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Synthesis of Azomethine Imines Using an Intramolecular Alkyne Hydrohydrazination Approach

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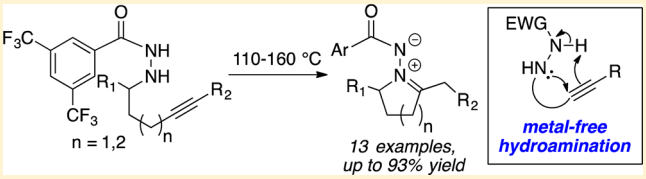
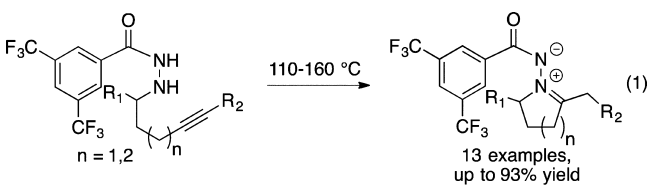
Supporting Information

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 hydrazonium 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 condensor (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, CO_2Me, 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 (R^1, entry 1 vs 9−11).

The overall reaction likely proceeds via a Cope-type hydrohydrazidation[11] (hydroamination) event to provide an enehydrazide 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 enehydrazide intermediate was observed by NMR.

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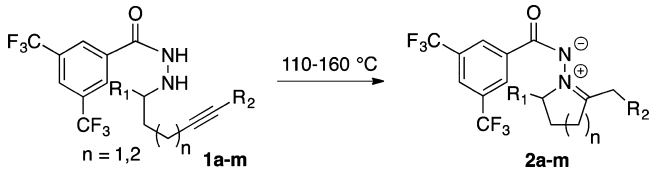
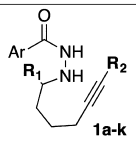
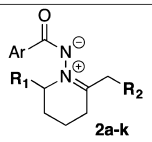
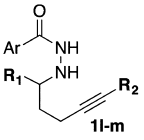
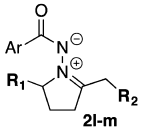
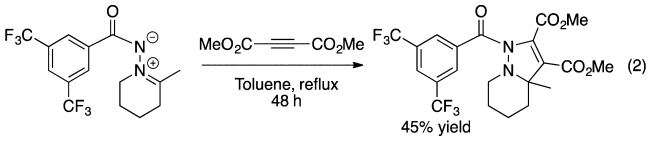
Table 1. Scope of Hydrohydrazination Route to Azomethine Imines[a]



Entry	Hydrazide	Temp (°C)	Product	Yield (%)
				
	1a-k		2a-k	
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-$Me_2C_6H_3$ (**1d**)	140	**2d**	92
5	R^1=H,R^2=4-BrC_6H_4 (**1e**)	140	**2e**	73
6	R^1=H, R^2=4-$MeOC_6H_4$ (**1f**)	140	**2f**	86
7	R^1=H, R^2=4-$MeO_2CC_6H_4$ (**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=*n*-Bu, R^2=H (**1j**)	120	**2j**	93
11	R^1=Ph, R^2=H (**1k**)	120	**2k**	91
				
	1l-m		2l-m	
12	R^1=R^2=H (**1l**)	140	**2l**	44[c]
13	R^1=H, R^2=Ph (**1m**)	150	**2m**	62

[a]Conditions: a solution of hydrazide in $PhCF_3$ (0.05M) was heated for 12−14 h (microwave reactor). [b]Performed on a 5.77 mmol scale in refluxing $PhCF_3$ overnight. [c]Yield after reduction with $NaBH_4$.

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 alkynyl-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 F_{254}. Visualization was accomplished under UV light followed by staining with $KMnO_4$ 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 CaH_2; $PhCF_3$ 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

dx.doi.org/10.1021/jo4011409 | J. Org. Chem. XXXX, XXX, XXX−XXX

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 ^{1}H 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). ^{1}H 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 $C_{15}H_{14}F_6N_2O$ 352.1010 [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). ^{1}H 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 $C_{16}H_{16}F_6N_2O$ 366.1167 [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). ^{1}H 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] IR (film) 3343, 2940, 2360, 1635, 1094 cm^{-1}; HRMS (EI-Q-TOF) exact mass calcd for $C_{21}H_{18}F_6N_2O$ 428.13233 [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). ^{1}H 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] IR (film) 3467, 2967, 1660, 1276, 1136 cm^{-1}; HRMS (EI-Q-TOF) exact mass calcd for $C_{23}H_{22}F_6N_2O$ 456.1636 [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). ^{1}H 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] IR (film) 3378, 2943, 1728, 1568, 1276 1132 cm^{-1}; HRMS (EI-Q-TOF) exact mass calcd for $C_{21}H_{17}BrF_6N_2O$ 506.0428 [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). ^{1}H 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] IR (film) 2956, 1569, 1514, 1316, 1279, 1132 cm^{-1}; HRMS (EI-Q-TOF) exact mass calcd for $C_{22}H_{20}F_6N_2O_2$ 458.1429 [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). ^{1}H 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] IR (film) 3287, 2954, 2235, 1725, 1679, 1573, 1279, 1133, 904 cm^{-1}; HRMS (EI-Q-TOF) exact mass calcd for $C_{23}H_{20}F_6N_2O_3$ 486.1378 [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). ^{1}H 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] IR (film) 3237, 2944, 1671, 1626, 1565, 1279, 1133 cm^{-1}; HRMS (EI-Q-TOF) exact mass calcd for $C_{19}H_{16}SF_6N_2O$ 434.0888 [M]$^+$, found 434.0912.

(3,5-Bis(trifluoromethyl)benzoyl(2,6-dimethyl-2,3,4,5-tetrahydropyridinium-1yl)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). ^{1}H 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 $C_{16}H_{16}F_6N_2O$ 366.11668 [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). ^{1}H 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 $C_{19}H_{22}N_2OF_6$ 408.1636 [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). ^{1}H 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), 2.49−241 (m, 1H), 2.37 (s, 3H), 2.21−214 (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] IR (film) 3279, 2945, 1660, 1569, 1278, 1133, 907 cm^{-1}; HRMS

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(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). ^{1}H 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). ^{1}H 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). ^{1}H 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;[15] 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). ^{1}H 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). ^{1}H 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-ol[16] (0.26 g, 2.23 mmol; procedure B). Chromatographic purification (40% Et_2O/pentane) afforded a white solid (0.33 g, 40% yield). ^{1}H 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-ol[17] (1.87 g, 10.7 mmol; procedure B). Chromatographic purification (20% EtOAc/hexanes) afforded a pink solid (quantitative). ^{1}H 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-ol[18] (1.10 g, 5.84 mmol; procedure B). Chromatographic purification (45% Et_2O/pentane) afforded a pink oil (1.48 g, 56% yield). ^{1}H 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). ^{1}H 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). ^{1}H 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-methoxy-phenyl)-hex-5-yn-1-ol[19] (2.03 g, 9.91 mmol; procedure B). Chromatographic purification (10% EtOAc/hexanes) afforded a beige solid (1.49 g, 33% yield). ^{1}H 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). ^{1}H 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.

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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% Et_2O/hexanes) afforded a white solid (1.25 g, 55% yield). ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{23}H_{20}F_6N_2O_3$ 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-ol[20] (2.00 g, 11.1 mmol; procedure B). Chromatographic purification (0.5% MeOH/CH_2Cl_2) afforded a white solid (1.14 g, 47% yield). ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{16}SF_6N_2O$ 434.0888 $[M]^+$, found 434.08915.

3,5-Bis(trifluoromethyl)-*N*′-(hept-6-yn-2-yl)benzohydrazide (1i). Synthesized using hept-6-yn-2-ol[21] (10.2 mmol; procedure B). Chromatographic purification (40% Et_2O/pentane) afforded a beige solid (1.38 g, 37% yield). ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 24.3 (CH_2), 18.5 (CH_2), 18.4 (CH_3); IR (film) 3249, 2953, 1637, 1379, 1276, 1136 cm^{-1}; HRMS (EI-Q-TOF) exact mass calcd for $C_{16}H_{16}F_6N_2O$ 352.0932 $[M - CH_3]^+$, 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 Et_3N (5.68 mL, 40.8 mmol) were premixed in CH_2Cl_2 (30.9 mL). SO_3·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 NH_4Cl), and extracted (CH_2Cl_2). 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 Et_2O, quenched (aqueous NH_4Cl), extracted (Et_2O), washed (brine), dried (Na_2SO_4), and concentrated. Due to instability, dec-9-yn-5-ol was used immediately (procedure B). Chromatographic purification (20% Et_2O/pentane) yielded a white solid (1.64 g, 40% yield). ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{22}F_6N_2O$ 408.1636 $[M]^+$, found 408.16348.

3,5-Bis(trifluoromethyl)-*N*′-(1-phenylhex-5-ynyl)-benzohydrazide (1k). Synthesized using 1-phenylhex-5-yn-1-ol[22] (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, $CDCl_3$) 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, 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{18}F_6N_2O$ 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% Et_2O/pentane) afforded a pink solid (1.87 g, 31% yield). ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{12}F_6N_2O$ 338.0854 $[M]^+$, found 338.08366.

3,5-Bis(trifluoromethyl)-*N*′-(5-phenylpent-4-ynyl)-benzohydrazide (1m). Synthesized using 5-phenylpent-4-yn-1-ol[23] (1.78 g, 11.9 mmol; procedure B). Chromatographic purification (40% Et_2O/pentane) afforded a pink oil (1.87 g, 38% yield). ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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)benzhydrazide 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.

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Notes

The authors declare no competing financial interest.

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