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Transition-Metal-Free Conversion of Trifluoropropanamides into Cyanoformamides through C−CF_3 Bond Cleavage and Nitrogenation

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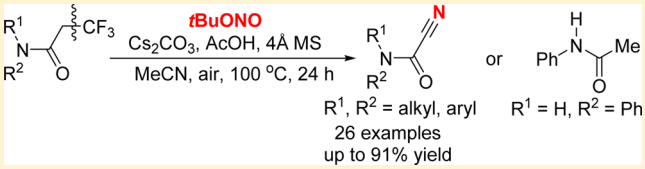
Supporting Information

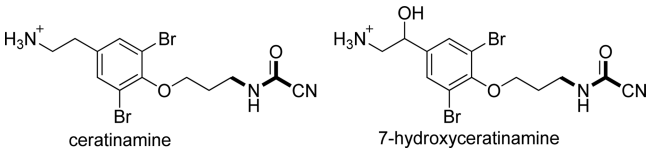
ABSTRACT: A new transition-metal-free transformation of trifluoropropanamides into cyanoformamides through a sequence of C−CF_3 bond cleavage and nitrogenation using *tert*-butyl nitrite as the nitrogen source is described. The method features direct detrifluoromethylation, broad substrate scopes, and excellent selectivity control, representing a new shortcut for constructing the nitrile group involving C−CF_3 σ-bond cleavage.



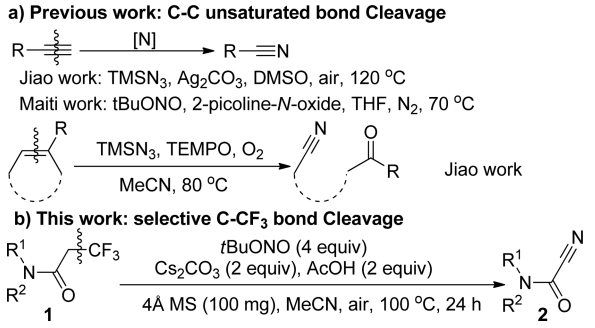
With the increased awareness of degrading the environmentally persistent nature of fluorinated molecules and improvement of fluorine-containing compounds in synthesis,[1] development of fluorocarbon disposal methods for such purposes is of increasing importance.[2] In the field, common and attractive strategies include the defluorination reaction, which has received much attention in the past decades. Typically, the elimination of fluorine atoms from fluorinated molecules, particularly trifluoromethylated compounds, is achieved via hydrodefluorination; however, these transformations are restricted to the requirement of strong reductive reagent and/or transition-metal catalysts because the fluorocarbon group is one of the most chemically and thermally stable functional groups.[3] Although approaches via direct cleavage of a C−CF_3 bond are especially fascinating for fluorocarbon degradation, such available examples are much less abundant.[4] Thus, the establishment of new efficient and practical methods for achieving the detrifluoromethylation, especially avoiding the use of strong reducing agents and transition-metal catalysts, is worthy of investigation.

Nitriles, including cyanoformamides (Scheme 1),[5] are prevalent as key structures in numerous pharmaceuticals, agricultural chemicals, and materials, as well as versatile building blocks in chemical synthesis.[6] Accordingly, considerable efforts have been devoted to development of new efficient and reliable synthetic processes that allow the preparation of diverse functionalized nitriles. Classical methods focus on transition-metal-catalyzed cyanation of aryl halides[7] and transition-metal-catalyzed C−H cyanation;[8] however, both suffer from the use of highly toxic metal cyanide as the nitrile group resources. Alternatively, attractive access to nitriles has been developed in recent years by direct transformations of functional groups into the nitrile group. Generally, the nitrile group is formed by the dehydration of the corresponding amides, oximes, or their precursors.[9] Recently, Jiao and coworkers reported a conceptually new C−C unsaturated bond cleavage and nitrogenation cascade for assembling the nitrile group using $TMSN_3$ as the nitrogen source (Scheme 2a).[10]

Scheme 1. Examples of Cyanoformamide-Containing Natural Products



Scheme 2. Construction of the Nitrile Group by C−C Bond Cleavage



Maiti and co-workers have subsequently developed a metal-free nitrogenation of terminal arylalkynes with *tert*-butyl nitrite (TBN) (the nitrogen source) in the presence of 2-picoline-*N*-oxide, which delivered aryl nitriles via C−C triple bond cleavage.[11] Despite recent advances in direct transformations of functional groups into the nitrile group, similar versions for the preparation of cyanoformamides are quite rare.[12] We envisioned that a combination of detrifluoromethylation and nitrogenation might be applicable to the construction of the

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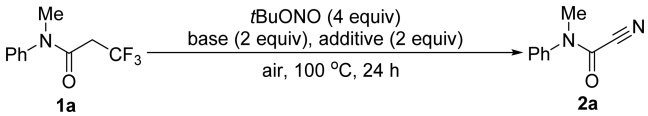
nitrile group. Herein, we report a new design cascade strategy for producing a wide range of cyanoformamides in moderate to high yields via transition-metal-free conversion of trifluoropropanamides into cyanoformamides using TBN as the nitrogen source, which represents the first example of direct construction of the nitrile group via the C−CF_3 single bond cleavage and nitrogenation cascades.

We began our studies by evaluating the reaction between 3,3,3-trifluoro-*N*-methyl-*N*-phenylpropanamide (**1a**) and TBN to optimize the reaction conditions (Table 1). Initially,

Table 1. Screening of Optimal Reaction Conditions[a]



entry	base	additive	solvent	yield (%)
1	Cs_2CO_3		MeCN	55
2	Cs_2CO_3		dioxane	29
3	Cs_2CO_3		DMF	47
4	Cs_2CO_3		toluene	38
5	CsOAc		MeCN	34
6	K_2CO_3		MeCN	27
7	K_3PO_4		MeCN	11
8	*t*-BuOK		MeCN	27
9	Cs_2CO_3	HOAc	MeCN	78
10	Cs_2CO_3	CF_3CO_2H	MeCN	trace
11		HOAc	MeCN	0
12	Cs_2CO_3	HOAc and 4 Å MS	MeCN	91
13[b]	Cs_2CO_3	HOAc and 4 Å MS	MeCN	39

[a]Reaction conditions: **1a** (0.2 mmol), *t*BuONO (0.8 mmol), base (2 equiv), acid (2 equiv), 4 Å MS (100 mg), dry solvent (2 mL), 100 °C, air and 24 h. [b]At 80 °C.

substrate **1a** was reacted with TBN and Cs_2CO_3 in MeCN at 100 °C for 24 h, giving the target product **2a** in 55% yield (entry 1). A rotamerization of amide **2a** was observed in NMR spectra (see Supporting Information). Encouraged by the results, three other solvents, including dioxane, DMF and toluene, were examined to enhance the yield (entries 2−4), which supported MeCN as the preferred solvent. A screen of the base effect revealed that other bases, such as CsOAc, K_2CO_3, K_3PO_4, and *t*-BuOK, were less effective than Cs_2CO_3 (entries 5−8). Gratifyingly, the yield increased from 55% (entry 1) to 78% when using 2 equiv of HOAc (entry 9). However, the reaction could not take place using CF_3CO_2H instead of HOAc (entry 10) or in the absence of Cs_2CO_3 (entry 11). We were pleased to find that molecular sieves (MS) improved the reaction: in the presence of 100 mg of 4 Å MS, a 91% yield of **2a** was obtained (entry 12). Notably, a lower reaction temperature (80 °C) had a negative effect on the reaction by comparison with the result at 100 °C (entry 13).

With the optimal reaction conditions in hand, we set out to investigate the substrate scope (Schemes 3 and 4). First, the substitution effect on the aromatic ring of the *N*-aryl moiety was examined: an array of substituents, including Me, MeO, F, Cl, Br, CF_3, CO_2Me, CH_3CO, and Ph, were well tolerated, and the electronic nature of the substrates had a fundamental influence on the reactivity (**2b−j**). Whereas trifluoropropanamides **1b,c**, bearing an electron-donating group (Me or MeO) on the *N*-aryl ring, afforded **2b,c** in good yields, substrates **1g−i** with a strong electron-withdrawing group, namely, CF_3, CO_2Me, and CH_3CO, furnished **2g−i** with lower yields. Importantly, halide substituents (F, Cl, and Br) were consistent with the optimal conditions (**2d−f**), thus providing potential handles for further modification, and the structure of product **2f** was confirmed by X-ray single-crystal diffraction analysis (see Supporting Information). Using 4-Ph-substituted amide **1j**, the reaction gave *N*-(4-biphenyl)cyanoformamide (**2j**) in 51% yield. The results showed that the steric hindrance effect slightly affected the reaction. Both *meta*-substituted and *ortho*-substituted trifluoropropanamides **1k−q** delivered **2k−q** in 65−86% yields. Moreover, *N*-methyl-*N*-(naphthalen-1-yl)-trifluoropropanamide **1r** was compatible with the optimal conditions, affording **2r** in 67% yield. Subsequently, the substitution effect on the nitrogen atom was examined. Gratifyingly, symmetrical and unsymmetrical disubstituted amines **1s−y**, either *N*,*N*-diaryl, *N*,*N*-dialkyl, or *N*-aryl-*N*-alkyl variations, were viable for the assembly of **2s−y** in moderate to good yields. For example, *N*,*N*-dihexyltrifluoropropanamide **1w** was successfully converted into **2w**, albeit giving a lower yield. For *N*,*N*-dibenzyltrifluoropropanamide **1x** and *N*,*N*-diphenyl-trifluoropropanamide **1y**, the corresponding products **2x,y** were obtained in 53 and 42% yields, respectively.

However, using N-monosubstituted trifluoropropanamide (**1z**) resulted in no occurrence of the cyanation reaction under the optimal conditions and furnished the *N*-acetylaniline **3z** in 68% yield (Scheme 4, eq 1). The reaction could be performed in the absence of TBN and/or HOAc, albeit with diminished yields (52%). These results suggest that product **3z** is formed from a sequence of detrifluoromethylation and workup hydrolyzation. The experiment was also confirmed by ^{19}F NMR experiments of the reaction mixture of **1z** under the standard conditions after 24 h, in which the generation of the volatile trifluoromethanol resulted in observation of no signal.[13]

To probe the mechanism of this detrifluoromethylative cyanation, some control experiments were conducted (Scheme 4). The reaction of *N*-methyl-*N*-phenylacetamide **1aa** with TBN was carried out under the optimal conditions. However, neither nitrosative product nor the target product **2a** could be observed (eq 2), suggesting that the elimination of the trifluoromethyl group occurred after the nitrosation. Furthermore, the reaction of substrate **1a** with TBN was completely inhibited by adding 4.5 equiv of 2,2,6,6-tetramethylpiperidine oxide (TEMPO), a radical scavenger (eq 3). These results indicated that the reaction might involve a radical process.

A plausible mechanism for this cascade reaction is proposed (Scheme 5).[14] Decomposition of *tert*-butyl nitrite readily takes place and gives the *tert*-butoxy radical and NO radical.[9d,14] Hydrogen abstraction of substrate **1a** by the *tert*-butoxy radical generates the alkyl radical intermediate **D**,[14a,e] which sequentially reacts with the NO radical to afford the intermediate **E**. The tautomerization of intermediate **E** delivers the corresponding oxime **F**. Finally, β-elimination of intermediate **F** with the aid of Cs_2CO_3 furnishes the desired detrifluoromethylative product **2a**.[4a]

In summary, we have developed a new convenient and efficient method for conversion of trifluoropropanamides into cyanoformamides via C−CF_3 bond cleavage and nitrogenation cascades, which exhibits a broad scope with regard to a wide range of trifluoropropanamides and excellent tolerance of functional groups. Most importantly, new C−C single bond cleavage and nitrogenation cascades to construct the nitrile group are established.

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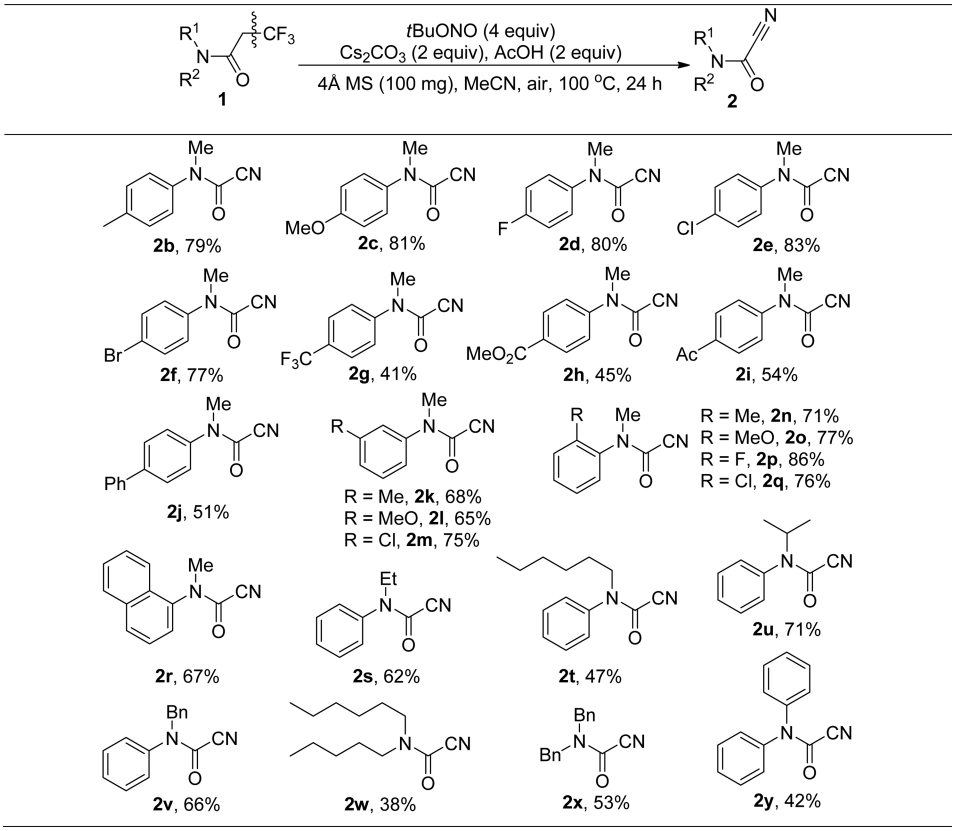
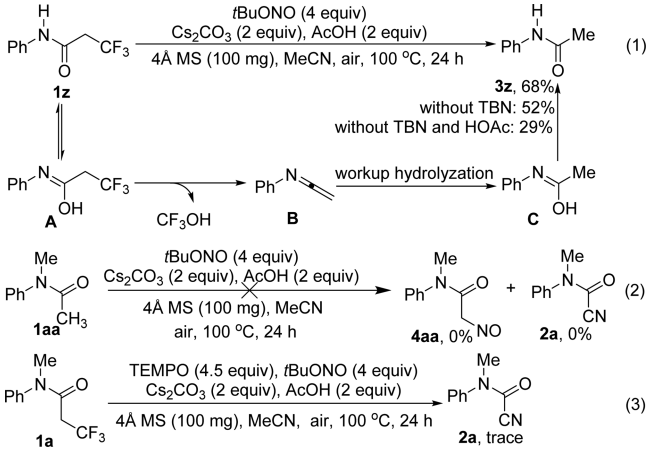
Scheme 3. Variation of the Trifluoropropanamides 1[a]

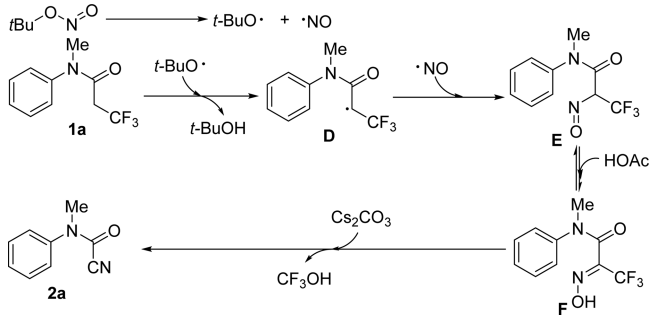


[a]Reaction conditions: **1** (0.2 mmol) and TBN (0.8 mmol), Cs_2CO_3 (2 equiv), AcOH (2 equiv), 100 mg of 4 Å MS and MeCN (dry 2 mL) under air atmosphere at 100 °C for 24 h.

Scheme 4. Reaction with Other Propanamides 1 and Control Experiments



Scheme 5. Possible Mechanism



EXPERIMENTAL SECTION

General Information. Chemicals were either purchased or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. All reactions under air atmosphere were conducted using standard Schlenk techniques. Melting points were measured on an X4 melting point apparatus and were uncorrected. Column chromatography was performed using EM silica gel 60 (300–400 mesh).

General Procedure for the Synthesis of Trifluoromethylacetanilides 1. To a stirred suspension of 3,3,3-trifluoropropionic acid (0.58 mL, 6.5 mmol) in dichloromethane (20 mL) was added oxalyl chloride (0.52 mL, 6 mmol) followed by three drops of DMF at 0 °C. The reaction mixture was stirred at rt for 3 h. To this solution was added a solution of anilines (5 mmol) in dichloromethane (10 mL) followed by triethylamine (1.74 mL, 12.5 mmol) at 0 °C. The reaction mixture was stirred for 12–24 h and then washed with water (15 mL) and 1 N HCl (15 mL). The organic layer was dried over Na_2SO_4 and evaporated to afford residue, which was purified by flash column chromatography (hexane/ethyl acetate) to afford trifluoromethylacetanilides **1**.[15]

General Procedure for the Synthesis of Cyanoformamides 2. To a flame-dried Schlenk tube with a magnetic stirring bar were charged **1** (0.2 mmol), TBN (0.8 mmol), Cs_2CO_3 (130.4 mg, 0.4

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mmol), HOAc (24 mg, 0.4 mmol), and 4 Å MS (100 mg) in dry MeCN (2 mL) under air atmosphere. The reaction mixture was stirred at 100 °C until complete consumption of the starting material as detected by TLC or GC-MS analysis. After the reaction equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (1 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired products. A rotamerization of amide **2** was observed in NMR spectra.

*Methyl(phenyl)carbamoyl Cyanide (**2a**, 1:14):*[12c] White solid (29.1 mg, 91% yield), mp 61−62 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.40 (m, 3H), 7.25−7.23 (m, 2H), 3.57 (s, 0.2H), 3.29 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 139.8, 130.1, 129.8, 127.0, 110.6, 36.8; LRMS (EI, 70 eV) *m*/*z* (%) 160 (M^+, 100), 132 (38), 106 (16), 91 (48).

*Methyl(p-tolyl)carbamoyl Cyanide (**2b**, 1:14):*[12c] Yellow solid (27.5 mg, 79% yield), mp 80−82 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 3.63 (s, 0.2H), 3.34 (s, 2.8H), 2.41 (s, 2.8H), 2.37 (s, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 140.0, 137.3, 130.7, 126.8, 110.7, 36.8, 21.2; LRMS (EI, 70 eV) *m*/*z* (%) 174 (M^+, 100), 146 (17), 105 (58).

*(4-Methoxyphenyl)(methyl)carbamoyl Cyanide (**2c**, 1:14):*[12c] Brown oil (30.8 mg, 81% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 2.8H), 3.82 (s, 0.2H), 3.61 (s, 0.2H), 3.32 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 144.8, 132.4, 128.3, 115.2, 110.7, 55.5, 36.9; LRMS (EI, 70 eV) *m*/*z* (%) 190 (M^+, 100), 159 (8), 120 (25).

*(4-Fluorophenyl)(methyl)carbamoyl Cyanide (**2d**, 1:14):* Yellow solid (28.5 mg, 80% yield), mp 85−87 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.30 (m, 2H), 7.22−7.18 (m, 2H), 3.63 (s, 0.2H), 3.34 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (d, *J* = 254.0 Hz), 144.6, 135.9, 129.2, 117.3 (d, *J* = 23.0 Hz), 110.4, 36.8; LRMS (EI, 70 eV) *m*/*z* (%) 178 (M^+, 100), 150 (11), 124 (39), 109 (27); HRMS (ESI) calcd for $C_9H_7FN_2ONa^+$ ([M + Na]$^+$) 201.0435, found 201.0431.

*(4-Chlorophenyl)(methyl)carbamoyl Cyanide (**2e**, 1:14):*[12c] Yellow oil (32.2 mg, 83% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H), 3.65 (s, 0.2H), 3.35 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 138.3, 135.9, 130.4, 128.4, 110.4, 36.8; LRMS (EI, 70 eV) *m*/*z* (%) 194 (M^+, 100), 166 (12), 131 (23), 125 (21).

*(4-Bromophenyl)(methyl)carbamoyl Cyanide (**2f**, 1:14):*[12c] Yellow solid (36.7 mg, 77% yield), mp 105−107 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 2H), 3.64 (s, 0.2H), 3.35 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 138.9, 133.5, 128.6, 123.9, 110.4, 36.7; LRMS (EI, 70 eV) *m*/*z* (%) 240/238 (M^+, 48), 184 (13), 131 (14), 105 (28), 67(100).

*Methyl(4-(trifluoromethyl)phenyl)carbamoyl Cyanide (**2g**, 1:14):* Yellow solid (18.7 mg, 41% yield), mp 81−83 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 3.60 (s, 0.2H), 3.30 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 142.9, 131.7 (q, J_{C-F} = 33.0 Hz), 127.5, 127.4, 123.4 (q, J_{C-F} = 270.1 Hz), 110.4, 36.6; LRMS (EI, 70 eV) *m*/*z* (%) 228 (M^+, 100), 200 (28), 174 (15), 159 (24), 145 (44); HRMS (ESI) calcd for $C_{10}H_8F_3N_2O^+$ ([M + H]$^+$) 229.0583, found 229.0580.

*(4-(Methoxycarbonyl)phenyl)(methyl)carbamoyl Cyanide (**2h**, 1:14):* White solid (19.6 mg, 45% yield), mp 75−76 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 2.8H), 3.93 (s, 0.2H), 3.70 (s, 0.2H), 3.40 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 144.2, 143.5, 131.5, 126.9, 124.5, 110.4, 52.5, 36.6; LRMS (EI, 70 eV) *m*/*z* (%) 218 (M^+, 100), 187 (94), 121 (56); HRMS (ESI) calcd for $C_{11}H_{11}N_2O_3^+$ ([M + H]$^+$) 219.0764, found 219.0772.

*(4-Acetylphenyl)(methyl)carbamoyl Cyanide (**2i**, 1:14):* Yellow solid (21.8 mg, 54% yield), mp 121−123 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 3.70 (s, 0.2H), 3.40 (s, 2.8H), 2.65(s, 2.8H), 2.61(s, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 144.1, 143.6, 137.8, 130.1, 127.0, 110.4, 36.6, 26.7; LRMS (EI, 70 eV) *m*/*z* (%) 202 (M^+, 48), 187 (100), 121 (33); HRMS (ESI) calcd for $C_{11}H_{10}N_2O_2Na^+$ ([M + Na]$^+$) 225.0634, found 225.0638.

*[1,1′-Biphenyl]-4-yl(methyl)carbamoyl Cyanide (**2j**, 1:14):*[12c] White solid (24.1 mg, 51% yield), mp 151−153 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.41−7.38 (m, 2H), 7.32−7.29(m, 3H), 3.62 (s, 0.2H) 3.32 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 142.8, 139.5, 138.9, 129.0, 128.8, 128.1, 127.3, 127.2 110.7, 36.8; LRMS (EI, 70 eV) *m*/*z* (%) 236 (M^+, 100), 207 (20), 182 (21), 170 (29), 167 (29), 154 (21), 152(48), 67(60).

*Methyl(m-tolyl)carbamoyl Cyanide (**2k**, 1:14):*[12c] Yellow oil (23.7 mg, 68% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.36 (m, 1H), 7.28−7.26(m, 1H), 7.11−7.10 (m, 2H), 3.63 (s, 0.2H), 3.34 (s, 2.8H), 2.41 (s, 2.8H), 2.37 (s, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 140.4, 139.8, 130.5, 129.8, 127.5, 124.0, 110.7, 36.7, 21.2; LRMS (EI, 70 eV) *m*/*z* (%) 174 (M^+, 100), 146 (36), 105 (96).

*(3-Methoxyphenyl)(methyl)carbamoyl Cyanide (**2l**, 1:14):* Yellow solid (24.7 mg, 65% yield), mp 77−78 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.38 (m, 1H), 7.01−7.00 (m, 1H), 6.91−6.89 (m, 1H), 6.83 (s, 1H), 3.84 (s, 2.8H), 3.80 (s, 0.2H), 3.63 (s, 0.2H), 3.35 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 144.5, 140.8, 130.9, 119.1, 115.3, 112.9, 110.7, 55.6, 36.7; LRMS (EI, 70 eV) *m*/*z* (%) 190 (M^+, 100), 159 (72), 120 (56); HRMS (ESI) calcd for $C_{10}H_{11}N_2O_2^+$ ([M + H]$^+$) 191.0815, found 191.0814.

*(3-Chlorophenyl)(methyl)carbamoyl Cyanide (**2m**, 1:14):*[12c] Yellow oil (29.1 mg, 75% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.44 (m, 2H), 7.34 (s, 1H), 7.25−7.23 (m, 1H), 3.65 (s, 0.2H), 3.36 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 140.9, 135.7, 131.2, 130.1, 127.4, 125.5, 110.4, 36.8; LRMS (EI, 70 eV) *m*/*z* (%) 194 (M^+, 100), 166 (46), 131 (32), 125 (50).

*Methyl(o-tolyl)carbamoyl Cyanide (**2n**, 1:14):*[12c] Yellow solid (24.7 mg, 71% yield), mp 75−76 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.32 (m, 3H), 7.22 (d, *J* = 7.0 Hz, 1H), 3.55 (s, 0.2H), 3.28 (s, 2.8H), 2.30 (s, 2.8H), 2.20 (s, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 138.6, 136.1, 131.9, 130.4, 128.4, 127.9, 110.6, 35.8, 17.2; LRMS (EI, 70 eV) *m*/*z* (%) 174 (M^+, 100), 157 (88), 146 (33), 118 (50).

*(2-Methoxyphenyl)(methyl)carbamoyl Cyanide (**2o**, 1:29):* Yellow solid (29.3 mg, 77% yield), mp 74−76 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.43 (m, 1H), 7.26−7.24 (m, 1H), 7.06−7.03 (m, 2H), 3.89 (s, 2.9H), 3.85 (s, 0.1H), 3.53 (s, 0.1H), 3.26 (s, 2.9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 145.8, 131.4, 129.0, 128.4, 121.3, 112.4, 110.9, 55.7, 35.7; LRMS (EI, 70 eV) *m*/*z* (%) 190 (M^+, 100), 159 (90), 120 (88); HRMS (ESI) calcd for $C_{10}H_{11}N_2O_2^+$ ([M + H]$^+$) 191.0815, found 191.0810.

*(2-Fluorophenyl)(methyl)carbamoyl Cyanide (**2p**, 1:14):* Yellow solid (30.6 mg, 86% yield), mp 81−83 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.47 (m, 1H), 7.38−7.35 (m, 1H), 7.30−7.26 (m, 2H), 3.61 (s, 0.2H), 3.34 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2 (d, *J* = 250.6 Hz), 144.9, 131.9, 129.6, 127.5 (d, *J* = 12.8 Hz), 125.1, 117.4 (d, *J* = 19.5 Hz), 110.3, 36.2; LRMS (EI, 70 eV) *m*/*z* (%) 178 (M^+, 100), 159 (24), 124 (25), 109 (30); HRMS (ESI) calcd for $C_9H_7FN_2ONa^+$ ([M + Na]$^+$) 201.0435, found 201.0443.

*(2-Chlorophenyl)(methyl)carbamoyl Cyanide (**2q**, 1:14):* Yellow oil (29.5 mg, 76% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.48 (m, 1H), 7.40−7.30 (m, 3H), 3.48 (s, 0.2H), 3.21 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 137.2, 133.3, 131.6, 131.1, 130.1, 128.7, 110.3, 36.6; LRMS (EI, 70 eV) *m*/*z* (%) 194 (M^+, 100), 166 (68), 131 (43), 125 (63); HRMS (ESI) calcd for $C_9H_7ClN_2ONa^+$ ([M + Na]$^+$) 217.0139, found 217.0131.

*Methyl(naphthalen-1-yl)carbamoyl Cyanide (**2r**, 1:29):* Yellow oil (28.1 mg, 67% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94−7.89 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.60−7.52 (m, 2H), 7.50−7.47 (m, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 3.65 (s, 0.1H), 3.39 (s, 2.9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 136.0, 134.8, 130.8, 130.0, 129.0, 128.3, 127.3, 126.6, 125.6, 121.3, 110.6, 36.8; LRMS (EI, 70 eV) *m*/*z* (%) 210 (M^+, 97), 182 (20), 154 (38), 141 (21), 128 (54), 115 (37), 67 (100); HRMS (ESI) calcd for $C_{13}H_{10}N_2ONa^+$ ([M + Na]$^+$) 233.0685, found 233.0692.

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*Ethyl(phenyl)carbamoyl Cyanide (**2s**, 1:9):*[12c] Yellow solid (21.6 mg, 62% yield), mp 94−95 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53−7.45 (m, 3H), 7.31−7.26 (m, 2H), 4.04 (q, J = 7.0 Hz, 0.2H), 3.83 (q, J = 7.0 Hz, 1.8H), 1.29 (t, J = 7.0 Hz, 0.3H), 1.18 (t, J = 7.0 Hz, 2.7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 138.3, 130.1, 129.9, 128.2, 110.6, 44.4, 12.4; LRMS (EI, 70 eV) m/z (%) 174 (M^+, 100), 159 (71), 146 (28), 118 (55), 105 (69).

*Hexyl(phenyl)carbamoyl Cyanide (**2t**, 1:9):* Yellow oil (21.6 mg, 47% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.39 (m, 3H), 7.21 (d, J = 7.5 Hz, 2H), 3.90 (t, J = 7.5 Hz, 0.2H) 3.69 (t, J = 7.5 Hz, 1.8H), 1.49−1.43 (m, 2H), 1.24−1.19 (m, 6H), 0.80−0.78 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 138.6, 130.1, 129.8, 128.1, 110.7, 49.4, 31.3, 27.1, 26.2, 22.4, 13.9; LRMS (EI, 70 eV) m/z (%) 230 (M^+, 26), 188 (20), 159 (100), 146 (51), 132 (33), 119 (28), 105 (66); HRMS (ESI) calcd for $C_{14}H_{18}N_2ONa^+$ ([M + Na]$^+$) 253.1311, found 253.1311.

*Isopropyl(phenyl)carbamoyl Cyanide (**2u**):* Yellow solid (26.7 mg, 71% yield), mp 92−94 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.40 (m, 3H), 7.20−7.16 (m, 2H), 4.73 (hept, J = 7.0 Hz, 1H), 1.09 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 135.3, 130.3, 130.2, 129.8, 110.7, 48.6, 20.4; LRMS (EI, 70 eV) m/z (%) 188 (M^+, 100), 173 (52), 146 (59), 119 (67); HRMS (ESI) calcd for $C_{11}H_{13}N_2O^+$ ([M + H]$^+$) 189.1022, found 189.1029.

*Benzyl(phenyl)carbamoyl Cyanide (**2v**, 1:19):* Yellow solid (31.2 mg, 66% yield), mp 119−121 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.39 (m, 3H), 7.30−7.29 (m, 3H), 7.17−7.15 (m, 2H), 7.10−7.08 (m, 2H), 5.14 (s, 0.1H), 4.91 (s, 1.9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 138.3, 134.6, 130.0, 129.98, 129.1, 128.8, 128.43, 128.35, 110.6, 53.1; LRMS (EI, 70 eV) m/z (%) 236 (M^+, 91), 119 (100), 91 (97); HRMS (ESI) calcd for $C_{15}H_{13}N_2O^+$ ([M + H]$^+$) 237.1022, found 237.1025.

*Dihexylcarbamoyl Cyanide (**2w**):* Colorless oil (18.1 mg, 38% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (t, J = 7.0 Hz, 2H), 3.29 (t, J = 7.0 Hz, 2H), 1.58−1.48 (m, 4H), 1.26−1.19 (m, 12H), 0.83−0.81 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 110.9, 49.1, 45.4, 31.3, 31.2, 28.8, 27.0, 26.4, 26.1, 22.44, 22.43, 13.89, 13.86; LRMS (EI, 70 eV) m/z (%) 238 (M^+, 1), 166 (51), 96 (100), 83 (50), 55 (28); HRMS (ESI) calcd for $C_{14}H_{27}N_2O^+$ ([M + H]$^+$) 239.2118, found 239.2125.

*Dibenzylcarbamoyl Cyanide (**2x**):*[12c] Yellow oil (26.5 mg, 53% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.20 (m, 6H), 7.13−7.07 (m, 4H), 4.52 (s, 2H), 4.36 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 134.4, 133.8, 129.3, 129.1, 128.9, 128.7, 128.5, 127.9, 110.9, 51.4, 47.1; LRMS (EI, 70 eV) m/z (%) 250 (M^+, 10), 159 (52), 109 (38), 92 (89), 91 (100), 79 (34), 65 (27).

*Diphenylcarbamoyl Cyanide (**2y**):* Yellow oil (18.7 mg, 42% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.41 (m, 3H), 7.33−7.29 (m, 4H), 7.22−7.20 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 139.4, 139.1, 130.3, 130.0, 129.4, 128.7, 127.8, 125.1, 110.9; LRMS (EI, 70 eV) m/z (%) 222 (M^+,95), 193 (28), 167 (45), 128 (100), 77 (47); HRMS (ESI) calcd for $C_{14}H_{11}N_2O^+$ ([M + H]$^+$) 223.0866, found 223.0856.

*Dibenzylcarbamoyl Cyanide (**3z**):*[16] Yellow solid (18.5 mg, 68% yield), mp 161−164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.20 (m, 2H), 7.00 (m, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 138.0, 128.9, 124.3, 120.1, 24.4; LRMS (EI, 70 eV) m/z (%) 135 (M^+, 58), 93 (100), 77 (7), 65 (5).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00626.

Copies of ^{1}H and ^{13}C NMR spectra for products **2a**−**2y** and **3z** (PDF)

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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