

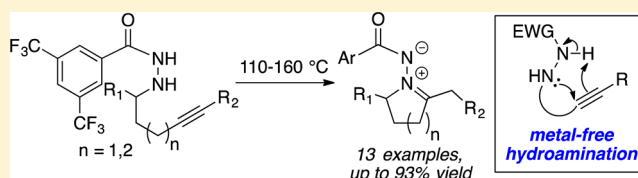
Synthesis of Azomethine Imines Using an Intramolecular Alkyne Hydrohydrazination Approach

Ashley D. Hunt, Isabelle Dion, Nicolas Das Neves, Sandrine Taing, and André M. Beauchemin*

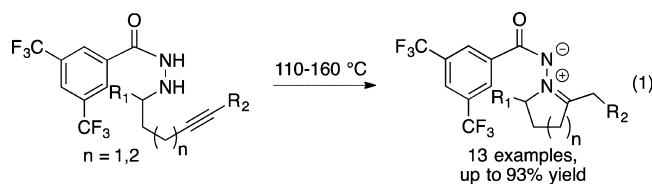
Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie-Curie, Ottawa, ON, K1N 6N5, Canada

Supporting Information

ABSTRACT: Azomethine imines can be accessed upon heating appropriate alkynylhydrazide precursors. This simple thermal hydroamination approach allows the formation of five- and six-membered dipoles in modest to excellent yields. The structure of the acyl group is important to minimize side reactions and allow the isolation of the azomethine imines by column chromatography.



Azomethine imines are valuable intermediates in synthetic organic chemistry.¹ In addition to being useful 1,3-dipoles in cycloadditions and rearrangements, azomethine imines are versatile electrophiles.² Several stereoselective reactions have recently emerged, providing access both to enantioenriched azomethine imines via kinetic resolution and to useful adducts via asymmetric synthesis.^{2c,d,3} The synthetic scope of all these transformations is inherently linked to the methods available to generate azomethine imines, which can be sensitive to decomposition or dimerization; the dipoles are thus often generated *in situ*.¹ Reactions to access these synthetic intermediates include^{1c} (1) condensation of a carbonyl precursor and a hydrazide;⁴ (2) *in situ* generation upon a 1,2-proton shift from an appropriate hydrazone;⁵ (3) deprotonation of suitable hydrazone salts;⁶ (4) oxidation of hydrazine derivatives;⁷ (5) N-alkylation of hydrazone precursors;⁸ and (6) aminocarbonylation of alkenes using hydrazones.^{9,10} While reliable, these approaches impose limitations on the types of substrates that can be accessed. In our efforts toward the development of metal-free hydroamination reactivity,¹¹ we became attracted by the opportunity of forming azomethine imines via intramolecular alkyne hydrohydrazination reactions.¹² Herein, we report that five- and six-membered azomethine imines are formed simply upon heating of appropriate alkynylhydrazides precursors (eq 1).¹³



In recent work on thermal hydrohydrazinations, we noted the increased reactivity associated with the use of 3,5-bis(trifluoromethyl)benzhydrazides.^{11b} Our current hypothesis is that these convenient, crystalline precursors facilitate both a concerted Cope-type hydroamination step and the proton-transfer steps

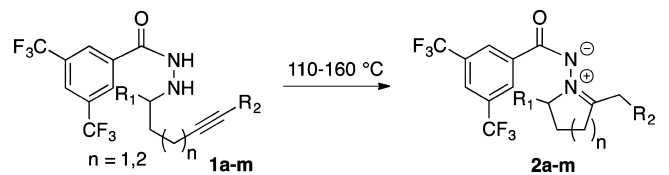
associated with this metal-free reactivity.^{11a} In addition, we speculated that the bis(trifluoromethyl)benzoyl group would stabilize the negative charge of the dipole sufficiently to allow isolation of azomethine imines from appropriate precursors. Satisfyingly, initial results showed the desired reactivity after some reaction optimization. As expected, the bis(trifluoromethyl)benzoyl group proved crucial to allow somewhat milder reaction conditions, to isolate the desired dipole, and to minimize byproduct formation, which is observed with the parent benzhydrazide (see Supporting Information details). The reaction scope is shown in Table 1.

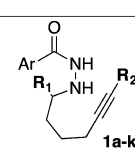
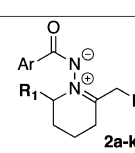
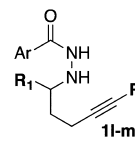
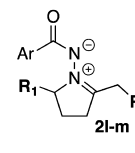
Gratifyingly, cyclization of the alkynylhydrazides occurred upon heating at 110–160 °C, providing access to both five- and six-membered azomethine imines. While heating was typically performed using microwave irradiation to minimize reaction time, this reactivity also proceeds well upon heating with a reflux condenser (entry 1). Terminal (entries 1, 9–12) and internal alkynes proved competent substrates, with both methyl (entry 2) and aryl groups (entries 3–8, 13) being well tolerated. A variety of aryl substituents were compatible with the reaction (Me, Br, OMe, CO₂Me, entries 4–8), and the reaction provided the desired dipole with both electron-poor (entry 7) and electron-rich (entries 6, 8) conjugated arylacetylenes. Improved yields are observed for substrates with substituents on the carbon bearing the hydrazide functionality (R¹, entry 1 vs 9–11).

The overall reaction likely proceeds via a Cope-type hydrohydrazination¹¹ (hydroamination) event to provide an ene-hydrazide intermediate,¹⁴ followed by tautomerization to provide the more stable azomethine imine. Such tautomerization has been observed in related intermolecular additions of hydrazides to dimethyl acetylenedicarboxylate (DMAD), which also afford azomethine imines.¹³ In all cases, none of the ene-hydrazide intermediate was observed by NMR.

Received: June 3, 2013

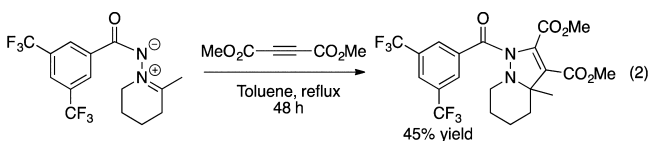
Published: July 30, 2013

Table 1. Scope of Hydrohydrazination Route to Azomethine Imines^a


Entry	Hydrazide	Temp (°C)	Product	Yield (%)
				
1	R ¹ =R ² =H (1a)	140	2a	68 (55 ^b)
2	R ¹ =H, R ² =Me (1b)	160	2b	67
3	R ¹ =H, R ² =Ph (1c)	140	2c	72
4	R ¹ =H, R ² =3,5-Me ₂ C ₆ H ₃ (1d)	140	2d	92
5	R ¹ =H, R ² =4-BrC ₆ H ₄ (1e)	140	2e	73
6	R ¹ =H, R ² =4-MeOC ₆ H ₄ (1f)	140	2f	86
7	R ¹ =H, R ² =4-MeO ₂ CC ₆ H ₄ (1g)	140	2g	53
8	R ¹ =H, R ² =thienyl (1h)	120	2h	53
9	R ¹ =Me, R ² =H (1i)	110	2i	91
10	R ¹ = <i>n</i> -Bu, R ² =H (1j)	120	2j	93
11	R ¹ =Ph, R ² =H (1k)	120	2k	91
				
12	R ¹ =R ² =H (1l)	140	2l	44 ^c
13	R ¹ =H, R ² =Ph (1m)	150	2m	62

^aConditions: a solution of hydrazide in PhCF₃ (0.05M) was heated for 12–14 h (microwave reactor). ^bPerformed on a 5.77 mmol scale in refluxing PhCF₃ overnight. ^cYield after reduction with NaBH₄.

Finally, we explored the reactivity of those azomethine imines by performing a [3 + 2] dipolar cycloaddition. Encouragingly, the desired cycloadduct **3a** was isolated in a modest yield despite the hindrance present in azomethine **1a** as shown in eq 2. In summary,



we have shown that a variety of cyclic azomethine imines can be obtained upon simple thermolysis of an appropriate alkyne-hydrazide precursor. This reactivity further illustrates that Cope-type hydroaminations are useful for the synthesis of a variety of nitrogen-containing molecules.

EXPERIMENTAL SECTION

General Information. All reactions were performed in oven-dried glassware under argon. Microwave reactions were run in a Biotage

microwave reactor, monitoring temperatures with an external sensor. Product purification was performed using silica gel (40–60 μm) flash column chromatography. Analytical thin layer chromatography (TLC) was performed on aluminum plates precoated with silica gel 60 F₂₅₄. Visualization was accomplished under UV light followed by staining with KMnO₄ solution and heating.

NMR spectra were recorded at ambient temperature, unless otherwise indicated. Spectral data was reported in ppm from tetramethylsilane using solvent as the reference. Data was reported as multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, and coupling constant(s) (with * denoting minor conformers). Infrared spectra were obtained with neat thin films on NaCl disks, recorded on a FTIR spectrometer. High-resolution mass spectrometry (HRMS) was performed on a mass spectrometer with a 70eV electron beam.

Materials. Commercial materials were used as purchased. Solvents were freshly distilled prior use: THF and ether over sodium; triethylamine and dichloromethane over CaH₂; PhCF₃ over molecular sieves.

General Procedure for Alkyne Cyclizations (Table 1). Procedure A. A microwave vial was charged with a stir bar, capped with a septum, and purged with argon. The hydrazide and

α,α,α -trifluorotoluene ([hydrazide] = 0.05 M) were added. The septum was removed, and the vial was quickly capped and heated in a microwave reactor for 12–14 h at 110–160 °C. The reaction was cooled, concentrated, and analyzed by ^1H NMR using 1,4-dimethoxybenzene as internal standard. Concentration and purification by chromatography yielded the product.

(3,5-Bis(trifluoromethyl)benzoyl(6-methyl-2,3,4,5-tetrahydropyridinium-1-yl)amide (2a). Synthesized using **1a** (0.250 g, 0.710 mmol; procedure A, 140 °C, 14 h). Chromatographic purification (2.5% MeOH/ CH_2Cl_2) afforded a yellow oil (0.169 g, 68% yield). ^1H NMR (300 MHz, DMSO- d_6) δ 8.46 (s, 2H), 8.14 (s, 1H), 3.75 (t, J = 5.2 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H), 2.12 (s, 3H), 1.96–1.88 (m, 2H), 1.77–1.69 (m, 2H); ^{13}C NMR (75 MHz, DMSO- d_6 , 120 °C) δ 170.3, 162.6, 140.7, 129.3 (q, J = 32.9 Hz, 2C), 126.9 (2C), 124.5 (q, J = 273.0 Hz, 2C), 121.3, 53.3, 30.9, 20.8, 20.1, 16.7; IR (film) 3260, 2937, 1649, 1276, 1132 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{15}\text{H}_{14}\text{F}_6\text{N}_2\text{O}$ 352.1010 $[\text{M}]^+$, found 352.09917.

(3,5-Bis(trifluoromethyl)benzoyl(6-ethyl-2,3,4,5-tetrahydropyridinium-1-yl)amide (2b). Synthesized using **1b** (0.0450 g, 0.123 mmol; procedure A, 160 °C, 14 h). Chromatographic purification (4% MeOH/ CH_2Cl_2) afforded a yellow oil (0.030 g, 67% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.50 (s, 2H), 7.87 (s, 1H), 3.94 (s, 2H), 2.73 (s, 2H), 2.65 (s, 2H), 2.04 (s, 2H), 1.94–1.85 (m, 2H), 1.17 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.1, 165.7, 139.6, 131.0 (q, J = 33.3 Hz, 2C), 128.0 (2C), 123.5 (q, J = 272.7 Hz, 2C), 123.1, 54.3, 29.6, 27.7, 21.8, 17.9, 9.2; IR (film) 3405, 2360, 1653, 1278, 1132 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{16}\text{H}_{16}\text{F}_6\text{N}_2\text{O}$ 366.1167 $[\text{M}]^+$, found 366.1170.

(6-Benzyl-2,3,4,5-tetrahydropyridinium-1-yl)(3,5-bis(trifluoromethyl)benzoyl)amide (2c). Synthesized using **1c** (0.250 g, 0.584 mmol; procedure A, 140 °C, 14 h). Chromatographic purification (2% MeOH/ CH_2Cl_2) afforded a yellow oil (0.178 g, 72% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.54 (s, 2H), *8.41 (s, 2H), *7.97 (s, 1H), 7.87 (s, 1H), 7.36–7.23 (m, 5H), 3.97 (s, 4H), 2.50 (s, 2H), 2.02–1.97 (m, 2H), 1.82–1.24 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.6, 133.4, 131.2 (q, J = 33.4 Hz, 2C), 129.7 (2C), 129.1 (2C), 128.0 (2C), 127.8, 123.4 (q, J = 272.6 Hz, 2C), 123.2, 54.6, 40.2, 30.1, 21.8, 17.8; ^{15}N IR (film) 3343, 2940, 2360, 1635, 1094 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{21}\text{H}_{18}\text{F}_6\text{N}_2\text{O}$ 428.13233 $[\text{M}]^+$, found 428.13260.

(3,5-Bis(trifluoromethyl)benzoyl(6-(3,5-dimethylbenzyl)-2,3,4,5-tetrahydropyridinium-1-yl)amide (2d). Synthesized using **1d** (0.250 g, 0.548 mmol; procedure A, 140 °C, 14 h). Chromatographic purification (1–3% MeOH/ CH_2Cl_2) afforded a yellow oil (0.229 g, 92% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.56 (s, 2H), 7.89 (s, 1H), 6.93 (s, 1H), 6.86 (s, 2H), 4.00 (t, J = 5.5 Hz, 2H), 3.89 (s, 2H), 2.55 (t, J = 5.7 Hz, 2H), 2.29 (s, 6H), 2.22–1.98 (m, 2H), 1.82–1.73 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 138.7, 133.2 (2C), 131.0 (q, J = 34.3 Hz, 2C), 129.4, 128.1 (2C), 127.6 (2C), 125.3 (q, J = 272.7 Hz, 2C), 123.2, 54.6, 40.1, 30.2, 21.8, 21.2 (2C), 17.8; ^{15}N IR (film) 3467, 2967, 1660, 1276, 1136 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{23}\text{H}_{22}\text{F}_6\text{N}_2\text{O}$ 456.1636 $[\text{M}]^+$, found 456.16288.

(3,5-Bis(trifluoromethyl)benzoyl(6-(4-bromobenzyl)-2,3,4,5-tetrahydropyridinium-1-yl)amide (2e). Synthesized using **1e** (0.250 g, 0.490 mmol; procedure A, 140 °C, 14 h). Chromatographic purification (2% MeOH/ CH_2Cl_2) afforded a red oil (0.18 g, 73% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.49 (s, 2H), 7.86 (s, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 3.95 (s, 2H), 3.88 (s, 2H), 2.45 (s, 2H), 1.98 (s, 2H), 1.82–1.68 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 132.5, 132.1 (2C), 131.4 (2C), 131.0 (q, J = 33.2 Hz, 2C), 127.9, 123.5 (q, J = 272.7 Hz, 2C), 123.2, 121.8, 54.5, 39.6, 30.0, 21.7, 17.8; ^{15}N IR (film) 3378, 2943, 1728, 1568, 1276 1132 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{21}\text{H}_{17}\text{BrF}_6\text{N}_2\text{O}$ 506.0428 $[\text{M}]^+$, found 506.04220.

(3,5-Bis(trifluoromethyl)benzoyl(6-(4-methoxybenzyl)-2,3,4,5-tetrahydropyridinium-1-yl)amide (2f). Synthesized using **1f** (0.250 g, 0.545 mmol; procedure A, 140 °C, 14 h). Chromatographic purification (1–2% MeOH/ CH_2Cl_2) afforded a yellow oil (0.215 g, 86% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.54 (s, 2H), 7.88 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.99

(s, 2H), 3.91 (s, 2H), 3.79 (s, 3H), 2.51 (s, 2H), 2.04–1.99 (m, 2H), 1.85–1.74 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.1, 139.4, 130.9 (q, J = 33.3 Hz, 2C), 130.8 (2C), 128.0 (2C), 124.8, 123.6 (q, J = 272.6 Hz, 2C), 123.1, 114.4 (2C), 55.1, 54.5, 39.3, 30.0, 21.7, 17.7; ^{15}N IR (film) 2956, 1569, 1514, 1316, 1279, 1132 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{22}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_2$ 458.1429 $[\text{M}]^+$, found 458.14221.

(3,5-Bis(trifluoromethyl)benzoyl(6-(4-methyl benzoate)-2,3,4,5-tetrahydropyridinium-1-yl)amide (2g). Synthesized using **1g** (0.250 g, 0.510 mmol; procedure A 140 °C, 14 h). Chromatographic purification (2% MeOH/ CH_2Cl_2) afforded a yellow solid (0.132 g, 53% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.50 (s, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.88 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 4.00 (s, 4H), 3.90 (s, 3H), 2.47 (s, 2H), 2.07–1.96 (m, 2H), 1.85–1.76 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.6, 138.7, 131.1 (q, J = 33.3 Hz, 2C), 130.3 (2C), 129.8 (2C), 129.7, 128.0 (2C), 123.4 (q, J = 272.7 Hz, 2C), 123.3, 54.6, 52.2, 40.2, 30.2, 21.8, 17.9; ^{15}N IR (film) 3287, 2954, 2235, 1725, 1679, 1573, 1279, 1133, 904 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{23}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_3$ 486.1378 $[\text{M}]^+$, found 486.13870.

(3,5-Bis(trifluoromethyl)benzoyl(6-(2-thiophene)-2,3,4,5-tetrahydropyridinium-1-yl)amide (2h). Synthesized using **1h** (0.496 g, 1.14 mmol; procedure A, 120 °C, 14 h). Chromatographic purification (1.5% MeOH/ CH_2Cl_2) afforded a yellow oil (0.263 g, 53% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.52 (s, 2H), 7.88 (s, 1H), 7.25 (dd, J = 1.3, 4.8 Hz, 1H), 7.02–6.94 (m, 2H), 4.10 (s, 2H), 3.95 (s, 2H), 2.57 (s, 2H), 1.99 (s, 2H), 1.88–1.76 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.6, 163.1, 134.1, 131.1 (q, J = 33.2 Hz, 2C), 128.2, 127.8 (2C), 127.2, 126.0, 123.4 (q, J = 272.7 Hz, 2C), 54.2, *51.3, 34.4, *32.5, 29.5, *23.2, 21.7, *20.7, 17.9; ^{15}N IR (film) 3237, 2944, 1671, 1626, 1565, 1279, 1133 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{19}\text{H}_{16}\text{SF}_6\text{N}_2\text{O}$ 434.0888 $[\text{M}]^+$, found 434.0912.

(3,5-Bis(trifluoromethyl)benzoyl(2,6-dimethyl-2,3,4,5-tetrahydropyridinium-1-yl)amide (2i). Synthesized using **1i** (0.250 g, 0.682 mmol; procedure A, 110 °C, 14 h). Chromatographic purification (2% MeOH/ CH_2Cl_2) afforded a yellow oil (0.228 g, 91% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.55–8.06 (m, 3H), *4.45–4.42 (m, 1H), 4.10–4.03 (m, 1H), 2.83–2.81 (m, 2H), 2.12 (s, 3H), 2.07–1.73 (m, 2H), *1.65 (s, 3H), 1.36 (dd, J = 6.57 Hz, 3H), *1.05 (dd, J = 6.57 Hz, 3H), 1.25–1.23 (m, 2H), *0.86–0.84 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 163.4 (C), 141.3 (C), 130.1 (q, J = 32.7 Hz, 2C, CCF_3), 128.1 (2C), 125.7 (q, J = 272.6 Hz, 2C, CF_3), 60.0 (CH), 32.4 (CH_2), *30.6 (CH_2), 28.1 (CH_2), 21.8 (CH_3), *21.4 (CH_3), *19.4 (CH_3), 18.8 (CH_3), 14.3 (CH_2); IR (film) 1280, 1136, 1082 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{16}\text{H}_{16}\text{F}_6\text{N}_2\text{O}$ 366.11668 $[\text{M}]^+$, found 366.11723.

(3,5-Bis(trifluoromethyl)benzoyl(2-butyl-6-methyl-2,3,4,5-tetrahydropyridinium-1-yl)amide (2j). Synthesized using **1j** (0.250 g, 0.610 mmol; procedure A, 120 °C, 14 h). Chromatographic purification (1% MeOH/ CH_2Cl_2) afforded a brown oil (0.230 g, 93% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.51 (s, 2H), 7.84 (s, 1H), 3.95–4.01 (m, 1H), 2.74 (s, 2H), 2.20 (s, 3H), 2.19–1.95 (m, 3H), 1.94–1.77 (m, 2H), 1.75–1.57 (m, 1H), 1.47–1.24 (m, 4H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.3, 165.1, 139.8, 130.8 (q, J = 33.1 Hz, 2C), 128.2 (2C), 123.2 (q, J = 272.3 Hz, 2C), 123.0, 64.6, 32.5, 31.1, 28.4, 24.8, 22.2, 21.9, 14.1, 13.7; IR (film) 2964, 1626, 1576, 1318, 1278, 1131 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{OF}_6$ 408.1636 $[\text{M}]^+$, found 408.16248.

(3,5-Bis(trifluoromethyl)benzoyl(2-phneyl-6-methyl-2,3,4,5-tetrahydropyridinium-1-yl)amide (2k). Synthesized using **1k** (0.170 g, 0.397 mmol; procedure A, 120 °C, 12 h). Chromatographic purification (2% MeOH/ CH_2Cl_2) afforded a yellow solid (0.156 g, 91% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.31 (s, 2H), 7.79 (s, 1H), 7.37–7.28 (m, 3H), 7.24–7.22 (m, 2H), 5.40 (s, 1H), 2.89 (t, J = 6.4 Hz, 2H), 2.49–2.41 (m, 1H), 2.37 (s, 3H), 2.21–2.14 (m, 1H), 1.87–1.72 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.1, 139.4, 137.8, 130.7 (q, J = 33.0 Hz, 2C), 128.6 (2C), 127.9 (2C), 127.1, 126.5 (2C), 123.3 (q, J = 272.7 Hz, 2C), 122.9, 67.7, 32.7, 30.0, 22.2, 18.8, 14.1; ^{15}N IR (film) 3279, 2945, 1660, 1569, 1278, 1133, 907 cm^{-1} ; HRMS

(EI-Q-TOF) exact mass calcd for $C_{21}H_{18}F_6N_2O$ 428.1323 $[M]^+$, found 428.13142.

N-(2-Methylpyrrolidin-1-yl)-3,5-bis(trifluoromethyl)benzamide [3l (reduction of 2l)]. Synthesized using **1l** (0.250 g, 0.739 mmol; procedure A, 140 °C, 14 h). 1H NMR analysis showed a 45% NMR yield. Due to instability, it was reduced for isolation. Dipole **2l** was dissolved in MeOH (7.5 mL), and $NaBH_4$ (0.084 g, 2.22 mmol) was added. After 2 h, the reaction was quenched (aqueous NH_4Cl), extracted (CH_2Cl_2), washed ($NaHCO_3$, brine), dried (Na_2SO_4), and concentrated. Chromatographic purification (50% Et_2O /pentane) afforded a yellow oil (0.110 g, 44% yield). 1H NMR (300 MHz, $CDCl_3$) δ 8.37–8.25 (m, 2H), 7.96 (s, 1H), 6.85 (br s, 1H), 3.51–2.63 (m, 3H), 2.10–1.63 (m, 4H), 1.24–1.22 (m, 2H), 0.99–0.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 131.9 (q, $J = 31.6$ Hz, 2C), 129.6, 127.5 (2C), 124.3, 122.9 (q, $J = 272.8$ Hz, 2C), 62.6, *56.5, 55.6, 30.3, *30.0, 20.5, *19.8, 17.7; IR (film) 3370, 2940, 2890, 1680, 1276, 1128, 1083 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{14}H_{14}F_6N_2O$ 340.10103 $[M]^+$, found 340.10162.

(5-Benzyl-3,4-dihydro-2H-pyrrolium-1-yl)(3,5-bis(trifluoromethyl)benzoyl)amide (2m). Synthesized using **1m** (0.250 g, 0.603 mmol; procedure A, 150 °C, 14 h). Chromatographic purification (2% MeOH/ CH_2Cl_2) afforded a yellow oil (0.153 g, 62% yield). 1H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 2H), *8.34 (s, 2H), *7.99 (s, 1H), 7.89 (s, 1H), 7.38–7.24 (m, 5H), 4.51 (s, 2H), 3.96 (s, 2H), 2.86 (t, $J = 7.2$ Hz, 2H), 2.28–2.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 133.0, 131.0 (q, $J = 33.3$ Hz, 2C), 129.3 (2C), 129.2 (2C), 128.3, 127.9, 127.7, 123.4 (q, $J = 272.8$ Hz, 2C), 123.4, 60.2, 35.9, 34.4, 17.9; IR (film) 3393, 3207, 1668, 1280, 1178, 1132, 908 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{20}H_{16}F_6N_2O$ 414.1167 $[M]^+$, found 414.1169.

Dimethyl 1-(3,5-bis(trifluoromethyl)benzoyl)-3a-methyl-1,3a,4,5,6,7-hexahydropyrazolo[1,5-a]pyridine-2,3-dicarboxylate (3a, eq 2). Synthesized by refluxing **2a** (0.090 g, 0.25 mmol) and dimethylacetylene dicarboxylate (0.044 g, 0.31 mmol) for 48 h in toluene (0.1 M). Evaporation and then chromatography (20% Et_2O /hexane) afforded a yellow oil (0.055 g, 45% yield). 1H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 2H), 8.03 (s, 1H), 3.98 (s, 3H), 3.81 (s, 3H), 2.83 (d, $J = 10.0$ Hz, 1H), 2.67 (d, $J = 11.1$ Hz, 2H), 1.53–1.76 (m, 6 H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 162.4, 161.6, 140.0, 134.0, 131.8, 131.3, 130.1 (2C), 125.5, 124.7, 121.2, 70.3, 53.2, 52.9, 52.1, 30.6, 29.7, 27.4, 23.0, 20.4; IR (film) 1652, 1508, 1330, 1278, 1143, 1095 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{21}H_{20}F_6N_2O_5$ 494.1276 $[M]^+$, found 494.1270.

Substrate Preparation. The procedure B to form the substrates has been reported.^{11b}

3,5-Bis(trifluoromethyl)-N'-(hex-5-ynyl)benzohydrazide (1a). Synthesized using hex-5-yn-1-ol (1.50 g, 15.3 mmol; procedure B). Chromatographic purification (50% Et_2O /pentane) afforded a pink solid (3.06 g, 57% yield). 1H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 2H), 8.03 (s, 1H), 3.00 (t, $J = 6.9$ Hz, 2H), 2.26 (td, $J = 6.68, 2.6$ Hz, 2H), 1.96 (t, $J = 2.6$ Hz, 1H), 1.74–1.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 134.9, 132.4 (q, $J = 34.0$ Hz, 2C), 127.3 (2C), 125.4, 122.8 (q, $J = 273.1$ Hz, 2C), 84.1, 68.7, 51.5, 26.7, 25.7, 18.2; IR (film) 3447, 2922, 2850, 1649, 1539, 1079 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{15}H_{14}F_6N_2O$ 352.1010 $[M]^+$, found 352.10145.

3,5-Bis(trifluoromethyl)-N'-(hept-5-ynyl)benzohydrazide (1b). Synthesized using hept-5-yn-1-ol¹⁶ (0.26 g, 2.23 mmol; procedure B). Chromatographic purification (40% Et_2O /pentane) afforded a white solid (0.33 g, 40% yield). 1H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 2H), 8.03 (s, 1H), 7.71 (br, 1H), 4.88 (br, 1H), 2.99 (t, $J = 7.1$ Hz, 2H), 2.23–2.14 (m, 2H), 1.77 (t, $J = 2.5$ Hz, 3H), 1.71–1.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 135.0, 132.3 (q, $J = 32.9$ Hz, 2C), 127.2 (2C), 125.4, 122.8 (q, $J = 274.8$ Hz, 2C), 78.7, 67.2, 51.7, 27.0, 26.4, 18.6, 3.4; IR (film) 3211, 2940, 1641, 1277, 1133 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{16}H_{16}F_6N_2O$ 366.11668 $[M]^+$, found 366.1195.

3,5-Bis(trifluoromethyl)-N'-(6-phenylhex-5-ynyl)benzohydrazide (1c). Synthesized using 6-phenylhex-5-yn-1-ol¹⁷ (1.87 g, 10.7 mmol; procedure B). Chromatographic purification (20% EtOAc/hexanes) afforded a pink solid (quantitative). 1H NMR

(400 MHz, $CDCl_3$) δ 8.21 (s, 2H), 8.01 (s, 1H), 7.37–7.35 (m, 2H), 7.27–7.24 (m, 3H), 3.05 (t, $J = 6.7$ Hz, 2H), 2.47 (t, $J = 6.5$ Hz, 2H), 1.80–1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 134.7, 132.4 (q, $J = 34.0$ Hz, 2C), 131.5 (2C), 128.2 (2C), 127.6, 127.3 (2C), 125.4, 123.7, 122.7 (q, $J = 273.3$ Hz, 2C), 89.5, 81.1, 51.7, 26.9, 26.0, 19.2; IR (film) 3295, 2918, 2878, 1649, 1082 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{21}H_{18}F_6N_2O$ 428.1323 $[M]^+$, found 428.13067.

3,5-Bis(trifluoromethyl)-N'-(6-(3,5-dimethylphenyl)hex-5-ynyl)benzohydrazide (1d). Synthesized using 6-(3,5-dimethylphenyl)hex-5-yn-1-ol¹⁸ (1.10 g, 5.84 mmol; procedure B). Chromatographic purification (45% Et_2O /pentane) afforded a pink oil (1.48 g, 56% yield). 1H NMR (300 MHz, $CDCl_3$) δ *8.43 (s, 2H), 8.20 (s, 2H), *8.05 (s, 1H), 8.01 (s, 1H), 7.00 (s, 2H), *6.96 (s, 2H), 6.90 (s, 1H), 3.04 (t, $J = 6.8$ Hz, 2H), 2.46 (t, $J = 6.5$ Hz, 2H), 2.25 (s, 6H), *2.23 (s, 6H), 1.79–1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, *163.5, 137.7 (2C), 134.8, 132.4 (q, $J = 34.0$ Hz, 2C), *131.3, *129.7, 129.5, 129.2 (2C), *129.1, 127.3 (2C), 125.4, 123.3, *122.9, 122.8 (q, $J = 272.9$ Hz, 2C), 88.7, *87.4, *82.1, 81.3, *57.4, 51.7, *27.0, 26.1, *25.3, 24.6, 21.0, *20.9, 19.2, *18.9; IR (film) 3465, 2945, 1645, 1280, 1136 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{23}H_{22}F_6N_2O$ 456.1636 $[M]^+$, found 456.16519.

6-(4-Bromophenyl)hex-5-yn-1-ol (Procedure C). To hex-5-yn-1-ol (1.00 g, 10.2 mmol) in Et_3N (30.0 mL) were added 1-bromo-4-iodobenzene (3.46 g, 12.2 mmol), CuI (0.040 g, 0.020 mmol), and $PdCl_2(PPh_3)_2$ (0.070 g, 0.010 mmol). The reaction was stirred at room temperature (16 h), quenched ($NaHCO_3$), extracted ($EtOAc$), washed (brine), dried (Na_2SO_4), and concentrated. Chromatographic purification (30% Et_2O /pentane) afforded a brown oil (1.95 g, 76% yield). 1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, $J = 8.5$ Hz, 2H), 7.24 (d, $J = 8.5$ Hz, 2H), 3.71 (t, $J = 6.2$ Hz, 2H), 2.44 (t, $J = 6.7$ Hz, 2H), 1.64–1.84 (m, 4H), 1.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9 (2C), 131.4 (2C), 122.8, 121.6, 91.1, 79.9, 62.4, 31.9, 24.9, 19.2; IR (film) 3370, 2941, 1486, 1072, 824 cm^{-1} . HRMS (EI-Q-TOF) exact mass calcd for $C_{12}H_{13}BrO$ 252.0150 $[M]^+$, found 252.01651.

N'-(6-(4-Bromophenyl)hex-5-ynyl)-3,5-bis(trifluoromethyl)benzohydrazide (1e). Synthesized using 6-(4-bromophenyl)hex-5-yn-1-ol (1.95 g, 7.72 mmol; procedure B). Chromatographic purification (20% Et_2O /pentane) afforded a white solid (0.48 g, 18% yield). 1H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 2H), 8.03 (s, 1H), 7.39 (d, $J = 8.1$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H), 3.07 (t, $J = 6.0$ Hz, 2H), 2.46 (t, $J = 6.0$ Hz, 2H), 1.82–1.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 134.8, 132.9 (2C), 132.4 (q, $J = 33.9$ Hz, 2C), 131.4 (2C), 127.3 (2C), 125.4, 121.8 (q, $J = 131.0$ Hz, 2C), 121.7, 90.8, 80.1, 51.7, 27.0, 25.9, 19.2; IR (film) 3308, 2941, 1654, 1279, 1137 cm^{-1} . HRMS (EI-Q-TOF) exact mass calcd for $C_{21}H_{17}BrF_6N_2O$ 506.04284 $[M]^+$, found 506.0430.

3,5-Bis(trifluoromethyl)-N'-(6-(4-methoxyphenyl)hex-5-ynyl)benzohydrazide (1f). Synthesized using 6-(4-methoxyphenyl)hex-5-yn-1-ol¹⁹ (2.03 g, 9.91 mmol; procedure B). Chromatographic purification (10% EtOAc/hexanes) afforded a beige solid (1.49 g, 33% yield). 1H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 2H), 8.00 (s, 1H), 7.28 (d, $J = 8.8$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 3.77 (s, 3H), 3.02 (t, $J = 6.7$ Hz, 2H), 2.45 (t, $J = 6.1$ Hz, 2H), 1.73–1.68 (m, 4H), 1.61 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 159.0, 134.8, 132.7 (2C), 132.2 (q, $J = 33.9$ Hz, 2C), 127.3 (2C), 125.2 (2C), 122.8 (q, $J = 273.0$ Hz, 2C), 115.8, 113.8 (2C), 87.9, 80.8, 55.1, 51.6, 27.1, 26.1, 19.2; IR (film) 3272, 2939, 1660, 1288, 1134 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{22}H_{20}F_6N_2O_2$ 458.1429 $[M]^+$, found 458.14039.

4-(6-Hydroxyhex-1-ynyl) Methyl Benzoate. Prepared using hex-5-yn-1-ol (0.47 g, 4.77 mmol; procedure C) to afford a yellow oil (1.09 g, 99% yield). 1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, $J = 8.5$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 3.90 (s, 3H), 3.71 (t, $J = 6.1$ Hz, 2H), 2.48 (t, $J = 6.7$ Hz, 2H), 1.80–1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 131.4 (2C), 129.4 (2C), 128.9, 128.7, 93.3, 80.4, 62.4, 52.1, 31.8, 24.8, 19.7; IR (film) 3383, 2949, 1721, 1276 cm^{-1} ; HRMS (EI-Q-TOF) exact mass calcd for $C_{14}H_{16}O_3$ 232.1099 $[M]^+$, found 232.11002.

3,5-Bis(trifluoromethyl)-N'-(6-(4-methyl benzoate)hex-5-ynyl)benzohydrazide (1g). Synthesized using 6-(4-methyl benzoate)-hex-5-yn-1-ol (2.03 g, 9.91 mmol; procedure B). Chromatographic purification (50% Et₂O/hexanes) afforded a white solid (1.25 g, 55% yield). ¹H NMR (300 MHz, CDCl₃) δ *8.37 (s, 2H), 8.19 (s, 2H), *8.07 (s, 1H), 8.02 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), *7.89 (d, J = 8.6 Hz, 2H), 7.76 (br s, 1H), 7.42 (d, J = 8.5 Hz, 2H), *7.36 (d, J = 8.5 Hz, 2H), 4.88 (br s, 1H), 3.91 (s, 3H), 3.04 (t, J = 6.4 Hz, 2H), 2.50 (t, J = 6.5 Hz, 2H), 1.79–1.70 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 166.7, *166.4, 164.4, *163.7, 134.8, 132.1 (q, J = 33.9 Hz, 2C), 131.3 (2C), *131.3 (2C), 129.3 (2C), *129.2 (2C), 128.8, *128.7, *128.6, 128.5, 127.3 (2C), 125.1, 122.8 (q, J = 273.2 Hz, 2C), *93.2, 93.0, *80.6, 80.5, 57.4, 52.1, *51.6, 27.1, *26.4, *26.0, 25.9, 19.3; IR (film) 3454, 2942, 1721, 1656, 1280, 1139 cm⁻¹; HRMS (EI-Q-TOF) exact mass calcd for C₂₃H₂₀F₆N₂O₃ 486.1378 [M]⁺, found 486.13996.

3,5-Bis(trifluoromethyl)-N'-(6-(thiophen-2-yl)hex-5-ynyl)benzohydrazide (1h). Synthesized using 6-(thiophen-2-yl)hex-5-yn-1-ol²⁰ (2.00 g, 11.1 mmol; procedure B). Chromatographic purification (0.5% MeOH/CH₂Cl₂) afforded a white solid (1.14 g, 47% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.20 (s, 2H), 8.02 (s, 1H), 7.77 (s, 1H), 7.16 (dd, J = 1.1, 5.2 Hz, 1H), 7.10 (dd, J = 1.0, 3.6 Hz, 1H), 6.92 (dd, J = 3.6, 5.2 Hz, 1H), 4.89 (s, 1H), 3.03 (t, J = 5.8 Hz, 2H), 2.53–2.46 (m, 2H), 1.77–1.68 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 164.5, 134.7, 132.1 (q, J = 34.0 Hz, 2C), 130.9, 127.3 (2C), 126.7, 125.9, 125.2, 123.7, 122.8 (q, J = 273.1 Hz, 2C), 93.6, 74.1, 51.5, 27.0, 25.8, 19.4; IR (film) 3219, 2938, 1653, 1380, 1128, 906 cm⁻¹; HRMS (EI-Q-TOF) exact mass calcd for C₁₉H₁₆SF₆N₂O 434.0888 [M]⁺, found 434.08915.

3,5-Bis(trifluoromethyl)-N'-(hept-6-yn-2-yl)benzohydrazide (1i). Synthesized using hept-6-yn-2-ol²¹ (10.2 mmol; procedure B). Chromatographic purification (40% Et₂O/pentane) afforded a beige solid (1.38 g, 37% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.22 (s, 2H), 8.02 (s, 1H), 3.18–3.08 (m, 1H), 2.25 (s, 2H), 1.95 (s, 1H), 1.75–1.47 (m, 4H), 1.13 (d, J = 6.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 164.6, 135.0 (C), 132.4 (q, J = 34.0 Hz, 2C), 127.3 (2C), 125.3, 122.8 (q, J = 272.9 Hz, 2C), 84.3 (CH), 68.7 (C), 55.5 (C), 33.3 (CH₂), 24.3 (CH₂), 18.5 (CH₂), 18.4 (CH₃); IR (film) 3249, 2953, 1637, 1379, 1276, 1136 cm⁻¹; HRMS (EI-Q-TOF) exact mass calcd for C₁₆H₁₆F₆N₂O 352.0932 [M – CH₃]⁺, found 352.09257.

N'-(Dec-9-yn-5-yl)-3,5-bis(trifluoromethyl)benzohydrazide (1j). Hex-5-yn-1-ol (1.00 g, 10.2 mmol) and Et₃N (5.68 mL, 40.8 mmol) were premixed in CH₂Cl₂ (30.9 mL). SO₃·pyridine (4.90 g, 30.6 mmol) in DMSO (30.9 mL) was added at 0 °C. The reaction was stirred until complete, quenched (aqueous NH₄Cl), and extracted (CH₂Cl₂). The organic extracts were washed with water and brine, dried, and concentrated to afford the crude aldehyde. To this aldehyde were added THF (25.5 mL) and *n*-BuMgCl (2.0 M in THF, 25.5 mL, 50.9 mmol) at 0 °C. The solution was warmed to room temperature over 2 h. It was then diluted with Et₂O, quenched (aqueous NH₄Cl), extracted (Et₂O), washed (brine), dried (Na₂SO₄), and concentrated. Due to instability, dec-9-yn-5-ol was used immediately (procedure B). Chromatographic purification (20% Et₂O/pentane) yielded a white solid (1.64 g, 40% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.19 (s, 2H), 8.00 (s, 1H), 7.72 (br s, 1H), 4.90 (br s, 1H), 2.97 (t, J = 5.5 Hz, 1H), 2.32–2.27 (m, 2H), 1.95 (t, J = 2.6 Hz, 1H), 1.72–1.27 (m, 12H), 0.91 (t, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 164.4, 135.0, 132.4 (q, J = 33.4 Hz, 2C), 127.2 (2C), 125.3, 122.8 (q, J = 279.3 Hz, 2C), 84.6, 68.7, 59.9, 32.0, 30.7, 27.9, 23.8, 22.9, 18.5, 14.0; IR (film) 3212, 2940, 1641, 1274, 1170, 1140 cm⁻¹; HRMS (EI-Q-TOF) exact mass calcd for C₁₉H₂₂F₆N₂O 408.1636 [M]⁺, found 408.16348.

3,5-Bis(trifluoromethyl)-N'-(1-phenylhex-5-ynyl)benzohydrazide (1k). Synthesized using 1-phenylhex-5-yn-1-ol²² (0.67 g, 3.82 mmol; procedure B). Chromatographic purification (10% EtOAc/hexanes) yielded a white solid (0.47 g, 29% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.35 (br, 1H), 8.00 (s, 2H), 7.98 (s, 1H), 7.37–7.32 (m, 4H), 7.31–7.28 (m, 1H), 5.21 (br, 1H), 4.11 (dd, J = 5.5, 8.3 Hz, 1H), 2.16 (td, J = 6.9, 2.6 Hz, 2H), 1.99–1.90 (m, 1H), 1.91 (t, J = 2.6 Hz, 1H), 1.86–1.77 (m, 1H), 1.54–1.45 (m, 1H), 1.43–1.35 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 164.6, 140.9, 134.9, 132.2 (q, J = 34.0 Hz,

2C), 128.6 (2C), 128.0 (2C), 127.8 (2C), 127.3, 125.2, 122.7 (q, J = 273.0 Hz, 2C), 83.8, 68.8, 64.7, 33.8, 24.6, 18.2; IR (film) 3302, 2945, 1641, 1277, 1134 cm⁻¹; HRMS (EI-Q-TOF) exact mass calcd for C₂₁H₁₈F₆N₂O 428.1323 [M]⁺, found 428.1298.

3,5-Bis(trifluoromethyl)-N'-(pent-4-ynyl)benzohydrazide (1l). Synthesized using 4-pentyn-1-ol (1.50 g, 17.8 mmol; procedure B). Chromatographic purification (40% Et₂O/pentane) afforded a pink solid (1.87 g, 31% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.25 (s, 2H), 8.03 (s, 1H), 3.13 (t, J = 6.9 Hz, 2H), 2.35 (td, J = 7.0, 2.7 Hz, 2H), 1.99 (t, J = 2.6 Hz, 1H), 1.80 (p, J = 7.1 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 164.4, 134.1, 132.4 (q, J = 34.1 Hz, 2C), 127.6 (2C), 125.7, 122.8 (q, J = 272.8 Hz, 2C), 83.3, 69.4, 50.9, 26.0, 16.0; IR (film) 3275, 2941, 2890, 1596, 1132 cm⁻¹; HRMS (EI-Q-TOF) exact mass calcd for C₁₄H₁₂F₆N₂O 338.0854 [M]⁺, found 338.08366.

3,5-Bis(trifluoromethyl)-N'-(5-phenylpent-4-ynyl)benzohydrazide (1m). Synthesized using 5-phenylpent-4-yn-1-ol²³ (1.78 g, 11.9 mmol; procedure B). Chromatographic purification (40% Et₂O/pentane) afforded a pink oil (1.87 g, 38% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.21 (s, 2H), 8.02 (s, 1H), 7.40–7.35 (m, 2H), 7.29–7.24 (m, 3H), 3.16 (t, J = 6.9 Hz, 2H), 2.56 (t, J = 6.9 Hz, 2H), 1.87 (p, J = 6.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 164.5, 134.8, 132.4 (q, J = 34.0 Hz, 2C), 131.5 (2C), 128.3 (2C), 127.7, 127.2 (2C), 127.2, 125.4, 123.5, 122.8 (q, J = 273.3 Hz, 2C), 89.1, 81.3, 51.0, 27.0, 17.1; IR (film) 3289, 3098, 2937, 1649, 1284, 1139 cm⁻¹; LRMS *m/z* (relative intensity) 323.0617 (37.1%), 241.0068 (100%), 173.1080 (90.5%), 145.0792 (29.6%), 129.0679 (24.9%), 128.0631 (56.7%), 115.0561 (81.9%).

■ ASSOCIATED CONTENT

📄 Supporting Information

Short discussion on the importance of the 3,5-bis-(trifluoromethyl)benzohydrazide substituent, results for other hydrazides investigated, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

✉ Corresponding Author

*E-mail: andre.beauchemin@uottawa.ca

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Ottawa, the Canadian Foundation for Innovation, the Ontario Ministry of Research and Innovation, and NSERC for support. I.D. thanks NSERC and FQRNT for graduate scholarships. An exchange scholarship from the Université Pierre et Marie Curie (S.T.) is also acknowledged.

■ REFERENCES

- (1) For reviews, see: (a) Struckwisch, C. G. *Synthesis* **1973**, 469. (b) Rodina, L. L.; Kolberg, A.; Schulze, B. *Heterocycles* **1998**, 49, 587. (c) Schantl, J. G. In *Science of Synthesis*; Padwa, A., Bellus, D., Eds.; Thieme Verlag: Stuttgart, 2004; Vol. 27, pp 731–824.
- (2) For a review on cycloadditions, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, 16, 10. For examples, see: (b) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, 133, 13337. (c) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, 3, 642. (d) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, 125, 10778. (e) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, 128, 6330. (f) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, 129, 5334. (g) Qian, Y.; Zavalij, P. J.; Hu, W.; Doyle, M. P. *Org. Lett.* **2013**, 15, 1564.

(3) For examples, see: (a) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244. (b) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (c) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971. (d) Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049.

(4) Godteredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1955**, *9*, 1498. Usually an aldehyde (or a derivative): see reviews in ref 1.

(5) (a) Grigg, R.; Dowling, M.; Jordan, M. W.; Sridharan, V. *Tetrahedron* **1987**, *43*, 5873. (b) Kanemasa, S.; Tomoshige, N.; Wada, E.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3944. (c) Noguchi, M.; Kiriki, Y.; Tsuruoka, T.; Mizui, T.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 99.

(6) (a) Huisgen, R.; Grashey, R.; Krischke, R. *Tetrahedron Lett.* **1962**, *3*, 387. (b) Potts, K. T.; Youzwak, H. P.; Zurawel, S. J., Jr. *J. Org. Chem.* **1980**, *45*, 90. For a comprehensive review, see ref 1b.

(7) (a) Cauquis, G.; Chabaud, B. *Tetrahedron* **1978**, *34*, 903. (b) Wilson, R. M.; Hengge, A. *Tetrahedron Lett.* **1985**, *26*, 3673. (c) Grigg, R.; Heaney, F.; Idle, J.; Somasunderam, A. *Tetrahedron Lett.* **1990**, *31*, 2767.

(8) (a) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L. *J. Org. Chem.* **1983**, *48*, 4567. (b) Dolle, R. E.; Barden, M. C.; Brennan, P. E.; Ahmed, G.; Tran, V.; Ho, D. M. *Tetrahedron Lett.* **1999**, *40*, 2907.

(9) (a) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111. (b) Gan, W.; Moon, P. J.; Clavette, C.; Das Neves, N.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 1890.

(10) For a review on the preparation of cyclic azomethine imines from azo compounds, see: Schantl, J. G. *Adv. Heterocycl. Chem.* **2010**, *99*, 185.

(11) For efforts using hydrazides, see: (a) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Whipp, C. J.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740. (b) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A.; Beauchemin, A. M. *Chem. Commun.* **2011**, 562. See also: (c) Baxter Vu, J. M.; Leighton, J. L. *Org. Lett.* **2011**, *13*, 4056.

(12) For examples of metal-catalyzed hydrohydrazinations, see: (a) Li, Y.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2004**, *126*, 1794. (b) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (c) Johns, A. M.; Liu, Z.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7259. (d) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2304 and references cited therein. (e) Hoover, J. M.; DiPasquale, A.; Mayer, J. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 5043.

(13) For related intermolecular reactivity using an activated alkyne (DMAD), see: Panfil, I.; Urbańczyk-Lipkowska, Z.; Suwińska, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1199.

(14) For other approaches to form ene-hydrazides, see: (a) Lerche, H.; Wanninger, G.; Severin, T. *Synthesis* **1982**, 1111. (b) Barluenga, J.; Moriel, P.; Aznar, F.; Valdes, C. *Org. Lett.* **2007**, *9*, 275. (c) Rodriguez Rivero, M.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (d) Dubois, M.; Deniau, E.; Couture, A.; Granclandon, P. *Tetrahedron* **2012**, *68*, 7140.

(15) Some quaternary carbons were not detected using ¹³C NMR (broad peaks): **2h**, **2i**, **2k**, **2m** (1), **2c**, **2e**, **2f** (2), **2d**, **2g** (3).

(16) Hosoya, T.; Wakao, M.; Kondo, Y.; Doi, H.; Suzuki, M. *Org. Biomol. Chem.* **2004**, *2*, 24.

(17) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076.

(18) Rizk, T.; Bilodeau, E.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8325.

(19) Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270.

(20) Pereira, R.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **2001**, *57*, 7871.

(21) Wu, Y.; Gao, J. *Org. Lett.* **2008**, *10*, 1533.

(22) Inaba, K.; Takaya, J.; Iwasawa, N. *Chem. Lett.* **2007**, *36*, 474.

(23) Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442.