMSO-d_6) δ 140.7, 136.7, 129.3, 125.8, 120.3, 112.5.

*4-Tolylcarbamoyl Cyanide (**3b**)*.[11b] The compound was prepared from **2b** (110.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 40:1 to 20:1) furnished **3b** (76.9 mg, 96% yield) as a colorless solid: R_f = 0.55 (PE/EA, 3:1); mp 179.6–180.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (brs, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} (100 MHz, DMSO-d_6) δ 140.5, 135.1, 134.3, 129.6, 120.2, 112.6, 20.6.

*(4-Methoxyphenyl)carbamoyl Cyanide **(3c)**.*[11b] The compound was prepared from **2c** (118.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 40:1 to 20:1) furnished **3c** (81.0 mg, 92% yield) as a colorless solid: R_f = 0.51 (PE/EA, 3:1); mp 146.1–147.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (brs, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 3.74 (s, 3H); ^{13}C{^{1}H} (100 MHz, DMSO-d_6) δ 156.9, 140.3, 129.7, 121.8, 114.3, 112.7, 55.3.

*(4-(tert-Butyl)phenyl)carbamoyl Cyanide **(3d)***. The compound was prepared from **2d** (131.2 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol) in anhydrous DCM (2.5 mL). The reaction time was 40 min. Purification by flash column chromatography (PE/EA, 40:1 to 20:1) furnished **3d** (94.0 mg, 93% yield) as a colorless solid: R_f = 0.56 (PE/EA, 5:1); mp 138.1–140.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (brs, 1H), 7.44–7.39 (m, 4H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.2, 140.4, 132.8,

126.5, 120.3, 111.9, 34.8, 31.4.

*(4-(Trifluoromethyl)phenyl)carbamoyl Cyanide (**3e**)*.[11b] The compound was prepared from **2e** (137.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 20 min. Purification by flash column chromatography (PE/EA, 40:1 to 15:1) furnished **3e** (96.4 mg, 90% yield) as a colorless solid: R_f = 0.57 (PE/EA, 3:1); mp 125.8−127.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.69−7.64 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.5, 138.3, 128.9 (q, $^2J_{CF}$ = 33.2 Hz), 127.0 (q, $^3J_{CF}$ = 3.7 Hz), 123.7 (q, $^1J_{CF}$ = 270.4 Hz), 120.4, 111.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.5.

*(4-Fluorophenyl)carbamoyl Cyanide (**3f**)*. The compound was prepared from **2f** (142.6 mg, 0.5 mmol) by following the general procedure. The reaction time was 30 min. Purification by flash column chromatography (PE/EA, 30:1 to 15:1) furnished **3f** (66.5 mg, 81% yield) as a colorless solid: R_f = 0.41 (PE/EA, 3:1); mp 117.4−119.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (brs, 1H), 7.51−7.48 (m, 2H), 7.13−7.07 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8 (d, $^1J_{CF}$ = 246.3 Hz), 140.5, 131.4 (d, $^4J_{CF}$ = 3.4 Hz), 122.5 (d, $^3J_{CF}$ = 8.1 Hz), 116.5 (d, $^2J_{CF}$ = 22.9 Hz), 111.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.6.

*(4-Chlorophenyl)carbamoyl Cyanide (**3g**)*.[11b] The compound was prepared from **2g** (120.3 mg, 0.5 mmol) by following the general procedure. The reaction time was 30 min. Purification by flash column chromatography (PE/EA, 30:1 to 20:1) furnished **3g** (84.0 mg, 93% yield) as a colorless solid: R_f = 0.39 (PE/EA, 3:1); mp 238.2−239.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (brs, 1H), 7.59 (d, *J* = 8.9 Hz, 2H), 7.47 (d, *J* = 8.9 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 140.8, 135.6, 129.5, 129.2, 121.9, 112.4.

*(4-Bromophenyl)carbamoyl Cyanide (**3h**)*. The compound was prepared from **2h** (142.6 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 30:1 to 20:1) furnished **3h** (108.0 mg, 96% yield) as a light yellow solid: R_f = 0.66 (PE/EA, 3:1); mp 265.4−267.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (brs, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 140.7, 136.0, 132.1, 122.2, 117.7, 112.3.

*Ethyl 4-((Cyanocarbonyl)amino)benzoate (**3i**)*. The compound was prepared from **2i** (139.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed

using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 30:1 to 15:1) furnished **3i** (103.7 mg, 95% yield) as a colorless solid: R_f = 0.45 (PE/EA, 3:1); mp 212.8−213.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (brs, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.0, 141.0, 140.8, 130.4, 126.6, 119.9, 112.3, 60.8, 14.2.

*(4-Acetylphenyl)carbamoyl Cyanide (**3j**)*. The compound was prepared from **2j** (124.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 40:1 to 10:1) furnished **3j** (84.7 mg, 90% yield) as a yellow solid: R_f = 0.50 (PE/EA, 2:1); mp 180.1−181.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (brs, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 2.55 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 196.6, 141.0, 140.7, 133.7, 129.6, 119.8, 112.3, 26.5.

*[1,1'-Biphenyl]-4-ylcarbamoyl Cyanide (**3k**)*. The compound was prepared from **2k** (141.2 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol) in anhydrous DCM (2.5 mL). The reaction time was 60 min. Purification by flash column chromatography (PE/EA, 30:1 to 20:1) furnished **3k** (70.0 mg, 63% yield) as a colorless solid: R_f = 0.54 (PE/EA, 3:1); mp 266.3−269.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (brs, 1H), 7.73−7.71 (m, 2H), 7.67−7.65 (m, 4H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.38−7.34 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 140.6, 139.2, 137.4, 136.0, 129.0, 127.5, 127.3, 126.5, 120.7, 112.5.

*(2-Methoxyphenyl)carbamoyl Cyanide (**3l**)*.[11b] The compound was prepared from **2l** (118.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 30 min. Purification by flash column chromatography (PE/EA, 30:1 to 15:1) furnished **3l** (81.9 mg, 93% yield) as a colorless solid: R_f = 0.50 (PE/EA, 3:1); mp 112.1−114.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (brs, 1H), 8.18 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.21−7.17 (m, 1H), 7.01−6.97 (m, 1H), 6.95−6.93 (m, 1H), 3.94 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.0, 140.0, 126.7, 125.4, 121.4, 120.9, 111.9, 110.4, 56.0.

*(3-Chlorophenyl)carbamoyl Cyanide (**3m**)*. The compound was prepared from **2m** (120.3 mg, 0.5 mmol) by following the general procedure. The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 40:1 to 25:1) furnished **3m** (84.0 mg, 93% yield) as a colorless solid: R_f = 0.59 (PE/EA, 3:1); mp 118.5−120.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (brs, 1H), 7.69 (t, *J* = 1.8 Hz, 1H), 7.49−7.42 (m, 2H), 7.29 (dt, *J* = 7.4, 1.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz,

DMSO-d_6) δ 140.9, 138.0, 133.4, 131.0, 125.6, 119.9, 118.8, 112.3.

*(3-Ethylphenyl)carbamoyl Cyanide (**3n**)*. The compound was prepared from **2n** (117.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 40:1 to 25:1) furnished **3n** (73.2 mg, 84% yield) as a colorless solid: R_f = 0.53 (PE/EA, 5:1); mp 107.9−110.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (brs, 1H), 7.34−7.28 (m, 3H), 7.11−7.08 (m, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.1, 140.4, 135.5, 129.5, 126.5, 120.0, 117.9, 111.9, 28.9, 15.5; HRMS (EI-TOF) m/z [M − HCN]$^+$ calcd for C_9H_9NO 147.0679, found 147.0679.

*(3-Methoxyphenyl)carbamoyl cyanide (**3o**)*. The compound was prepared from **2o** (118.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 30:1 to 15:1) furnished **3o** (82.8 mg, 94% yield) as a colorless solid: R_f = 0.46 (PE/EA, 3:1); mp 94.5−96.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (brs, 1H), 7.24–7.22 (m, 1H), 7.14 (t, *J* = 2.4 Hz, 1H), 6.98−6.95 (m, 1H), 6.77−6.74 (m, 1H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.2, 139.3, 135.4, 129.2, 111.45, 111.40, 110.6, 105.4, 54.4.

*(3-Ethynylphenyl)carbamoyl Cyanide (**3p**)*. The compound was prepared from **2p** (115.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 40:1 to 20:1) furnished **3p** (80.1 mg, 93% yield) as a colorless solid: R_f = 0.53 (PE/EA, 3:1); mp 261.2−263.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (brs, 1H), 7.64−7.63 (m, 1H), 7.52−7.49 (m, 1H), 7.38−7.35 (m, 2H), 3.13 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.5, 135.5, 130.5, 129.7, 123.9, 123.7, 120.9, 111.6, 82.4, 78.8; HRMS (EI-TOF) m/z [M − HCN]$^+$ calcd for C_9H_5NO 143.0366, found 143.0363.

*(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl Cyanide (**3q**)*. The compound was prepared from **2q** (166.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 20 min. Purification by flash column chromatography (PE/EA, 40:1 to 20:1) furnished **3q** (108.8 mg, 80% yield) as a colorless solid: R_f = 0.47 (PE/EA, 4:1); mp 167.4−168.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (brs, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 1.34 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.3, 137.9, 136.2, 119.4, 111.7, 84.2, 25.0 (The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.); HRMS (EI-TOF) m/z [M − HCN]$^+$ calcd for $C_{13}H_{16}BNO_3$ 245.1218, found 245.1217.

*(2,4-Dimethylphenyl)carbamoyl Cyanide (**3r**)*.[11b] The compound was prepared from **2r** (117.1 mg,

0.5 mmol) by following the general procedure. The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 50:1 to 30:1) furnished **3r** (80.1 mg, 92% yield) as a colorless solid: R_f = 0.63 (PE/EA, 5:1); mp 86.3−88.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24 (brs, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 2.26 (s, 3H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 141.7, 136.7, 132.4, 131.3, 130.7, 126.9, 125.4, 112.7, 20.6, 17.6.

*(4-Chloro-2,5-dimethoxyphenyl)carbamoyl Cyanide (**3s**)*.[11b] The compound was prepared from **2s** (150.4 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 40:1 to 20:1) furnished **3s** (110.7 mg, 92% yield) as a colorless solid: R_f = 0.49 (PE/EA, 3:1); mp 142.7−144.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (brs, 1H), 7.95 (s, 1H), 6.97 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.3, 142.1, 139.9, 124.5, 119.3, 112.9, 111.6, 105.6, 57.0, 56.7.

*Naphthalen-2-ylcarbamoyl Cyanide (**3t**)*. The compound was prepared from **2t** (128.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 40:1 to 25:1) furnished **3t** (89.3 mg, 91% yield) as a light yellow solid: R_f = 0.58 (PE/EA, 3:1); mp 248.1−250.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (brs, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 7.97−7.90 (m, 3H), 7.59 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.55−7.48 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 140.8, 134.2, 132.9, 130.8, 129.0, 127.7, 127.6, 126.9, 125.9, 119.7, 117.5, 112.5.

*(2,3-Dihydro-1H-inden-1-yl)carbamoyl Cyanide (**3u**)*. The compound was prepared from **2u** (123.1 mg, 0.5 mmol) by following the general procedure. The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 40:1 to 25:1) furnished **3u** (82.9 mg, 89% yield) as a colorless solid: R_f = 0.50 (PE/EA, 6:1); mp 115.3−117.0 °C. A rotamerization of **3u** was observed in NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 7.22−7.13 (m, 4H), 6.51 (brs, 1H), 5.38−5.33 (m, 1H), 2.99−2.91 (m, 1H), 2.86−2.78 (m, 1H), 2.55−2.47 (m, 1H), 1.88−1.79 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) (major rotamer) δ 143.6, 142.9, 140.5, 129.1, 127.3, 125.3, 124.3, 111.6, 56.1, 33.3, 30.3; HRMS (EI-TOF) m/z [M − HCN]$^+$ calcd for $C_{10}H_9NO$ 159.0679, found 159.0676.

*Benzylcarbamoyl Cyanide (**3v**)*.[11b] The compound was prepared from **2v** (110.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5

equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 40:1 to 15:1) furnished **3v** (71.3 mg, 89% yield) as a colorless solid: R_f = 0.48 (PE/EA, 3:1)); mp 70.4−71.0 °C. A rotamerization of **3v** was observed in NMR spectra (19:1 mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 7.39−7.36 (m, 3H), 7.30−7.27 (m, 2H), 6.49 (brs, 1H), 4.51 (d, *J* = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (major rotamer) δ 143.1, 135.2, 129.3, 128.7, 128.2, 111.5, 44.6.

*(4-Fluorophenethyl)carbamoyl Cyanide (**3w**)*. The compound was prepared from **2w** (126.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 40:1 to 15:1) furnished **3w** (88.4 mg, 92% yield) as a colorless oil: R_f = 0.48 (PE/EA, 3:1). A rotamerization of **3w** was observed in NMR spectra (19:1 mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 7.17−7.13 (m, 2H), 7.03−6.99 (m, 2H), 6.90 (brs, 1H), 3.56 (q, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (major rotamer) δ 162.0 (d, $^1J_{CF}$ = 243.4 Hz) , 143.4, 133.1 (d, $^4J_{CF}$ = 3.0 Hz), 130.3 (d, $^3J_{CF}$ = 7.9 Hz), 115.8 (d, $^2J_{CF}$ = 20.9 Hz), 111.6, 41.7, 34.0; ^{19}F NMR (376 MHz, $CDCl_3$) (major rotamer) δ −115.6.

*(4-Methylphenethyl)carbamoyl Cyanide (**3x**)*. The compound was prepared from **2x** (124.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 30:1 to 10:1) furnished **3x** (87.5 mg, 93% yield) as a colorless oil: R_f = 0.61 (PE/EA, 3:1). A rotamerization of **3x** was observed in NMR spectra (19:1 mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 7.16 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.36 (brs, 1H), 3.59 (q, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (major rotamer) δ 143.2, 136.9, 134.1, 129.8, 128.6, 111.6, 41.7, 34.4, 21.1.

*(3,4-Dimethoxyphenethyl)carbamoyl Cyanide (**3y**)*.[11a] The compound was prepared from **2y** (147.2 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 40:1 to 15:1) furnished **3y** (107.8 mg, 92% yield) as a colorless solid: R_f = 0.63 (PE/EA, 1:1); mp 87.2−89.0 °C. A rotamerization of **3y** was observed in NMR spectra (19:1 mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 6.84 (d, *J* = 8.0 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.68 (d, *J* = 2.1 Hz, 1H), 6.19 (brs, 1H), 3.879 (s, 3H), 3.875 (s, 3H),

3.60 (q, *J* = 6.8 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (major rotamer) δ 149.3, 148.2, 143.3, 129.9, 120.8, 111.9, 111.8, 111.6, 56.1, 56.0, 41.7, 34.4.

*(2-(Thiophen-2-yl)ethyl)carbamoyl Cyanide (**3z**)*. The compound was prepared from **2z** (120.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 15 min. Purification by flash column chromatography (PE/EA, 40:1 to 10:1) furnished **3z** (81.1 mg, 90% yield) as a colorless oil: R_f = 0.42 (PE/EA, 4:1). A rotamerization of **3z** was observed in NMR spectra (19:1 mixture of rotamers). ^1H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 7.21 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.99−6.97 (m, 1H), 6.88−6.87 (m, 1H), 6.54 (brs, 1H), 3.63 (q, *J* = 6.4 Hz, 2H), 3.10 (t, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (major rotamer) δ 143.3, 139.5, 127.5, 126.1, 124.8, 111.5, 41.8, 29.1; HRMS (EI-TOF) m/z $[M - HCN]^+$ calcd for C_7H_7NOS 153.0243, found 153.0246.

*(3-Phenylpropyl)carbamoyl Cyanide (**3aa**)*. The compound was prepared from **2aa** (124.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 1.5 equiv of **1d** (249.9 mg, 0.75 mmol). The reaction time was 30 min. Purification by flash column chromatography (PE/EA, 40:1 to 10:1) furnished **3aa** (82.8 mg, 88% yield) as a colorless oil: R_f = 0.53 (PE/EA, 4:1). A rotamerization of **3aa** was observed in NMR spectra (19:1 mixture of rotamers). ^1H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 7.24−7.21 (m, 2H), 7.17−7.08 (m, 2H), 6.53 (brs, 1H), 3.27 (q, *J* = 6.9 Hz, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.82 (p, *J* = 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (major rotamer) δ 143.3, 140.5, 128.8, 128.4, 126.5, 111.7, 40.3, 33.0, 30.2; HRMS (EI-TOF) m/z $[M - HCN]^+$ calcd for $C_{10}H_{11}NO$ 161.0835, found 161.0835.

*1,4-Phenylenedicarbamoyl Cyanide (**3ab**)*. The compound was prepared from **2ab** (167.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed using 3 equiv of **1d** (499.9 mg, 1.5 mmol) in dry MeCN (5.0 mL). The reaction time was 60 min. Purification by flash column chromatography (PE/EA, 30:1 to 5:1) furnished **3t** (101.7 mg, 95% yield) as a yellow solid: R_f = 0.58 (PE/EA, 1:1); mp >280 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 2H), 7.60 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 140.6, 134.0, 121.0, 112.4; HRMS (EI-TOF) m/z $[M - H_2C_2N_2]^+$ calcd for $C_8H_4N_2O_2$ 160.0267, found 160.0268.

*Benzyl(methyl)carbamoyl Cyanide (**3ac**)*.[11f] The compound was prepared from **2ac** (117.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed at 80 °C. The reaction time was 30 min. Purification by flash column chromatography (PE/EA, 40:1 to

20:1) furnished **3ac** (78.4 mg, 90% yield) as a colorless oil: R_f = 0.49 (PE/EA, 5:1). A rotamerization of **3ac** was observed in NMR spectra (1:1 mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.33 (m, 1H), 7.33−7.31 (m, 2H), 7.30−7.27 (m, 3H), 7.20−7.16 (m, 4H), 4.69 (s, 2H), 4.52 (s, 2H), 3.10 (s, 3H), 2.84 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.3, 144.9, 134.3, 133.9, 129.4, 129.2, 128.9, 128.60, 128.57, 127.7, 110.9, 110.6, 54.8, 50.5, 35.5, 32.3.

*Diethylcarbamoyl Cyanide (**3ad**)*.[11b] The compound was prepared from **2ad** (93.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed at 80 °C. The reaction time was 30 min. Purification by flash column chromatography (PE/EA, 40:1) furnished **3ad** (52.4 mg, 83% yield) as a colorless oil: R_f = 0.53 (PE/EA, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (q, *J* = 7.2 Hz, 2H), 3.44 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.4, 110.9, 43.8, 40.1, 14.6, 12.5.

*4-Methylpiperidine-1-carbonyl Cyanide (**3ae**)*.[11f] The compound was prepared from **2ae** (106.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed at 80 °C. The reaction time was 30 min. Purification by flash column chromatography (PE/EA, 40:1 to 30:1) furnished **3ae** (58.6 mg, 77% yield) as a colorless oil: R_f = 0.48 (PE/EA, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35−4.41 (m, 1H), 4.20−4.15 (m, 1H), 3.21 (td, *J* = 13.1, 3.0 Hz, 1H), 2.75 (td, *J* = 12.9, 3.1 Hz, 1H), 1.85−1.62 (m, 3H), 1.26−1.07 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.2, 110.6, 47.6, 42.5, 34.3, 33.1, 30.8, 21.4.

*Methyl 2-((Cyanocarbonyl)amino)thiophene-3-carboxylate (**3af**)*. The compound was prepared from **2af** (135.1 mg, 0.5 mmol) by following the general procedure with the following exception: the reaction performed at 80 °C. The reaction time was 10 min. Purification by flash column chromatography (PE/EA, 50:1 to 40:1) furnished **3af** (91.4 mg, 87% yield) as a colorless solid: R_f = 0.45 (PE/EA, 5:1); mp 111.2−112.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.76 (brs, 1H), 7.28 (d, *J* = 5.7 Hz, 1H), 6.96 (d, *J* = 5.7 Hz, 1H), 3.94 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 145.1, 139.1, 124.5, 119.2, 116.0, 110.9, 52.6; HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_8H_6N_2O_3S$ 210.0094, found 210.0092.

*1,3-Dicyclohexylimidazolidine-2,4,5-trione (**4**)*.[16a] A colorless solid. R_f = 0.41 (PE/EA, 10:1); mp 176.0−176.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (tt, *J* = 12.4, 3.9 Hz, 2H), 2.11−2.01 (m, 4H), 1.87−1.84 (m, 4H), 1.75−1.66 (m, 6H), 1.38−1.17 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.6, 153.6, 52.6, 29.7, 25.8, 24.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{22}N_2O_3Na$ 301.1523, found 301.1525.

Gram-scale Reaction. A flame-dried 100 mL Schlenk flask was charged with **2a** (1.03 g, 5 mmol, 1.0 equiv), DCID **1d** (1.75 g, 5.25 mmol, 1.05 equiv), and anhydrous MeCN (20 mL) in sequence under an argon atmosphere. The reaction mixture was stirred at 25 °C for 15 min. Then removing the organic solvent in a vacuum and purification of the residue via flash column chromatography (PE/EA, 40:1 to 30:1) afforded the desired product **3a** (0.69 g, 94% yield).

Transformations of Cyanoformamide 3a. An oven-dried 10 mL Schlenk tube was charged with **3a** (73.1 mg, 0.5 mmol), Boc_2O (272.8 mg, 1.25 mmol), $CoCl_2{\cdot}6H_2O$ (178.4 mg, 0.75 mmol), and MeOH (4.0 mL) in sequence, followed by adding $NaBH_4$ (75.7 mg, 2 mmol) in one portion at 0 °C. After 3 h stirring at 0 °C, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (ca. 5 mL), then taken up to 1 M NaOH (25 mL) and extracted with ethyl acetate (38 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (PE/EA, 20:1 to 5:1) to furnish **5** as a colorless solid (113.9 mg, 91% yield). R_f = 0.50 (PE/EA, 2:1); mp 142.9−144.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (brs, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 5.44 (brs, 1H), 3.94 (s, 2H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.0, 156.7, 137.6, 129.1, 124.6, 120.1, 80.8, 45.7, 28.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{19}N_2O_3$ 251.1390, found 251.1394. The spectra data were consistent with values reported in the literature.[25]

To a solution of **3a** (73.1 mg, 0.5 mmol) and *n*$Bu_2Sn(O)$ (10.5 mg, 0.04 mmol) in anhydrous toluene (9 mL) was added trimethylsilyl azide (195.9 mg, 1.7 mmol) at room temperature. The resulting mixture was then stirred overnight at 80 °C. After cooling to room temperature, the mixture was concentrated and purified by flash column chromatography (DCM/MeOH, 10:1) to give **6** as a colorless solid (82.3 mg, 87% yield). R_f = 0.54 (DCM/MeOH, 5:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (brs, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 158.7, 157.0, 138.9, 128.6, 123.6, 120.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_8H_7N_5ONa$ 212.0543, found 212.0554.

Hydroxylamine hydrochloride (173.7 mg, 2.5 mmol) was added to a solution of **3a** (146.2 mg, 1.0 mmol) in dry pyridine (2.0 mL). The resulting mixture was stirred at 50 °C for 1 h. Subsequently, dry toluene (14 mL) and benzoyl chloride (154.6 mg, 1.1 mmol) was added and the mixture was refluxed for 1.5 h. After that, TBAF (1.0 M solution in THF, 0.5 mL) was added to the reaction

mixture and refluxed for days. Upon completion of the reaction (monitored by TLC), the mixture was diluted with 5% aqueous HCl (40 mL) and extracted with EtOAc (40 mL × 3). The combined organic phase was washed with water (25 mL × 2), dried over anhydrous Na_2SO_4, and evaporated in vacuum. The resulting residue was purified by column chromatography (PE/EA, 25:1 to 10:1) to afford **7** as a colorless solid (148.6 mg, 56% overall yield). R_f = 0.38 (PE/EA, 5:1); mp 134.4−135.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.23−8.20 (m, 2H), 7.75−7.73 (m, 2H), 7.68−7.64 (m, 1H), 7.59−7.55 (m, 2H), 7.43−7.39 (m, 2H), 7.23−7.19 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.2, 164.3, 154.1, 136.8, 133.8, 129.5, 129.4, 128.6, 125.6, 123.3, 120.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_3O_2$ 266.0924, found 266.0930.

Confirmation of the Formation of Acetyl Chloride. A 10 mL dry Schlenk tube was charged with the substrate **2c** (236.2 mg, 1 mmol, 1.0 equiv), DCID **1d** (400.0 mg, 1.2 mmol, 1.2 equiv), and anhydrous MeCN (5.0 mL) under an argon atmosphere. Then the reaction mixture was stirred at 25 °C for 10 min (complete conversion of **2c**). The aniline (274 μL, 279.4 mg, 3 mmol, 3.0 equiv) was added in one portion. After stirring for an additional 15 minutes, the mixture was diluted with DCM (25 mL) and washed with saturated brine (20 mL × 2). The organic phase was dried with anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography (PE/EA, 10:1 to 2:1) to afford ***N*-Phenylacetamide** as a colorless solid (93.3 mg, 69% yield). R_f = 0.43 (PE/EA, 1:1); mp 110.5−111.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (brs, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 2.16 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.8, 138.0, 129.1, 124.4, 120.1, 24.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for C_8H_9NONa 158.0576, found 158.0579. The spectra data were consistent with values reported in the literature.[26]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C NMR spectra for new starting materials and products (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: zjli@njtech.edu.cn.

*E-mail: guok@njtech.edu.cn.

ORCID

Zhenjiang Li: 0000-0002-1100-7297

Kai Guo: 0000-0002-0013-3263

Notes

The authors declare no competing finacial interest.

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