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Allyl-Assisted, Cu(I)-Catalyzed Azide−Alkyne Cycloaddition/Allylation Reaction: Assembly of the [1,2,3]Triazolo-4,5,6,7-tetrahydropyridine Core Structure

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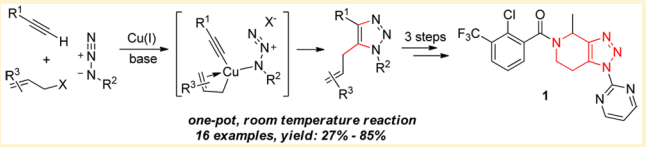
Supporting Information

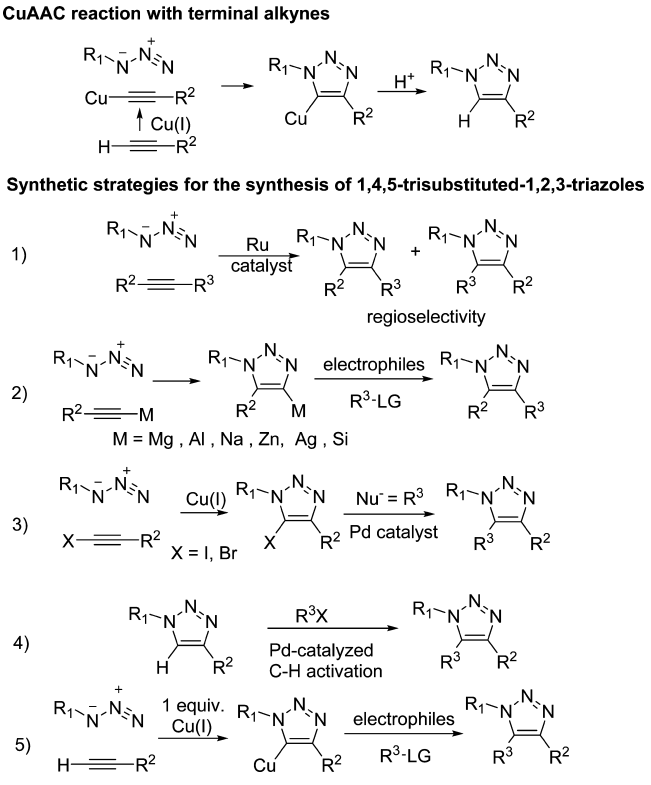
ABSTRACT: We report a Cu(I)-catalyzed azide−alkyne−allyl halide three-component reaction for a one-pot synthesis of 1,4-disubstituted 5-allyl-1,2,3-triazoles. The allyl moiety provides not only the electrophile but also a coordinating ligand to Cu, which is essential for the reaction to occur under mild conditions. A concise synthesis of a potential drug candidate **1** is realized based on this key reaction.



INTRODUCTION

In the past decade, Cu-catalyzed 1,3-dipolar azide−terminal alkyne cycloadditions (CuAAC "click" chemistry) have enjoyed increasing popularity with wide applications in organic synthesis, medicinal chemistry, and material and polymer science.[1] The major contributing factors for this popularity are the high regioselectivity and rather forgiving reaction conditions.[2] Mechanistic studies have shown that formation of the reactive Cu acetylide intermediate is critical for achieving such high reactivity and regiospecificity (Scheme 1). Not surprisingly, this type of copper catalysis is not applicable to internal alkynes due to the lack of terminal protons. Therefore, synthesis of fully substituted 1,2,3-triazoles remains a significant challenge for organic chemists. In recent years, a number of strategies have been formulated to address this problem. (1) Ru complexes have been identified as the effective catalysts for the 1,3-dipolar cycloaddition reaction of azides with internal alkynes. However, this Ru-catalyzed reaction often affords both possible regioisomers.[3] (2) To mimic the reactive Cu acetylide intermediate in the CuAAC reaction, a number of other acetylides, such as Mg,[4] Al,[5] Na,[6] Zn,[7] Ag,[8] and Si,[9] either generated in situ or preprepared, have been successfully utilized in the azide−alkyne cycloaddition reaction. Trapping of the 5-triazolyl metal intermediates with suitable electrophiles affords trisubstituted 1,2,3-triazoles, usually regioselectively. It is worth noting that different metals can lead to different regioisomeric products. Two major drawbacks of this approach are the use of stoichiometric amounts of metal and the difficulty in handling the reactive metal acetylides. (3) Terminal alkynes can be activated by the formation of 1-haloalkynes, which undergo Cu-catalyzed cycloaddition with azides to regioselectively generate 5-halo-1,2,3-triazoles. Further derivatization on the 5-halo position by, for example, Pd-catalyzed cross-coupling reactions provides 1,4,5-trisubstituted 1,2,3-triazoles.[10] (4) Recently, there have been some successes with Pd-catalyzed C−H activation of 1,4-disubstituted 1,2,3-triazoles. However, the reaction conditions are usually quite harsh, and the reaction scope is rather limited.[11] (5) Finally, a few instances have been

Scheme 1. Syntheses of Substituted 1,2,3-Triazoles



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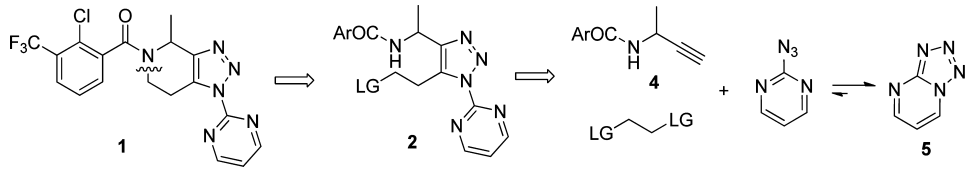
Scheme 2. Retrosynthetic Analysis



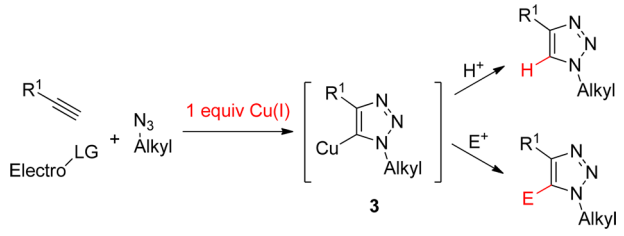
reported wherein the 5-triazolylcopper(I) intermediates have been trapped with strong electrophiles to prepare 1,4,5-trisubstituted 1,2,3-triazoles.[12] Probably because of the weak nucleophilicity of the 5-triazolylcopper(I) intermediate, the reaction scope is rather limited and stoichiometric amounts of Cu are usually required. Nevertheless, this approach is rather appealing to us because of its simplicity. Herein, we report our findings on a Cu(I)-catalyzed azide−alkyne−allyl halide three-component one-pot assembly of 1,4-disubstituted 5-allyl-1,2,3-triazoles. The reaction is catalytic in Cu and is performed at ambient temperature. It appears that this reaction goes through a slightly different mechanism: instead of the simple trapping of the 5-triazolylcopper(I) intermediate with allyl halide, we believe that the allyl group serves as a ligand to Cu by forming a (5-triazolyl)(allyl)copper(III) complex, which undergoes reductive elimination to afford 1,4-disubstituted 5-allyl-1,2,3-triazole. The reaction scope is broad, and the allyl group provides ample opportunities for further functionalization. To showcase the utility of this reaction, synthesis of a drug candidate is realized in a concise fashion.

RESULTS AND DISCUSSION

In connection with one of our drug discovery programs, we were pursuing an efficient synthesis of compound **1** (Scheme 2).[13] We envisioned an intramolecular cyclization of elaborated precursor **2**[14] that could be derived from an azide−alkyne−electrophile three-component reaction.

In the few literature reports describing the requisite azide−alkyne−electrophile three-component reaction, a pathway involving the trapping of the 5-triazolylcopper(I) intermediate **3** was proposed (Scheme 3).[12] However, a few drawbacks

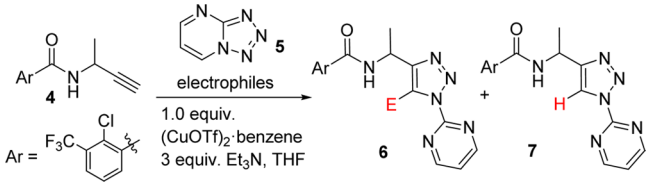
Scheme 3. Azide−Alkyne−Electrophile Three-Component Reaction



limited its synthetic utility. First, presumably due to the weak nucleophilicity of 5-triazolylcopper(I) intermediate **3**, the suitable electrophiles for the reaction were limited to the very strong ones, such as ICl and acid chloride, which would not serve our purpose. Second, multiple equivalents of electrophiles with a stoichiometric amount of Cu(I) salt were typically required to suppress the competing protonation process. Third, the literature precedents mostly involved the use of reactive alkyl azides, presumably to facilitate the formation of intermediate **3**, which could potentially be an issue for us because 2-pyrimidine azide is known for its low reactivity toward the CuAAC reaction due to its predominant existence in the closed tetrazole form **5** (Scheme 2).[15]

With the above concerns in mind, we set out to explore the azide−alkyne−electrophile three-component reaction with a number of electrophilic two-carbon building blocks (Table 1).

Table 1. Survey of Electrophiles for Cu(I)-Mediated Azide−Alkyne−Electrophile Three-Component Reaction



entry	electrophiles	conditions	product **6**	product **7**[a]
1		rt -160 °C[b]	none	main product
2		neat, rt-160 °C[b]	none	main product
3		neat, rt-160 °C[b]	none	main product
4		rt, ON	complex mixture	
5		rt-160 °C[b]	complex mixture	
6		neat, rt, ON	none	main product
7		neat, 160 °C[b]	35%	10%
8		rt, ON	trace	main product
9		rt-160 °C[b]	none	main product
10		rt, ON	50%	5%
11		rt, ON	47%	5%
12		rt, ON	none	main product
13		rt, ON	none	main product
14		rt-160 °C[b]	none	main product
15		rt, ON	10%	main product
16		neat, rt, ON	none	main product

[a]Based on the HPLC trace of the crude reaction mixture. [b]Microwave conditions, 10 min.

One equivalent of $(CuOTf)_2$·benzene complex was used for the initial screening because it was shown to mediate the click reaction of terminal alkynes and closed-form heterocyclic azides similar to **5**.[15a] With ethylene oxide as the electrophile (entry 1), compound **7** was the exclusive product at room temperature. No desired product **6** was generated even at 160 °C under microwave heating conditions. Similar results were

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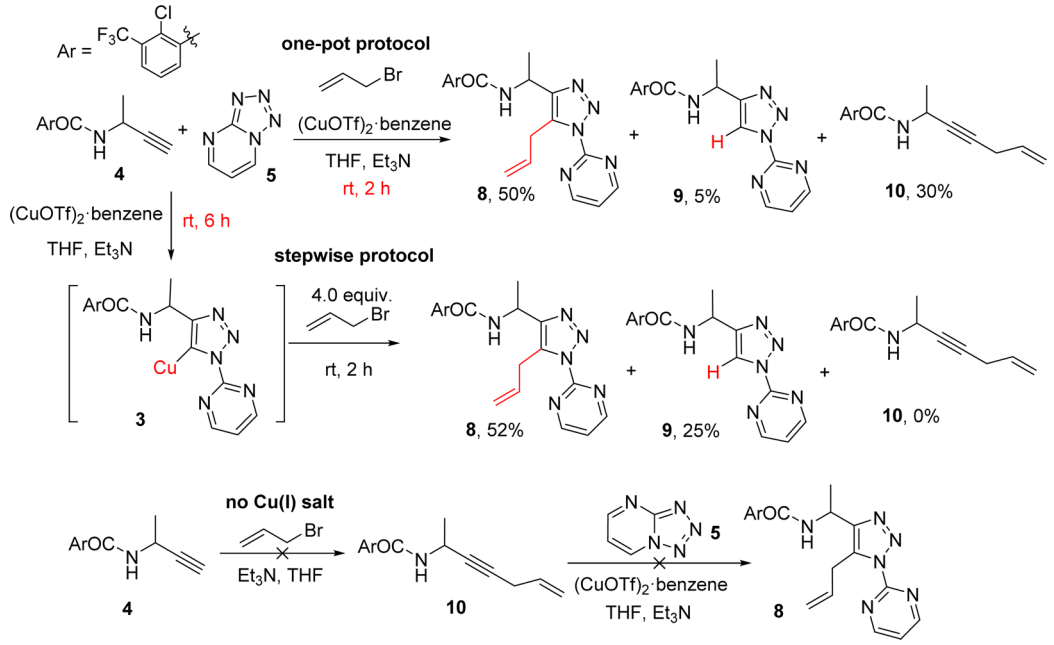
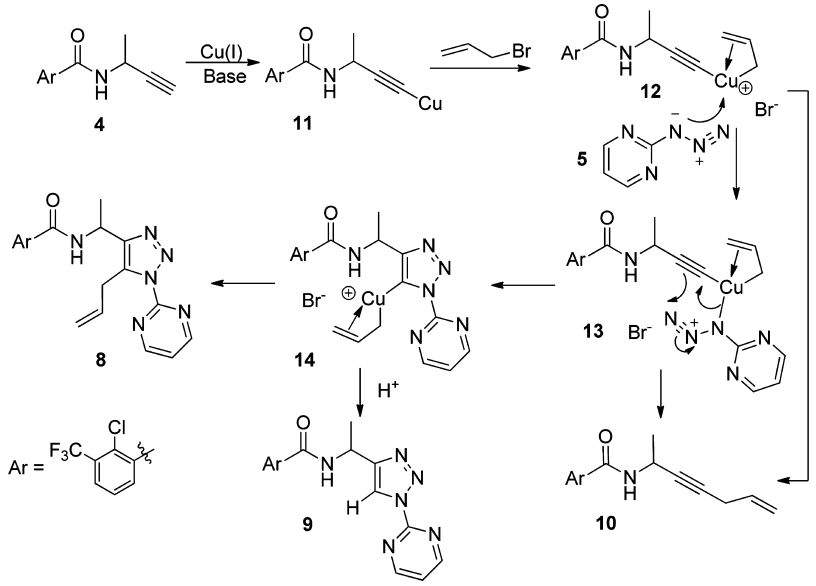
Scheme 4. Observations



Scheme 5. Proposed Reaction Pathways



obtained with alkyl halides (entries 2 and 3). More electrophilic α-keto halides (entries 4 and 5) were then investigated with the hope of better trapping the 5-triazolylcopper(I) intermediate **3**. Unfortunately, the reactions resulted in complex mixtures. More interesting were reactions with α-bromoethyl acetate as the electrophile. Whereas the exclusive formation of compound **7** was observed at room temperature overnight (entry 6), heating the same reaction to 160 °C under microwave conditions afforded compound **6** as the main product (entry 7), albeit in low isolated yield. These results suggested that the 5-triazolylcopper(I) intermediate **3** might be stable at room temperature, and that the protonation process was occurring during the workup of the reaction. Using other α-haloacetates as the electrophiles (entries 8 and 9) did not improve the yield of **6**. Intriguingly, allyl bromide (entry 10) and allyl iodide (entry 11) afforded similar yields of the desired product **6**. In comparison, compound **7** was the only product obtained with the less electrophilic allyl chloride (entry 12) and allyl acetate (entry 13). Other electrophiles with a β-unsaturated bond (entries 14–16) failed to deliver useful yields of compound **6**.

The drastic reactivity difference of allyl bromide and allyl iodide (Table 1, entries 10 and 11) from other electrophiles prompted us to study the Cu(I)-mediated azide–alkyne–allyl halide three-component reaction in greater detail (Scheme 4). With the one-pot protocol, in addition to the two major products **8** and **9** mentioned, compound **10** was also isolated in 30% yield, apparently from allylation of compound **4**. Without the Cu(I) salt, the allylation reaction of compound **4** with allyl bromide does not occur under the same reaction conditions. Entries 6 and 7 in Table 1 suggested the feasibility of performing the azide–alkyne–allyl halide three-component reaction in a stepwise fashion, that is, to generate 5-

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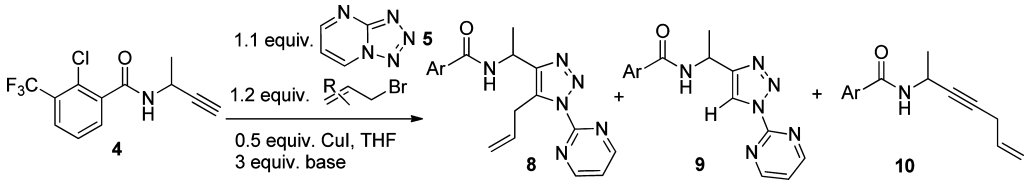
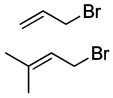
Table 2. Optimization



entry	CuI equiv.	AllylBr	Base	temperature	Yield:[a] 8	9	10
1	1.2		Et_3N	rt	50%	4%	20%
2	1.2		Hunig base	rt	51%	4%	20%
3	0.5		Hunig base	rt	50%	6%	20%
4	0.25		Hunig base	rt	40%	7%	30%
5	0.1		Hunig base	rt	30%	7%	50%
6	0.5		Hunig base	-78 °C -rt	50%	5%	20%
7	0.5		Cs_2CO_3	rt	67%[b]	2%	15%
8	0.5		Cs_2CO_3	rt	**15**, 77%[b]	trace	8%

[a]Based on the HPLC trace of the crude reaction mixture. [b]Isolated yield.

triazolylcopper(I) intermediate **3** first followed by an allyl bromide quenching. Indeed, the stepwise protocol afforded desired product **8** in 52% yield.[16] Compound **9** was also isolated in 25% yield even with 4.0 equiv of allyl bromide. Interestingly, we noticed significant differences in reaction rate and product distribution between the one-pot protocol and the stepwise protocol. For instance, with the one-pot protocol, the three-component reaction was complete in less than 2 h at room temperature, whereas with the stepwise protocol, the formation of intermediate **3** required 6 h at room temperature. This reaction rate difference might suggest participation of allyl bromide in the initial Cu(I)-mediated azide/alkyne cycloaddition step. It is important to note that, once formed, internal alkyne **10** does not afford compound **8** through Cu(I)-mediated cycloaddition with azide **5**. The formation of a significant amount of compound **10** in the one-pot protocol might also suggest the participation of allyl bromide in the initiation phase of the reaction cycle.

On the basis of the above observations, we proposed the reactions pathways for this azide−alkyne−allyl halide three-component reaction, as shown in Scheme 5. The initiation step was the well-documented formation of terminal alkyne−Cu(I) complex **11**,[17] which underwent a nucleophilic attack on allyl bromide to afford **12**.[18] The allyl group also served as a coordinating ligand to help stabilize Cu(III) complex **12**. Nucleophilic attack of azide **5** on **12** generating **13** followed by an intramolecular cycloaddition afforded **14**. This cycloaddition process is most likely assisted by another Cu molecule as suggested by a recent isotope study.[19] From **14**, two competing pathways could occur: reductive elimination to provide desired product **8** and protonation to afford byproduct **9**. It is foreseeable that byproduct **10** could result from reductive elimination of either **12** or **13**. The relative reaction rates of these competing pathways would determine the distribution of the three products (**8**, **9**, and **10**).

Guided by the mechanistic insights, we set out to optimize the azide−alkyne−allyl halide three-component reaction. The main goal was to shut down the competing pathways leading to byproducts **9** and **10**, therefore increasing the yield of desired product **8**. Typical solvent screening showed that this reaction could be performed successfully in most common aprotic solvents such as THF, DCM, 2-MeTHF, CH_3CN, EtOAc, and DMF. The ratios of the three major products were not affected. Screening on various Cu(I) salts identified CuI or CuBr as good replacements of expensive $(CuOTf)_2$·benzene to afford almost identical results. Therefore, we chose THF as the solvent and CuI as the catalyst for further optimization, and the results are listed in Table 2. Entries 1 and 2 showed that different organic bases did not change the reaction outcome much. Consistent with the proposed mechanism, the reaction could be performed with substoichiometric quantities of CuI. Reducing CuI loading to 50 mol % had little effect on the reaction profile (entry 3). However, further reduction of the CuI loading significantly decreased the yield of desired product **8** with the increase of byproduct **10** (entries 4 and 5). It appears that the azide−alkyne−allyl halide three-component reaction was rather insensitive to the reaction temperature. The product composition did not change much when the reactions were run at various temperatures from −78 °C to room temperature (entry 6). The use of an inorganic base such as Cs_2CO_3 increased the yield of product **8** while reducing byproduct **9**, presumably by removing the proton source from the reaction system. Our best result came with 3,3-dimethylallyl bromide, where desired product **15** was isolated in 77% yield with significantly less byproducts **9** and **10**, probably because the increased steric bulkiness of the 3,3-dimethylallyl group slowed the other two competing processes.

With the standard conditions established, the reaction scope with respect to allyl bromides was investigated. Substituents on the double bond are well-tolerated (Table 3, entries 1−6). A secondary allyl bromide also afforded the desired product in a reasonable yield (entry 7).

Reaction scope with respect to azides was investigated next. Heterocyclic azides (Table 4, entries 1−3), phenyl azide (entry

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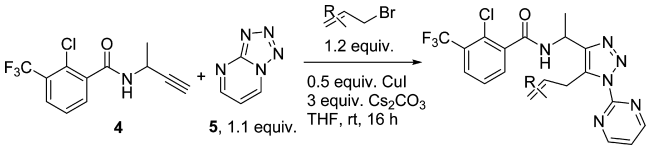
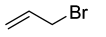
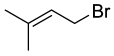
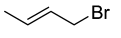
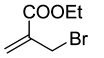
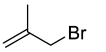
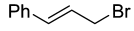
Table 3. Reaction Scope with Respect to Allyl Bromides



entry	allyl halide	yield	entry	allyl halide	yield
1		**8**, 72%	5		**15**, 77%[b]
2		**16**, 68%	6		**19**, 27%
3		**17**, 76%	7		**20**, 56%
4		**18**, 54%[a]			

[a]Byproduct **9** was isolated in 32% yield. [b]Same as entry 8 in Table 2.

4), and alkyl azides (entries 5 and 6) all afforded the desired products in moderate to good yields. We then briefly investigated three alternate alkynes. Alkyl alkynes worked well to afford the desired products in high yields (entries 7 and 8). For the less reactive phenyl alkyne (entry 9), higher temperature (120 °C under microwave conditions) was required for the reaction to occur. It is worth noting that, in most cases, the byproducts analogous to **9** and **10** were observed to some extent and occasionally isolated in significant amounts. Targeted optimization following the guidelines outlined above should improve the yields.

With the key azide−alkyne−allyl halide three-component reaction optimized, we finished the synthesis of drug candidate **1** (Scheme 6). Ozonolysis of compound **15** with a reductive $NaBH_4$ workup afforded alcohol **30**. Mesylation followed by a NaH-mediated intramolecular cyclization afforded compound **1** in good yield. This sequence was easily applied to multigram scales.

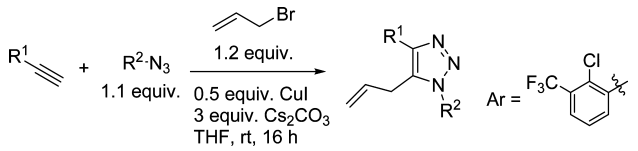
In summary, we developed an allyl-assisted, Cu(I)-catalyzed azide−alkyne cycloaddition/allylation reaction for the one-step synthesis of 1,4-disubstituted 5-allyl-1,2,3-triazoles. The unique coordinating capability of the allyl group to the Cu catalyst was critical for the reaction to occur under mild conditions. The competing reaction pathways were carefully investigated, and optimization guidelines based on mechanistic insights were provided. Based on this reaction as the key step, a concise synthesis of drug candidate **1** was realized on multigram scales. We expect this sequence to be used in the synthesis of other structurally related compounds.

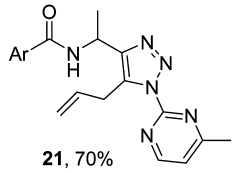
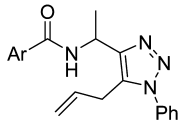
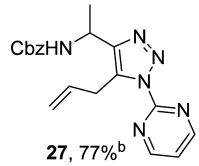
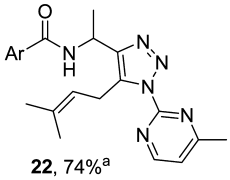
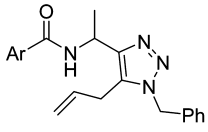
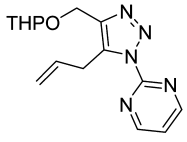
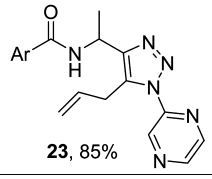
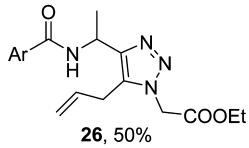
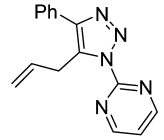
EXPERIMENTAL SECTION

Proton and carbon NMR spectra were recorded on 600 MHz or 500 MHz NMR spectrometers. Flash column chromatography was performed using silica gel. The analytical HPLC conditions were as follows: XDB-C18 5 mm; 4.6 × 150 mm column; gradient profile, 5−99% acetonitrile (ACN) in 0.05% trifluoroacetic acid (TFA) over 3.8 min, then holding at 99% acetonitrile for 0.6 min. Flow rate was 3 mL/min, and column temperature was set to 35 °C. HRMS (ESI) was performed on a μTof apparatus.

All the reagents and solvents were purchased from commercial sources and used without further purification. Many of the triazole compounds showed two sets of peaks on the NMR spectra, presumably from the inseparable rotamers.

Table 4. Reaction Scope with Respect to Azides and Alkynes



entry	product	entry	product	entry	product
1	 **21**, 70%	4	 **24**, 41%	7	 **27**, 77%[b]
2	 **22**, 74%[a]	5	 **25**, 62%	8	 **28**, 85%
3	 **23**, 85%	6	 **26**, 50%	9	 **29**, 30%[c]

[a]3,3-Dimethylallyl bromide was used. [b]Protonation byproduct **27b** was isolated in 14% yield. [c]Microwave, 120 °C, 10 min. Protonation byproduct **29b** was isolated in 20% yield.

DOI: 10.1021/acs.joc.5b02174
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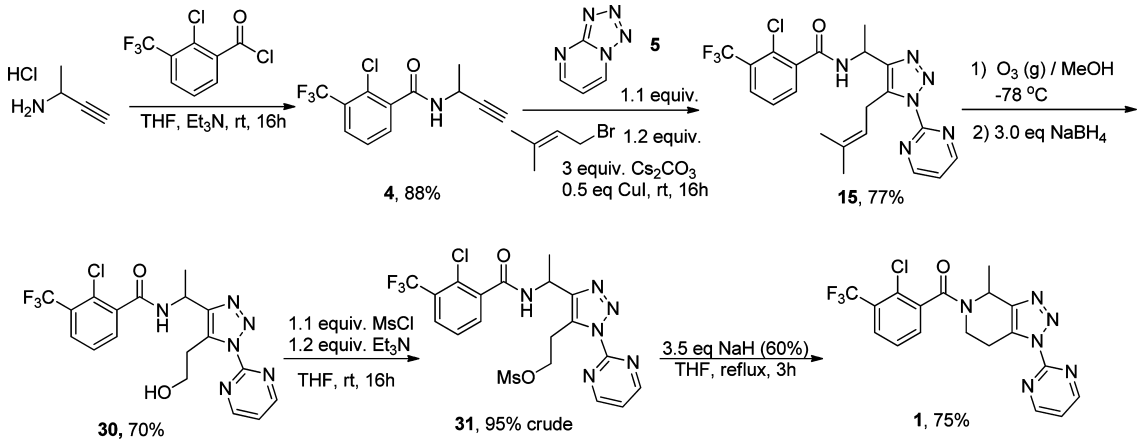
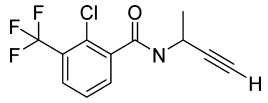
Scheme 6. Concise Synthesis of Compound 1



***N*-(But-3-yn-2-yl)-2-chloro-3-(trifluoromethyl)benzamide (4):**

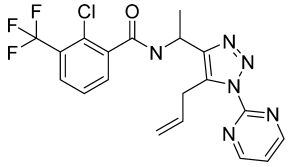


To the suspension of but-3-yn-2-amine·HCl salt (10 g, 94.7 mmol, 1.0 equiv) in THF (150 mL) were added Et_3N (27.5 mL, 199 mmol, 2.1 equiv) and (2-chloro-3-(trifluoromethyl)benzoyl chloride (23.1 g, 94.7 mmol, 1.0 equiv) sequentially at 0 °C. The reaction mixture was then stirred at room temperature for 16 h. The precipitate was filtered off and washed with THF. The filtrate solution was concentrated and redissolved in EtOAc. The EtOAc solution was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Trituration of the crude product from EtOAc/hexanes afforded compound **4** (23 g, 83.8 mmol, 88%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82−7.75 (dd, J = 7.9, 1.6 Hz, 1H), 7.73−7.66 (dd, J = 7.7, 1.6 Hz, 1H), 7.48−7.41 (dd, J = 8.2, 7.3 Hz, 1H), 6.35−6.02 (d, J = 7.9 Hz, 1H), 5.09−4.90 (dqd, J = 8.1, 6.9, 2.3 Hz, 1H), 2.47−2.20 (m, 1H), 1.58−1.54 (d, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 137.9, 132.5, 129.4 (q, J_{C-F} = 31.5 Hz), 129.1, 129.0 (q, J_{C-F} = 5.2 Hz), 127.1, 122.5 (q, J_{C-F} = 273.4 Hz), 83.2, 71.2, 37.8, 22.1; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{10}ClF_3NO$, 276.0398; found, 276.0390.

General Procedures for 5-Allyl-1,4-trisubstituted 1,2,3-Triazole Synthesis. One-Pot Protocol: To the suspension of *N*-(but-3-yn-2-yl)-2-chloro-3-(trifluoromethyl)benzamide (**4**) (138 mg, 0.5 mmol, 1.0 equiv), tetrazolo[1,5-*a*]pyrimidine **5** (67 mg, 0.55 mmol, 1.1 equiv), allyl bromide (73 mg, 0.6 mmol, 1.2 equiv), and Cs_2CO_3(0.49 g, 1.5 mmol, 3.0 equiv) in THF (2 mL) was added CuI (48 mg, 0.25 mmol, 0.5 equiv) at room temperature in one portion under N_2. The reaction mixture was then stirred at room temperature under N_2 for 16 h. Celite and EtOAc (5 mL) were added, and the suspension was stirred for 20 min. The insoluble solid was filtered off and washed with EtOAc. The filtrate solution was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography with EtOAc/hexanes as eluents to afford *N*-(1-(5-allyl-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-2-chloro-3-(trifluoromethyl)benzamide (**8**) (146 mg, 0.34 mmol, 67% yield) as a white solid. Byproducts 2-chloro-*N*-(1-(1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-3-(trifluoromethyl)-benzamide (**9**) (30 mg, 0.075 mmol, 15% yield) and 2-chloro-*N*-(hept-6-en-3-yn-2-yl)-3-(trifluoromethyl)benzamide(10) (2% yield) were also isolated.

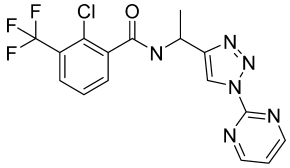
Stepwise Protocol: To the suspension of *N*-(but-3-yn-2-yl)-2-chloro-3-(trifluoromethyl)benzamide (**4**) (138 mg, 0.5 mmol, 1.0 equiv), tetrazolo[1,5-*a*]pyrimidine **5** (67 mg, 0.55 mmol, 1.1 equiv), and Hunig's base (0.3 mL, 1.75 mmol, 3.5 equiv) was added $(CuOTf)_2$·benzene (150 mg, 0.6 mmol, 1.2 equiv) at room temperature in one portion under N_2. After 6 h at room temperature, HPLC analysis indicated the complete consumption of *N*-(but-3-yn-2-yl)-2-chloro-3-(trifluoromethyl)benzamide (**4**). Allyl bromide (242 mg, 2.0 mmol, 4.0 equiv) was added, and the reaction solution was stirred for another 2 h. The same workup/purification procedure was followed to afford *N*-(1-(5-allyl-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-2-chloro-3-(trifluoromethyl)benzamide (**8**) (113 mg, 0.26 mml, 52% yield) along with byproduct 2-chloro-*N*-(1-(1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-3-(trifluoromethyl)benzamide (**9**) (49 mg, 0.12 mmol, 25% yield).

***N*-(1-(5-Allyl-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-2-chloro-3-(trifluoromethyl)benzamide (8):**



^{1}H NMR (600 MHz, $CDCl_3$) δ 8.95−8.85 (d, J = 4.8 Hz, 2H), 7.78−7.72 (dd, J = 7.8, 1.6 Hz, 1H), 7.67−7.61 (dd, J = 7.7, 1.6 Hz, 1H), 7.46−7.43 (s, 1H), 7.43−7.38 (td, J = 7.8, 0.9 Hz, 1H), 6.93−6.79 (d, J = 8.3 Hz, 1H), 5.96−5.85 (dddd, J = 16.7, 10.1, 6.4, 5.5 Hz, 1H), 5.57−5.47 (dq, J = 8.3, 6.8 Hz, 1H), 5.08−4.92 (m, 2H), 4.15−4.05 (m, 1H), 4.04−3.95 (m, 1H), 1.76−1.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 159.1, 155.7, 146.8, 138.3, 133.2, 132.6, 132.2, 129.3 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.2 Hz), 126.9, 122.5 (q, J_{C-F} = 273.4 Hz), 120.8, 117.2, 41.3, 27.9, 21.5; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{19}H_{17}ClF_3N_6O$, 437.1099; found, 437.1088.

2-Chloro-*N*-(1-(1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)-ethyl)-3-(trifluoromethyl)benzamide (9):



^{1}H NMR (600 MHz, $CDCl_3$) δ 8.91−8.84 (d, J = 4.8 Hz, 2H), 8.65−8.57 (s, 1H), 7.81−7.74 (dd, J = 7.8, 1.6 Hz, 1H), 7.72−7.64 (dd, J = 7.7, 1.6 Hz, 1H), 7.51−7.38 (m, 2H), 6.80−6.64 (d, J = 8.1 Hz, 1H), 5.71−5.49 (p, J = 7.1 Hz, 1H), 1.87−1.69 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.3, 159.3, 154.4, 149.0, 138.2, 132.4, 129.3 (q, J_{C-F} = 31.5 Hz), 129.2, 128.7 (q, J_{C-F} = 5.2 Hz), 127.0, 122.5 (q, J_{C-F} = 273.4 Hz), 120.8, 120.1, 42.5, 21.1; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{16}H_{13}ClF_3N_6O$, 397.0786; found, 397.0780.

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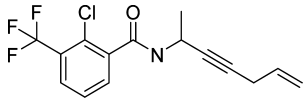
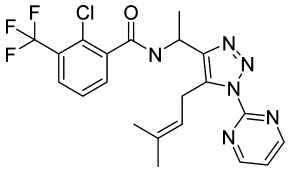
2-Chloro-*N*-(hept-6-en-3-yn-2-yl)-3-(trifluoromethyl)-benzamide (10):



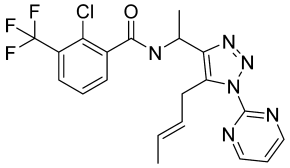
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81−7.72 (dd, J = 7.7, 1.7 Hz, 1H), 7.70−7.60 (dd, J = 7.6, 1.7 Hz, 1H), 7.52−7.37 (t, J = 7.8 Hz, 1H), 6.37−6.21 (d, J = 8.2 Hz, 1H), 5.86−5.72 (ddt, J = 17.1, 10.2, 5.2 Hz, 1H), 5.37−5.27 (m, 1H), 5.18−5.07 (dq, J = 10.8, 1.9 Hz, 1H), 5.06−4.92 (ddt, J = 8.4, 4.5, 2.3 Hz, 1H), 3.13−2.76 (dq, J = 5.1, 2.0 Hz, 2H), 1.61−1.32 (d, J = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 138.2, 132.4, 132.1, 129.3 (q, J_{C-F} = 31.5 Hz), 129.1, 128.8 (q, J_{C-F} = 5.2 Hz), 127.0, 122.5 (q, J_{C-F} = 273.4 Hz), 116.2, 81.9, 80.0, 38.3, 22.9, 22.5; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{15}H_{14}ClF_3NO$, 316.0711; found, 316.0726.

2-Chloro-*N*-(1-(5-(3-methylbut-2-en-1-yl)-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-3-(trifluoromethyl)benzamide (15):



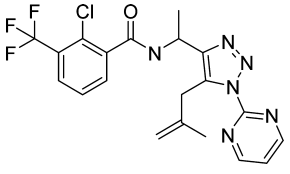
Following the one-pot protocol described above, the title compound was isolated in 77% yield (179 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.94−8.87 (d, J = 4.8 Hz, 2H), 7.77−7.70 (dd, J = 7.8, 1.7 Hz, 1H), 7.67−7.61 (dd, J = 7.7, 1.6 Hz, 1H), 7.47−7.43 (t, J = 4.8 Hz, 1H), 7.43−7.36 (t, J = 7.7 Hz, 1H), 7.04−6.91 (d, J = 8.3 Hz, 1H), 5.58−5.48 (m, 1H), 5.10−5.02 (m, 1H), 3.98−3.90 (d, J = 6.8 Hz, 2H), 1.76−1.72 (s, 3H), 1.72−1.68 (d, J = 6.8 Hz, 3H), 1.65−1.60 (d, J = 1.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0, 159.0, 155.8, 146.1, 138.4, 134.7, 134.3, 132.2, 129.3 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.2 Hz), 126.9, 122.5 (q, J_{C-F} = 273.4 Hz), 120.7, 118.8, 41.4, 25.5, 23.1, 21.6, 18.1; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{21}H_{21}ClF_3N_6O$, 465.1412; found, 465.1393.

(*E*)-*N*-(1-(5-(But-2-en-1-yl)-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-2-chloro-3-(trifluoromethyl)benzamide (16):



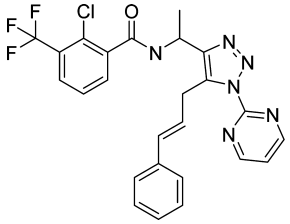
Following the one-pot protocol described above, the title compound was isolated in 68% yield (153 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.95−8.88 (d, J = 4.8 Hz, 2H), 7.76−7.71 (dd, J = 7.9, 1.7 Hz, 1H), 7.66−7.61 (dd, J = 7.7, 1.7 Hz, 1H), 7.51−7.43 (t, J = 4.8 Hz, 1H), 7.42−7.36 (t, J = 7.8 Hz, 1H), 7.05−6.93 (d, J = 8.4 Hz, 1H), 5.56−5.50 (td, J = 6.9, 1.5 Hz, 1H), 5.50−5.40 (m, 2H), 4.03−3.94 (m, 1H), 3.94−3.83 (m, 1H), 1.74−1.68 (d, J = 6.9 Hz, 3H), 1.61−1.49 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0, 159.0, 155.7, 146.4, 138.4, 133.5, 132.2, 129.4 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.4 Hz), 128.2, 126.9, 125.6, 122.5 (q, J_{C-F} = 273.4 Hz), 120.7, 41.4, 26.8, 21.5, 17.7; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{20}H_{19}ClF_3N_6O$, 451.1255; found, 451.1239.

2-Chloro-*N*-(1-(5-(2-methylallyl)-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-3-(trifluoromethyl)benzamide (17):



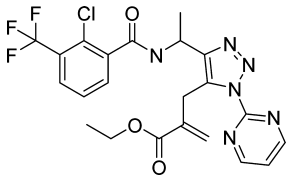
Following the one-pot protocol described above, the title compound was isolated in 76% yield (171 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99−8.77 (m, 2H), 7.75−7.71 (dd, J = 7.9, 1.6 Hz, 1H), 7.64−7.60 (dd, J = 7.7, 1.6 Hz, 1H), 7.45−7.41 (t, J = 4.8 Hz, 1H), 7.41−7.37 (m, 1H), 7.05−6.99 (d, J = 8.3 Hz, 1H), 5.54−5.45 (dd, J = 8.3, 6.8 Hz, 1H), 4.71−4.64 (dd, J = 2.7, 1.4 Hz, 1H), 4.33−4.25 (m, 1H), 4.08−4.02 (m, 1H), 3.99−3.92 (m, 1H), 1.77−1.74 (dd, J = 1.4, 0.8 Hz, 3H), 1.74−1.71 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 159.0, 155.7, 147.2, 141.5, 138.4, 132.6, 132.2, 129.3 (q, J_{C-F} = 31.3 Hz), 129.2, 128.7 (q, J_{C-F} = 5.4 Hz), 126.9, 122.5 (q, J_{C-F} = 273.6 Hz), 120.7, 111.8, 41.3, 31.2, 22.9, 21.4; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{20}H_{19}ClF_3N_6O$, 451.1255; found, 451.1254.

2-Chloro-*N*-(1-(5-cinnamyl-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-3-(trifluoromethyl)benzamide (18):



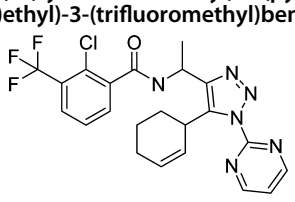
Following the one-pot protocol described above, the title compound was isolated in 54% yield (138 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.93−8.88 (m, 2H), 7.75−7.69 (dd, J = 7.9, 1.6 Hz, 1H), 7.60−7.54 (dd, J = 7.7, 1.6 Hz, 1H), 7.45−7.40 (t, J = 4.8 Hz, 1H), 7.37−7.29 (t, J = 7.8 Hz, 1H), 7.26−7.21 (m, 4H), 7.21−7.17 (m, 1H), 6.92−6.80 (d, J = 8.3 Hz, 1H), 6.40−6.34 (m, 1H), 6.31−6.24 (m, 1H), 5.63−5.54 (m, 1H), 4.27−4.21 (m, 1H), 4.20−4.14 (m, 1H), 1.77−1.71 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 159.1, 155.7, 146.9, 138.3, 136.6, 132.9, 132.3, 129.4 (q, J_{C-F} = 31.5 Hz), 129.3, 128.8 (q, J_{C-F} = 5.4 Hz), 128.5, 127.6, 126.9, 126.2, 124.7, 122.5 (q, J_{C-F} = 273.4 Hz), 120.8, 116.9, 41.3, 27.3, 21.4; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{25}H_{21}ClF_3N_6O$, 513.1412; found, 513.1392.

Ethyl 2-((4-(1-(2-Chloro-3-(trifluoromethyl)benzamido)-ethyl)-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-5-yl)methyl)acrylate (19):



Following the one-pot protocol described above, the title compound was isolated in 27% yield (68 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.88−8.83 (d, J = 4.9 Hz, 2H), 7.78−7.72 (dd, J = 7.9, 1.7 Hz, 1H), 7.68−7.61 (dd, J = 7.7, 1.6 Hz, 1H), 7.45−7.38 (m, 2H), 6.98−6.87 (d, J = 8.3 Hz, 1H), 6.15 (s,1H), 5.57−5.45 (dq, J = 8.2, 6.8 Hz, 1H), 5.22 (s, 1H), 4.39−4.27 (d, J = 9.6 Hz, 2H), 4.23−4.16 (q, J = 7.1 Hz, 2H), 1.74−1.71 (d, J = 6.9 Hz, 3H), 1.31−1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 165.1, 159.3, 159.0, 155.6, 147.6, 138.3, 136.8, 132.2, 131.6, 129.4 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.4 Hz), 126.9, 125.9, 122.5 (q, J_{C-F} = 273.4 Hz), 120.8, 61.1, 41.4, 26.0, 21.4, 14.2; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{22}H_{21}ClF_3N_6O_3$, 509.1310; found, 509.1310.

2-Chloro-*N*-(1-(5-(cyclohex-2-en-1-yl)-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-3-(trifluoromethyl)benzamide (20):



Following the one-pot protocol described above, the title compound was isolated in 56% yield (133 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.96−8.91 (m, 2H), 7.75−7.71 (m, 1H), 7.67−7.60 (m, 1H), 7.50−7.46 (t, J = 4.9 Hz, 1H), 7.43−7.37 (m, 1H), 7.04−6.87 (m, 1H), 6.05−5.97 (ddd, J = 10.1, 5.0, 2.6 Hz, 1H), 5.83−5.60 (m, 2H), 4.48−4.32 (d, J = 6.2 Hz, 1H), 2.42−2.08 (m, 3H), 2.01−1.79 (m, 2H), 1.70−1.58 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 159.1, 159.1, 155.9, 155.9, 146.4, 146.1, 138.6, 138.6, 137.5, 137.5, 132.2, 132.1, 130.6, 130.4, 129.3 (q, J_{C-F} = 31.3 Hz), 129.3, 128.6 (q, J_{C-F} =

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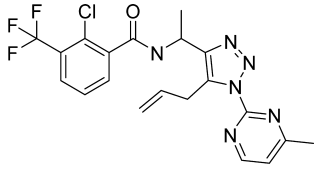
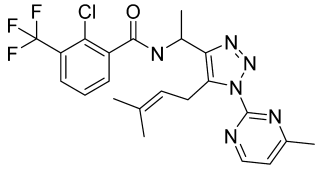
5.4 Hz), 126.9, 126.8, 126.0, 125.8, 122.5 (q, J_{C-F} = 273.6 Hz),121.0, 120.9, 41.8, 41.5, 32.2, 32.0, 29.9, 29.3, 24.6, 22.5, 22.2, 21.8, 21.6; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{22}H_{21}ClF_3N_6O$, 477.1412; found, 477.1403.

_N_-(1-(5-Allyl-1-(4-methylpyrimidin-2-yl)-1_H_-1,2,3-triazol-4-yl)ethyl)-2-chloro-3-(trifluoromethyl)benzamide (21):



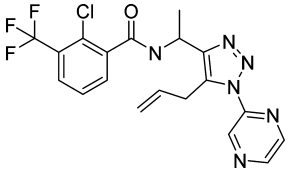
Following the one-pot protocol described above, the title compound was isolated in 70% yield (157 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76−8.70 (d, J = 5.0 Hz, 1H), 7.78−7.69 (d, J = 7.7 Hz, 1H), 7.68−7.59 (dd, J = 7.7, 1.7 Hz, 1H), 7.45−7.34 (t, J = 7.8 Hz, 1H), 7.29−7.27 (m, 1H), 7.08−6.94 (d, J = 7.9 Hz, 1H), 5.98−5.80 (ddt, J = 16.5, 10.1, 6.0 Hz, 1H), 5.55−5.44 (m, 1H), 5.08−4.92 (m, 2H), 4.09−4.04 (m, 1H), 4.01−3.94 (m, 1H), 2.71−2.62 (s, 3H), 1.87−1.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 165.1, 158.4, 155.4, 146.6, 138.4, 133.3, 132.5, 132.2, 129.3 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.2 Hz), 126.9, 122.5 (q, J_{C-F} = 273.4 Hz), 120.4, 117.2, 41.3, 28.0, 24.2, 21.5; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{20}H_{19}ClF_3N_6O$, 451.1255; found, 451.1272.

2-Chloro-_N_-(1-(5-(3-methylbut-2-en-1-yl)-1-(4-methylpyrimidin-2-yl)-1_H_-1,2,3-triazol-4-yl)ethyl)-3-(trifluoromethyl)-benzamide (22):



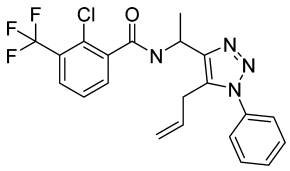
Following the one-pot protocol described above, the title compound was isolated in 74% yield (177 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.88−8.62 (s, 1H), 7.81−7.69 (d, J = 7.8 Hz, 1H), 7.69−7.56 (d, J = 7.7 Hz, 1H), 7.49−7.34 (t, J = 7.6 Hz, 1H), 7.34−7.24 (t, J = 4.7 Hz, 1H), 7.17−6.96 (d, J = 8.4 Hz, 1H), 5.62−5.41 (t, J = 7.3 Hz, 1H), 5.20−5.00 (t, J = 6.9 Hz, 1H), 4.05−3.81 (d, J = 7.0 Hz, 2H), 2.75−2.51 (s, 3H), 1.79−1.68 (m, 6H), 1.66−1.58 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 165.0, 158.3, 155.4, 145.9, 138.5, 134.4, 134.2, 132.2, 129.3 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.2 Hz), 126.9, 122.5 (q, J_{C-F} = 273.4 Hz), 120.4, 118.9, 41.4, 25.5, 24.2, 23.0, 21.6, 18.1; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{22}H_{23}ClF_3N_6O$, 479.1568; found, 479.1561.

_N_-(1-(5-Allyl-1-(pyrazin-2-yl)-1_H_-1,2,3-triazol-4-yl)ethyl)-2-chloro-3-(trifluoromethyl)benzamide (23):



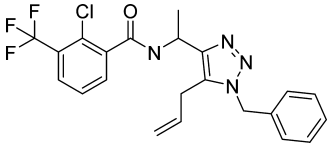
Following the one-pot protocol described above, the title compound was isolated in 85% yield (185 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33−9.27 (d, J = 1.4 Hz, 1H), 8.70−8.66 (d, J = 2.5 Hz, 1H), 8.58−8.50 (dd, J = 2.4, 1.4 Hz, 1H), 7.77−7.71 (dd, J = 7.8, 1.6 Hz, 1H), 7.68−7.61 (dd, J = 7.7, 1.6 Hz, 1H), 7.45−7.38 (t, J = 7.8 Hz, 1H), 7.08−6.95 (d, J = 8.3 Hz, 1H), 5.96−5.84 (m, 1H), 5.58−5.47 (dq, J = 8.4, 6.9 Hz, 1H), 5.09−5.02 (dq, J = 10.0, 1.4 Hz, 1H), 5.01−4.93 (dq, J = 17.1, 1.5 Hz, 1H), 4.08−3.93 (m, 2H), 1.78−1.69 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 147.2, 147.0, 144.1, 142.0, 139.3, 138.3, 132.9, 132.6, 132.3, 129.3 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.2 Hz), 126.9, 122.5 (q, J_{C-F} = 273.4 Hz), 117.4, 41.2, 27.5, 21.3; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{19}H_{17}ClF_3N_6O$, 437.1099; found, 437.1090.

_N_-(1-(5-Allyl-1-phenyl-1_H_-1,2,3-triazol-4-yl)ethyl)-2-chloro-3-(trifluoromethyl)benzamide (24):



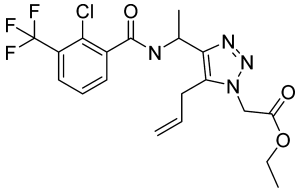
Following the one-pot protocol described above, the title compound was isolated in 41% yield (89 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78−7.72 (dd, J = 7.9, 1.6 Hz, 1H), 7.68−7.63 (dd, J = 7.7, 1.6 Hz, 1H), 7.60−7.50 (m, 3H), 7.48−7.43 (m, 2H), 7.43−7.37 (t, J = 7.8 Hz, 1H), 7.04−6.91 (d, J = 8.3 Hz, 1H), 5.90−5.80 (ddt, J = 17.2, 10.2, 5.6 Hz, 1H), 5.50−5.41 (dq, J = 8.2, 6.9 Hz, 1H), 5.18−5.12 (m, 1H), 4.97−4.87 (m, 1H), 3.69−3.60 (ddt, J = 17.1, 5.8, 1.7 Hz, 1H), 3.53−3.41 (m, 1H), 1.76−1.72 (d, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 146.0, 138.4, 136.1, 132.8, 132.2, 131.3, 129.8, 129.5, 129.4 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.2 Hz), 126.9, 125.3, 122.5 (q, J_{C-F} = 273.4 Hz), 117.8, 41.6, 26.8, 21.4; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{21}H_{19}ClF_3N_4O$, 435.1194; found, 435.1207.

_N_-(1-(5-Allyl-1-benzyl-1_H_-1,2,3-triazol-4-yl)ethyl)-2-chloro-3-(trifluoromethyl)benzamide (25):



Following the one-pot protocol described above, the title compound was isolated in 62% yield (139 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75−7.69 (dd, J = 7.9, 1.6 Hz, 1H), 7.64−7.58 (dd, J = 7.7, 1.6 Hz, 1H), 7.41−7.37 (t, J = 7.8 Hz, 1H), 7.36−7.29 (m, 3H), 7.16−7.10 (m, 2H), 7.03−6.92 (d, J = 8.3 Hz, 1H), 5.77−5.65 (ddt, J = 17.1, 10.1, 5.8 Hz, 1H), 5.52−5.41 (m, 2H), 5.41−5.33 (dq, J = 8.4, 6.9 Hz, 1H), 5.15−5.09 (dt, J = 10.1, 1.4 Hz, 1H), 4.96−4.88 (m, 1H), 3.51−3.41 (m, 1H), 3.40−3.30 (m, 1H), 1.70−1.64 (d, J = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 146.2, 138.4, 134.7, 132.2, 132.1, 130.6, 129.3 (q, J_{C-F} = 31.5 Hz), 129.3, 129.0, 128.7 (q, J_{C-F} = 5.2 Hz), 128.4, 127.2, 126.9, 122.5 (q, J_{C-F} = 273.4 Hz), 117.7, 52.0, 41.5, 26.4, 21.3; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{22}H_{21}ClF_3N_4O$, 449.1351; found, 449.1351.

Ethyl 2-(5-Allyl-4-(1-(2-chloro-3-(trifluoromethyl)-benzamido)ethyl)-1_H_-1,2,3-triazol-1-yl)acetate (26):



Following the one-pot protocol described above, the title compound was isolated in 50% yield (111 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78−7.71 (dd, J = 7.9, 1.6 Hz, 1H), 7.65−7.59 (dd, J = 7.7, 1.6 Hz, 1H), 7.45−7.35 (m, 1H), 6.97−6.87 (d, J = 8.2 Hz, 1H), 5.92−5.76 (ddt, J = 17.2, 10.1, 5.9 Hz, 1H), 5.49−5.37 (m, 1H), 5.24−5.14 (dd, J = 10.1, 1.3 Hz, 1H), 5.09−5.00 (m, 3H), 4.30−4.17 (q, J = 7.1 Hz, 2H), 3.65−3.55 (m, 1H), 3.54−3.42 (m, 1H), 1.75−1.63 (d, J = 6.9 Hz, 3H), 1.34−1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.2, 165.1, 145.8, 138.4, 132.2, 132.1, 131.4, 129.3 (q, J_{C-F} = 31.5 Hz), 129.3, 128.7 (q, J_{C-F} = 5.2 Hz), 126.9, 122.5 (q, J_{C-F} = 273.4 Hz), 118.1, 62.4, 49.2, 41.4, 26.6, 21.2, 14.1; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{19}H_{21}ClF_3N_4O_3$, 445.1249; found, 445.1243.

DOI: 10.1021/acs.joc.5b02174
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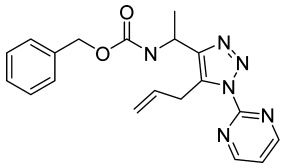
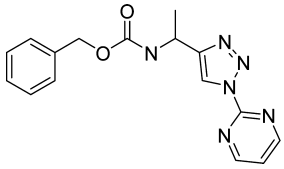
Benzyl (1-(5-Allyl-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)-ethyl)carbamate (27):



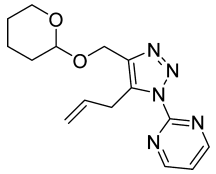
Following the one-pot protocol described above, the title compound was isolated in 77% yield (140 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.91−8.85 (dd, J = 4.9, 1.1 Hz, 2H), 7.43−7.38 (td, J = 4.8, 0.9 Hz, 1H), 7.36−7.31 (m, 4H), 7.31−7.27 (td, J = 5.8, 5.3, 4.0 Hz, 1H), 5.91−5.80 (td, J = 16.4, 6.0 Hz, 1H), 5.77−5.62 (d, J = 8.3 Hz, 1H), 5.18−5.01 (m, 3H), 5.01−4.86 (m, 2H), 4.12−3.86 (ddd, J = 61.5, 16.2, 5.9 Hz, 2H), 1.69−1.54 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.0, 155.7, 155.6, 147.5, 136.4, 133.4, 132.4, 128.4, 128.0, 127.9, 120.7, 116.9, 66.6, 42.3, 27.8, 21.6; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{19}H_{21}N_6O_2$, 365.1721; found, 365.1738.

Benzyl (1-(1-(Pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-carbamate (27b):



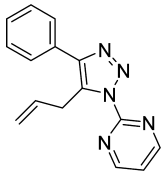
Byproduct was isolated in 14% yield (22 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.87−8.84 (d, J = 4.8 Hz, 2H), 8.57−8.46 (s, 1H), 7.42−7.38 (t, J = 4.8 Hz, 1H), 7.38−7.28 (m, 5H), 5.57−5.36 (d, J = 7.8 Hz, 1H), 5.26−4.99 (m, 3H), 1.71−1.58 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2, 155.6, 154.4, 150.0, 136.3, 128.5, 128.1, 128.1, 120.7, 119.9, 66.8, 43.5, 21.2; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{16}H_{17}N_6O_2$, 325.1408; found, 325.1420.

2-(5-Allyl-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)pyrimidine (28):



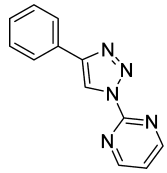
Following the one-pot protocol described above, the title compound was isolated in 85% yield (128 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.96−8.86 (d, J = 4.8 Hz, 2H), 7.51−7.39 (t, J = 4.8 Hz, 1H), 5.96−5.80 (m, 1H), 5.03−4.93 (m, 2H), 4.94−4.88 (d, J = 12.2 Hz, 1H), 4.81−4.75 (t, J = 3.6 Hz, 1H), 4.74−4.69 (d, J = 12.2 Hz, 1H), 4.03−3.99 (dt, J = 6.2, 1.4 Hz, 2H), 3.97−3.91 (ddd, J = 11.7, 9.0, 2.9 Hz, 1H), 3.64−3.54 (dt, J = 10.6, 4.6 Hz, 1H), 1.88−1.77 (m, 1H), 1.76−1.68 (td, J = 13.5, 3.5 Hz, 1H), 1.67−1.57 (dq, J = 14.2, 4.8 Hz, 2H), 1.57−1.47 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.0, 155.8, 143.3, 135.4, 133.3, 120.7, 117.0, 97.8, 62.1, 59.5, 30.4, 28.0, 25.4, 19.2; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{15}H_{20}N_5O_2$, 302.1612; found, 302.1617.

2-(5-Allyl-4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrimidine (29):



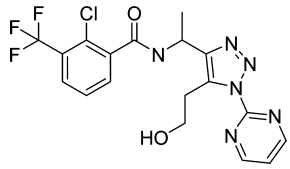
Following the one-pot protocol described above, the title compound was isolated in 30% yield (39 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.94−8.88 (d, J = 4.8 Hz, 2H), 7.79−7.73 (dd, J = 8.3, 1.3 Hz, 2H), 7.50−7.46 (m, 2H), 7.45−7.42 (t, J = 4.8 Hz, 1H), 7.42−7.39 (m, 1H), 6.02−5.91 (m, 1H), 5.08−5.00 (dq, J = 10.2, 1.5 Hz, 1H), 4.95−4.88 (dq, J = 17.3, 1.7 Hz, 1H), 4.12−4.03 (dt, J = 5.5, 1.8 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.0, 155.9, 146.6, 133.7, 132.3, 130.7, 128.7, 128.3, 128.0, 120.6, 117.0, 28.3; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{15}H_{14}N_5$, 264.1244; found, 264.1246.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pyrimidine (29b):



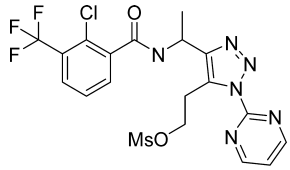
Byproduct was isolated in 20% yield (22 mg): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90−8.87 (d, J = 4.8 Hz, 2H), 8.84−8.82 (s, 1H), 7.99−7.94 (dd, J = 8.3, 1.3 Hz, 2H), 7.51−7.45 (m, 2H), 7.43−7.41 (t, J = 4.8 Hz, 1H), 7.41−7.36 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 154.4, 148.1, 129.8, 128.9, 128.7, 126.1, 120.7, 118.3; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{10}N_5$, 224.0931; found, 224.0929.

2-Chloro-*N*-(1-(5-(2-hydroxyethyl)-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-4-yl)ethyl)-3-(trifluoromethyl)benzamide (30):



A stream of O_3 generated from an ozonator was passed though the solution of compound **15** (200 mg, 0.43 mmol, 1.0 equiv) in MeOH (30 mL) at −78 °C until the color of the reaction solution became blue (∼10 min). $NaBH_4$ (49 mg, 1.3 mmol, 3.0 equiv) was added at −78 °C. The reaction solution was warmed to room temperature and partitioned between EtOAc and brine. The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography with EtOAc/hexanes as eluents to afford the title compound (140 mg, 0.30 mmol, 70% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95−8.88 (d, J = 4.9 Hz, 2H), 7.81−7.73 (dd, J = 7.8, 1.7 Hz, 1H), 7.67−7.58 (dd, J = 7.7, 1.6 Hz, 1H), 7.50−7.44 (t, J = 4.9 Hz, 1H), 7.43−7.36 (t, J = 7.8 Hz, 1H), 6.95−6.83 (d, J = 8.1 Hz, 1H), 5.62−5.44 (m, 1H), 4.06−3.89 (m, 2H), 3.66−3.56 (ddd, J = 14.7, 6.1, 4.6 Hz, 1H), 3.44−3.34 (ddd, J = 14.7, 7.7, 4.9 Hz, 1H), 3.20−3.14 (t, J = 5.9 Hz, 1H), 1.88−1.71 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.5, 159.0, 155.5, 147.4, 138.3, 133.1, 132.2, 129.2, 129.1 (q, J_{C-F} = 31.5 Hz), 128.5 (q, J_{C-F} = 5.2 Hz), 126.8, 122.5 (q, J_{C-F} = 273.4 Hz), 120.7, 61.1, 41.4, 27.3, 20.7; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{18}H_{17}ClF_3N_6O_2$, 441.1048; found, 441.1038.

2-(4-(1-(2-Chloro-3-(trifluoromethyl)benzamido)ethyl)-1-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-5-yl)ethylmethanesulfonate (31):



To the solution of compound **30** (100 mg, 0.22 mmol, 1.0 equiv) in THF (10 mL) were added Et_3N (37 μL, 0.27 mmol, 1.2 equiv) and MsCl (29 mg, 0.24 mmol, 1.1 equiv) sequentially. The reaction solution was stirred at room temperature for 16 h. EtOAc and water were added. The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude product (112 mg, 0.21 mmol, 95% yield) was used directly in the next reaction without further purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.97−8.88 (d, J = 4.8 Hz, 2H), 7.80−7.72 (dd, J = 7.9, 1.6 Hz, 1H), 7.66−7.59 (dd, J = 7.7, 1.6 Hz, 1H), 7.50−7.45 (t, J = 4.8 Hz, 1H), 7.44−7.36 (t, J = 7.8 Hz, 1H), 6.86−6.77 (d, J = 8.3 Hz, 1H), 5.60−5.47 (dd, J = 8.3, 7.0 Hz, 1H), 4.66−4.57 (ddd, J = 7.5, 6.0, 3.9 Hz, 2H), 3.92−3.79 (m, 1H), 3.73−3.59 (d, J = 14.6 Hz, 1H), 3.04−2.95 (s, 3H), 1.83−1.72 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.3, 159.3, 155.5, 148.2, 138.1, 132.2, 129.8, 129.4 (q, J_{C-F} = 31.5 Hz), 129.2, 128.9 (q, J_{C-F} = 5.2 Hz), 127.0, 122.5 (q, J_{C-F} = 273.4 Hz), 120.9, 67.6, 41.1, 37.3, 24.4, 21.0; HRMS-ESI

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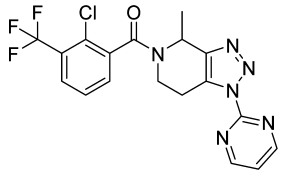
(m/z) [M + H]$^+$ calcd for $C_{19}H_{19}ClF_3N_6O_4S$, 519.0824; found, 519.0805.

(2-Chloro-3-(trifluoromethyl)phenyl)(4-methyl-1-(pyrimidin-2-yl)-1,4,6,7-tetrahydro-5*H*-[1,2,3]triazolo[4,5-*c*]pyridin-5-yl)-methanone (1):



To the solution of compound **31**(112 mg, 0.21 mmol, 1.0 equiv) in THF (20 mL) was added NaH (60 wt % in mineral oil, 30 mg, 0.74 mmol, 3.5 equiv) in one portion. The reaction solution was heated to reflux temperature for 3 h and then cooled to room temperature. The reaction solution was partitioned between EtOAc and brine. The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to afford compound **1** (68 mg, 0.16 mmol, 75% yield) as a white solid: ^{1}H NMR (600 MHz, MeOD) δ 8.97−8.86 (m, 2H), 7.98−7.88 (dd, J = 7.8, 1.7 Hz, 1H), 7.83−7.52 (m, 3H), [6.05−5.78 (m), 4.87−4.82 (m), 4.72−4.66 (m), 1H] [5.04−4.98 (m), 3.94−2.86 (m), 4H], [1.72−1.66 (m), 1.59−1.48 (m), 3 H]; ^{13}C NMR (151 MHz, MeOD) δ 168.36, 168.27, 168.25, 160.68, 160.64, 160.63, 156.44, 156.42, 156.40, 146.71, 146.59, 146.46, 139.78, 139.59, 139.56, 139.37, 134.20, 133.93, 133.22, 132.96, 132.90, 132.61, 132.47, 130.47, 130.37, 130.27, 130.16, 130.06, 129.85, 129.82, 129.78, 129.76, 129.72, 129.69, 129.65, 129.59, 129.57, 129.48, 129.46, 129.33, 129.30, 129.13, 129.04, 126.83, 125.03, 124.91, 123.22, 123.10, 122.50, 122.47, 122.41, 121.41, 51.90, 51.40, 46.88, 46.66, 41.78, 41.01, 36.04, 35.83, 26.17, 25.75, 25.21, 25.17, 20.28, 20.13, 18.84, 18.51; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{18}H_{15}ClF_3N_6O$, 423.0942; found, 423.0937.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02174.

^{1}H and ^{13}C NMR spectra for compounds **1**, **4**, **8**−**10**, and **15**−**31** (PDF)

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Notes

The authors declare no competing financial interest.

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