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Synthesis of 3-Trifluoromethyl-1,2,4-triazolines and 1,2,4-Triazoles via Tandem Addition/Cyclization of Trifluoromethyl *N*-Acylhydrazones with Cyanamide

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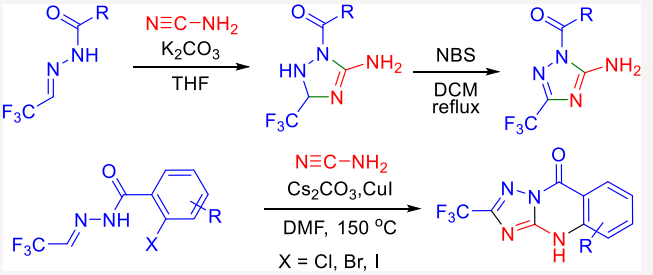
ABSTRACT: A tandem addition/cyclization reaction between trifluoromethyl *N*-acylhydrazones and cyanamide is described, which provides a novel and efficient process for the synthesis of polysubstituted 3-trifluoromethyl-1,2,4-triazolines and their derivatives. The method has the advantages of mild reaction conditions, a broad substrate scope, good product yields, and atom economy.



INTRODUCTION

As important heterocyclic compounds, 1,2,4-triazole derivatives show a broad spectrum of bioactivities such as antihypertensive, anti-inflammatory, antitumor, antifungal, and antibacterial activities.[1] Many prominent 1,2,4-triazole drugs, including triazolam, alprazolam, estazolam, itraconazole, voriconazole, fluconazole, rizatriptan, ribavirin, anastrozole, letrozole, and and so forth,[2] have been sold in the market. Among 1,2,4-triazole derivatives, amino-1,2,4-triazole scaffolds have been paid much attention by the agrochemical and medicinal communities because of their interesting and diverse biological activities (Figure 1, **1** and **2**).[3] They are also versatile building blocks for the synthesis of other potential bioactive 1,2,4-triazole-containing scaffolds.[4]

On the other hand, trifluoromethyl groups have been demonstrated to be important structural motifs that can enhance the metabolic stability, binding selectivity, and lipophilicity of pharmaceuticals and agrochemicals and thus have been extensively applied in the design and development of new drugs and pesticides.[5] In a large number of trifluoromethylated drugs, the trifluoromethyl-1,2,4-triazole derivatives have recently received considerable attention due to their wide application in drug discovery.[6] Many drugs, such as anti-HIV-1 reagent, anticonvulsant drug, sitagliptin, and Gly T1 inhibitor, contain a 3-trifluoromethyl-1,2,4-triazole structure (Figure 1, **3**−**6**). Thus, efficient synthetic strategies for 3-trifluoromethyl-1,2,4-triazole derivatives are of great importance for the related drug discovery. In recent years, the synthetic protocols employing different trifluoromethyl synthons have emerged as widespread strategies to construct 3-trifluoromethyl-1,2,4-triazoles. For instance, trifluoroacetimidoyl halides were used to react with hydrazones or hydrazides to afford many 3-trifluoromethyl-1,2,4-triazole derivatives (Scheme 1, a).[7] Trifluoroacetimidohydrazides were other trifluoromethyl building blocks to be reacted with aryl iodides, methylhetarenes, or methyl ketones, respectively, to produce a series of 3-trifluoromethyl-1,2,4-triazoles (Scheme 1, b).[8] In addition, Ma's group used trifluorodiazoethane as an appealing trifluoromethyl 1,3-dipole to react with aryldiazonium salts and nitriles to access 3-trifluoromethyl-1,2,4-triazoles (Scheme 1, c).[9] Although amino-1,2,4-triazole scaffolds play important roles in agrochemical and medicinal communities, research studies about the synthesis of trifluoromethylated amino-1,2,4-triazoles have not been reported until now. In our group, we have used trifluoromethylated *N*-acylhydrazones as formal 1,3-dipoles to react with a series of electron-deficient olefins via [3 + 2] cycloaddition to obtain trifluoromethyl-substituted nitrogen heterocycles such as pyrazoles and pyrazolidines.[10] In addition, trifluoromethyl *N*-acylhydrazones can also be used as dipolarophiles to react with azomethineylide to produce trifluoromethyl-substituted imidazolidines.[11] Furthermore, cyanamide is an industrial chemical reagent used for the synthesis of N-heterocycles.[12] In order to further investigate the application of trifluoromethyl *N*-acylhydrazones as versatile trifluoromethyl building blocks, we report herein that

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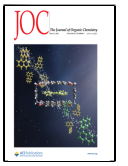

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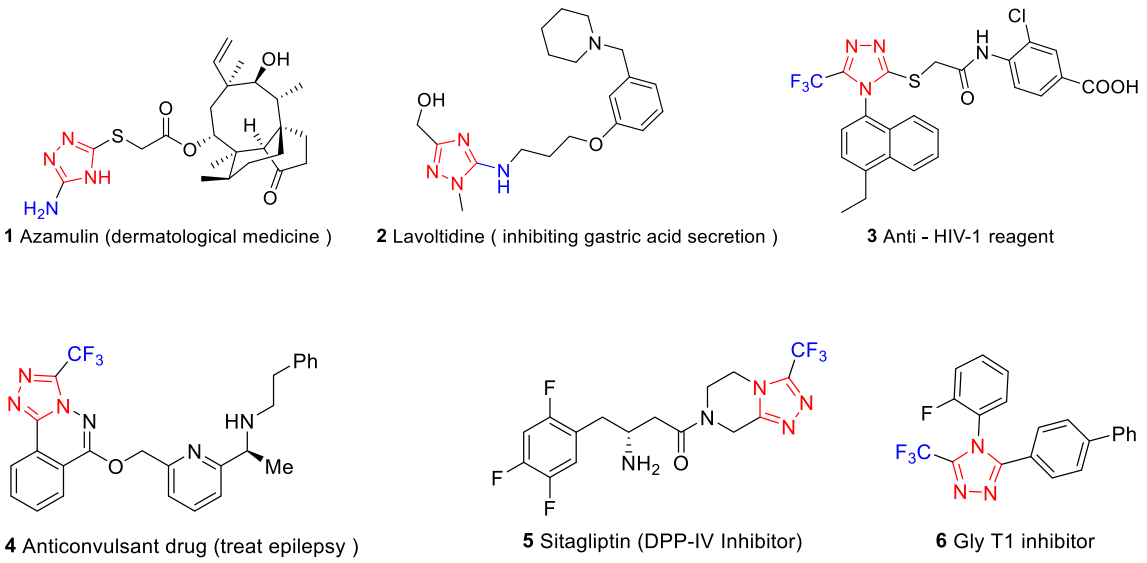
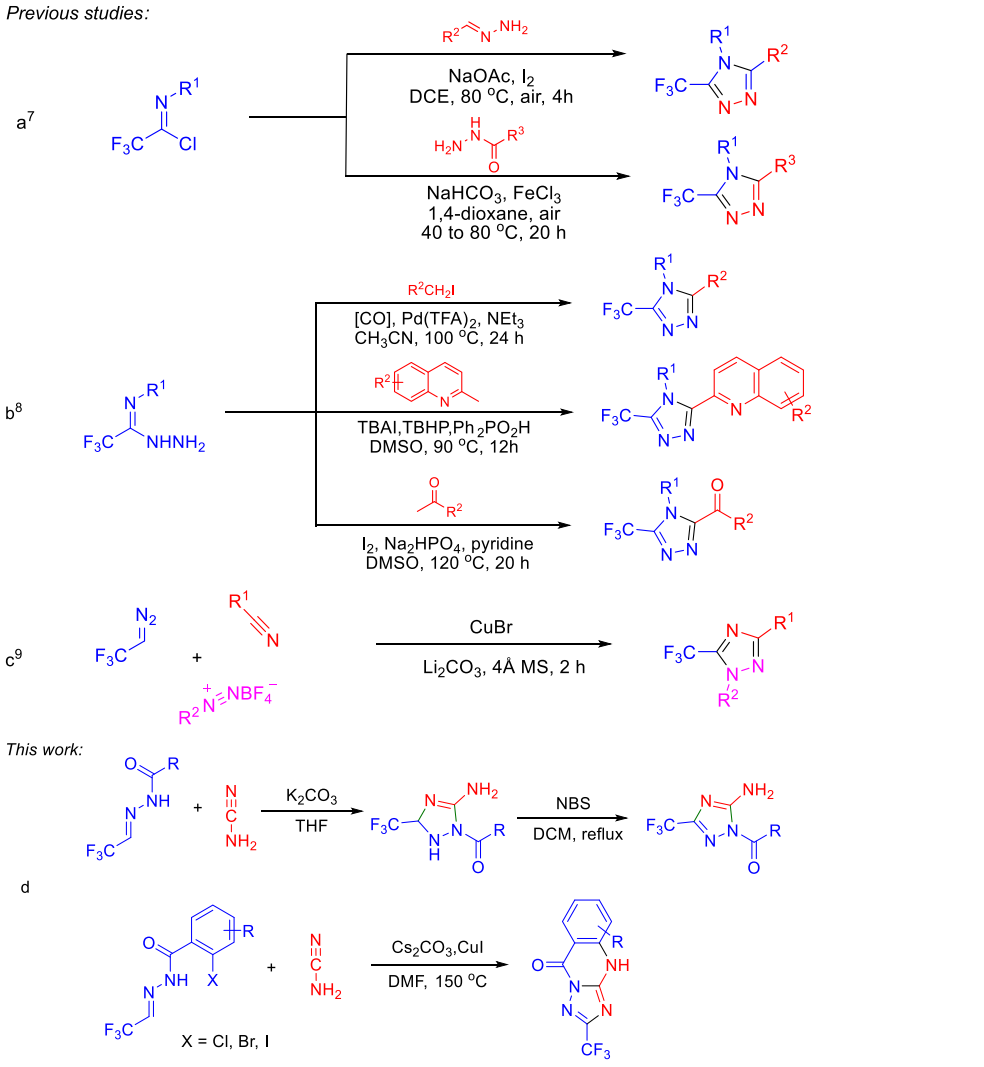


Figure 1. Selected examples of drugs containing amino- or trifluoromethyl-1,2,4-triazole cores.

Scheme 1. Synthesis of Trifluoromethyl-Substituted 1,2,4-Triazole Derivatives



trifluoromethyl *N*-acylhydrazones can smoothly conduct a tandem addition/cyclization reaction with cyanamide to afford 5-amino-3-trifluoromethyl-1,2,4-triazolines, which can be further oxidized to 5-amino-3-trifluoromethyl-1,2,4-triazoles. If a

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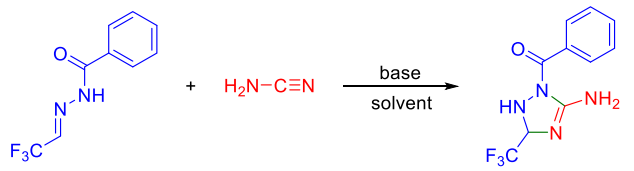
halogen atom was attached to the ortho-position of aromatic trifluoromethyl *N*-acylhydrazones, trifluoromethylated [1,2,4]-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one derivatives can be produced in one step. The method provides an efficient process for the synthesis of 5-amino-3-trifluoromethyl-1,2,4-triazolines and their derivatives (Scheme 1, d).

RESULTS AND DISCUSSION

To commence the investigation, *N*′-(2,2,2-trifluoroethylene)-benzohydrazide (**1a**) and cyanamide were used as model substrates to test the reaction (Table 1). Fortunately, when the reaction was performed with **1a** (1 equiv, 0.2 mmol) and cyanamide (2 equiv) in the presence of K_2CO_3 (2.5 equiv) in tetrahydrofuran (THF) (2 mL) at room temperature for 6 h, the desired product 5-amino-3-trifluoromethyl-1,2,4-triazoline **2a** was produced in 85% yield (Table 1, entry 1). In order to improve the yield of product **2a**, the mole ratio of substrates was initially investigated (Table 1, entries 1−6). The results showed that the reaction would give product **2a** in the highest yield when the mole ratio of *N*′-(2,2,2-trifluoroethylene)-benzohydrazide (**1a**), cyanamide, and K_2CO_3 is 1:2.5:2.5 (Table 1, entry 2). Next, different solvents were screened, including dichloromethane (DCM), $CHCl_3$, CCl_4, CH_3CN, MeOH, and 1,4-dioxane, and all of the results were inferior to that of the reactions in THF (Table 1, entries 2 and 8−13). The screening of other commonly used bases such as Na_2CO_3, Cs_2CO_3, Et_3N, N,N-diisopropylethylamine (DIPEA), and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) indicated that K_2CO_3 was the suitable base (Table 1, entries 14−19). Thus, the optimized reaction conditions were the use of **1a**, cyanamide, and K_2CO_3 in a molar ratio of 1:2.5:2.5 in THF at room temperature (Table 1, entry 2).

Table 1. Optimization of Reaction Conditions



1a **2a**

entry	molar ratio of **1a**/cyanamide/base	base	solvent	time (h)	yield (%)[b]
1	1/2.0/2.5	K_2CO_3	THF	6	85
2	1/2.5/2.5	K_2CO_3	THF	6	92
3	1/3/2.5	K_2CO_3	THF	4	80
4	1/2.5/2	K_2CO_3	THF	10	87
5	1/2.5/1.5	K_2CO_3	THF	20	89
6	1/2.5/1	K_2CO_3	THF	24	72
7	1/1/1	K_2CO_3	THF	24	20
8	1/2.5/2.5	K_2CO_3	DCM	12	48
9	1/2.5/2.5	K_2CO_3	$CHCl_3$	24	N.R.[c]
10	1/2.5/2.5	K_2CO_3	CCl_4	24	trace
11	1/2.5/2.5	K_2CO_3	CH_3CN	10	72
12	1/2.5/2.5	K_2CO_3	MeOH	24	N.R.[c]
13	1/2.5/2.5	K_2CO_3	1,4-dioxane	10	65
14	1/2.5/2.5	Na_2CO_3	THF	24	30
15	1/2.5/2.5	Cs_2CO_3	THF	6	90
16	1/2.5/2.5	Et_3N	THF	24	65
17	1/2.5/2.5	DIPEA	THF	10	74
18	1/2.5/2.5	DABCO	THF	24	N.R.[c]
19	1/2.5/2.5	DBU	THF	10	83

[a]Reaction conditions: All reactions were carried out by using 0.2 mmol **1a** in 2 mL of the solvent at 25 °C under an air atmosphere. [b]Isolated yields. [c]N.R.: no reaction.

With the optimized reaction conditions in hand, the generality of the substrates was examined (Table 2). The scope of aromatic trifluoromethyl *N*-acylhydrazones was examined first. The results showed that the steric hindrance of the substituents on the phenyl ring of aromatic trifluoromethyl *N*-acylhydrazones have an obvious influence on the reaction. For instance, when the substituents on the phenyl rings were methyl groups, *para*-methyl trifluoromethyl *N*-acylhydrazones gave product **2d** in the highest yield compared to those of *ortho*- and *meta*-methyl ones (Table 2, **2b**−**2d**). In addition, the electron properties of the substituents on the phenyl rings also had great effects on the reaction. When the substituents were electron-donating groups such as methyl and methoxy groups and weak electron-withdrawing groups such as halides F-, Cl-, and Br-groups, the reaction occurred smoothly to afford the corresponding products in good yields (Table 2, **2b**−**2k**). However, if the strong electron-withdrawing groups such as $-CF_3$, $-NO_2$, and −COOMe groups were attached on the phenyl rings of the aromatic trifluoromethyl *N*-acylhydrazones, there were no products formed (Table 2, **2l**−**2n**). The reason may be that the strong electron-withdrawing groups on the phenyl rings of aromatic trifluoromethyl *N*-acylhydrazones decreased the nucleophilicity of the nitrogen atom connected to the carbonyl group. Further investigation indicated that the trifluoromethyl *N*-acylhydrazones derived from naphthalene hydrazide and electron-rich heteroaromatic hydrazides could produce the corresponding products in good yields (Table 2, **2o**−**2r**), but the substrate derived from electron-poor heteroaromatic hydrazide did not produce product **2s**. Finally, aliphatic trifluoromethyl *N*-acylhydrazones were investigated. It was found that various aliphatic trifluoromethyl *N*-acylhydrazones reacted with cyanamide to give the corresponding 5-amino-3-trifluoromethyl-1,2,4-triazolines in good to excellent yields (Table 2, **2t**−**2x**).

Next, the reaction of *N*-phenylcyanamide or *N*,*N*-dimethylcyanamide with **1a** was performed under standard reaction conditions (Scheme 2), but no desired product formed.

Due to the importance of 3-trifluoromethyl-1,2,4-triazoles, we try to transform 3-trifluoromethyl-1,2,4-triazolines (**2**) obtained in the above reactions into 5-amino-3-trifluoromethyl-1,2,4-triazoles (**3**). Fortunately, when **2a** (1 equiv, 0.2 mmol) was refluxed in DCM in the presence of N-iodosuccinimide (NIS) (1.5 equiv), 5-amino-3-trifluoromethyl-1,2,4-triazole **3a** was obtained in 83% yield (Supporting Information, Table S1, entry 2). Screening of other oxidation reagents including NIS, N-bromosuccinimide (NBS), trichloroisocyanuric acid (TCCA), *t*-butyl hydroperoxide (TBHP), benzoyl peroxide (BPO), and $CuCl_2$ indicated that NBS was the suitable oxidant, which gave product **3a** in 84% yield (Supporting Information, Table S1). Under the optimized reaction conditions, the generality of the reaction was examined. As shown in Table 3, various 5-amino-3-trifluoromethyl-1,2,4-triazolines could be transformed into 5-amino-3-trifluoromethyl-1,2,4-triazoles in good to excellent yields (Table 3).

The [1,2,4]triazolo[1,5-*a*]pyrimidine scaffold possesses antitubercular and anticancer activities and has been used as phosphodiesterase inhibitors for diabetes treatment.[13] How-

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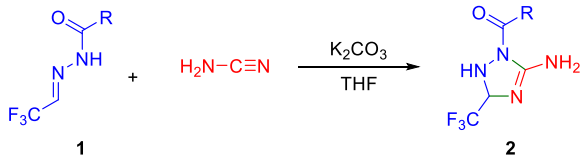
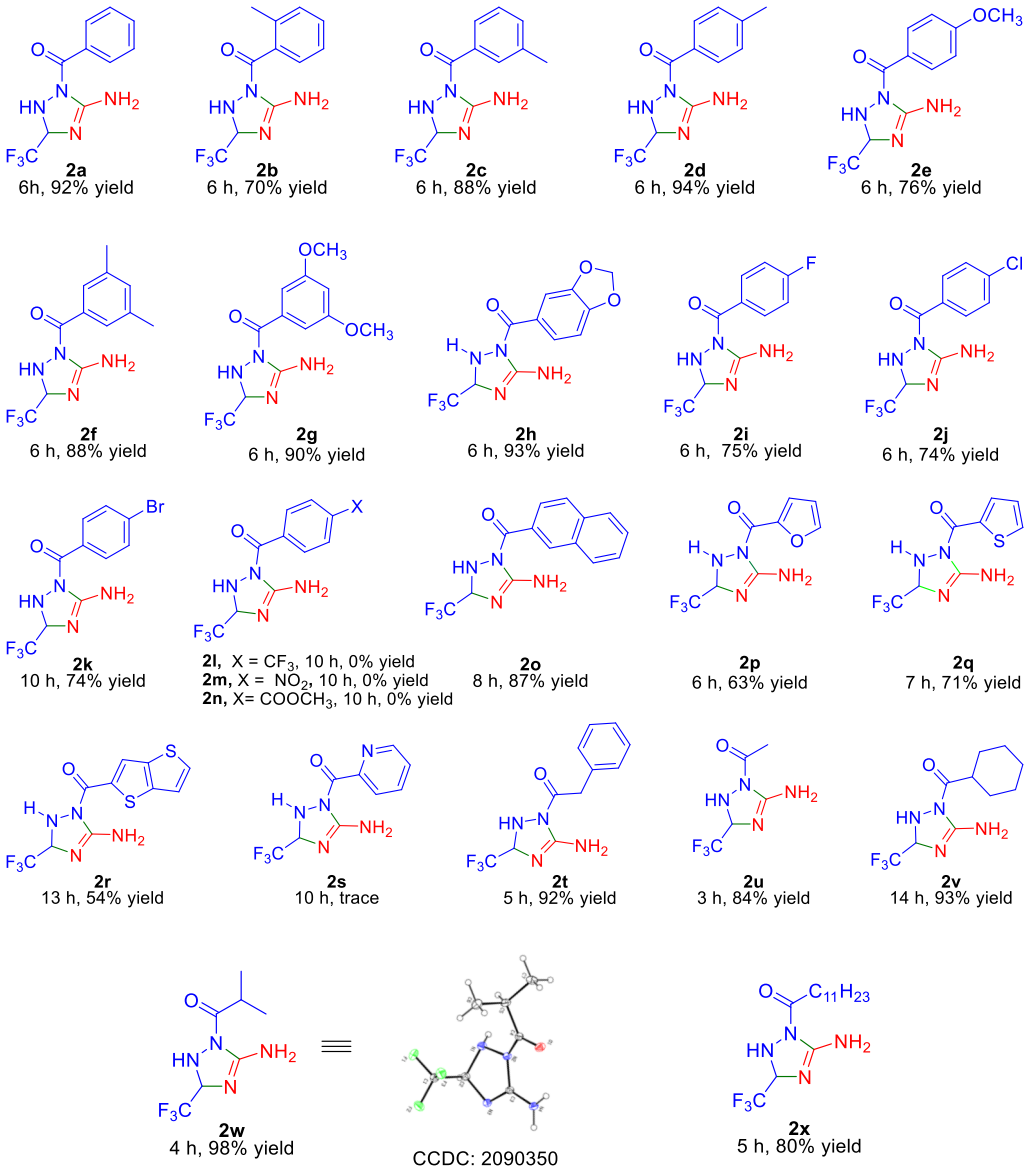
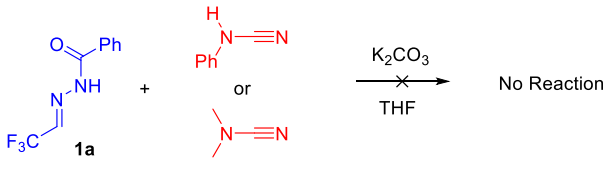
Table 2. Scope of Trifluoromethyl *N*-Acylhydrazones[a]





[a]Reaction conditions: All reactions were carried out by using 0.2 mmol **1**, 2.5 equiv of cyanamide, and 2.5 equiv of K_2CO_3 in 2 mL of THF at 25 °C under an air atmosphere. [b]Isolated yields.

Scheme 2. Scope of Cyanamides



ever, research studies on the synthesis of 3-trifluoromethyl-[1,2,4]triazolo[1,5-*a*]pyrimidines have not been reported. As an extension of this work, we supposed that trifluoromethylated [1,2,4]triazolo[1,5-*a*]pyrimidines could be produced in one step via the tandem addition/cyclization process if the halogen atom was attached to the ortho-position of phenyl rings of aromatic trifluoromethyl *N*-acylhydrazones. To test this idea, the reaction of *N*′-(2,2,2-trifluoroethylene)-*ortho*-bromobenzohydrazide (**1a**′) with cyanamide was performed (Supporting Information, Table S2). Fortunately, when the reaction was conducted with **1a**′ and cyanamide in the presence of Cs_2CO_3 and CuI in dimethyl sulfoxide (DMSO) at 150 °C for 3 h under an air atmosphere, the desired product trifluoromethylated [1,2,4]triazolo[1,5-*a*] pyrimidines **4a** was

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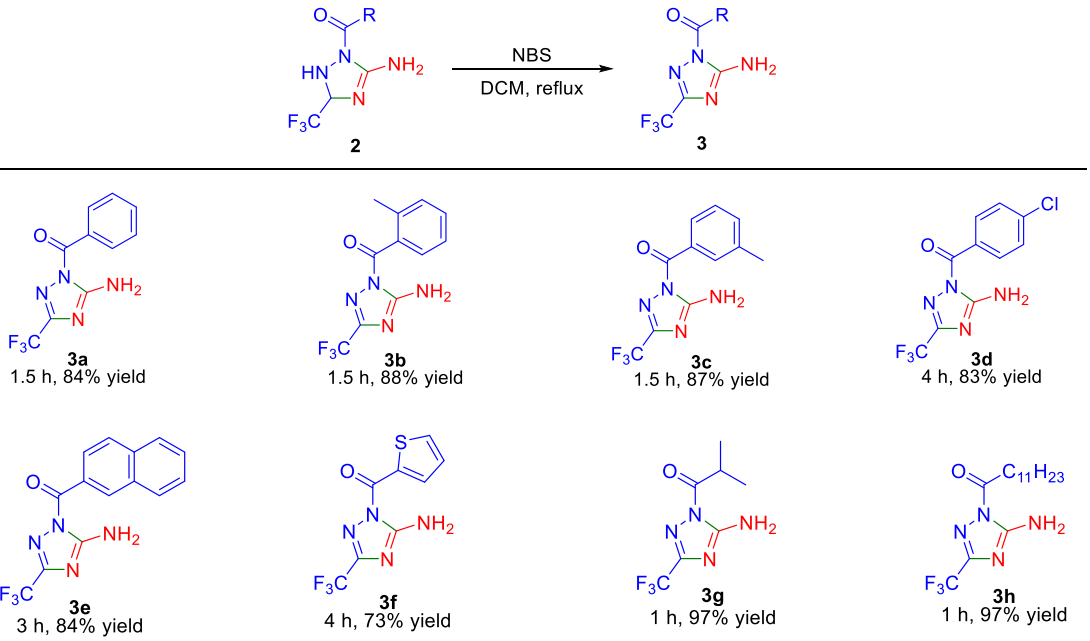
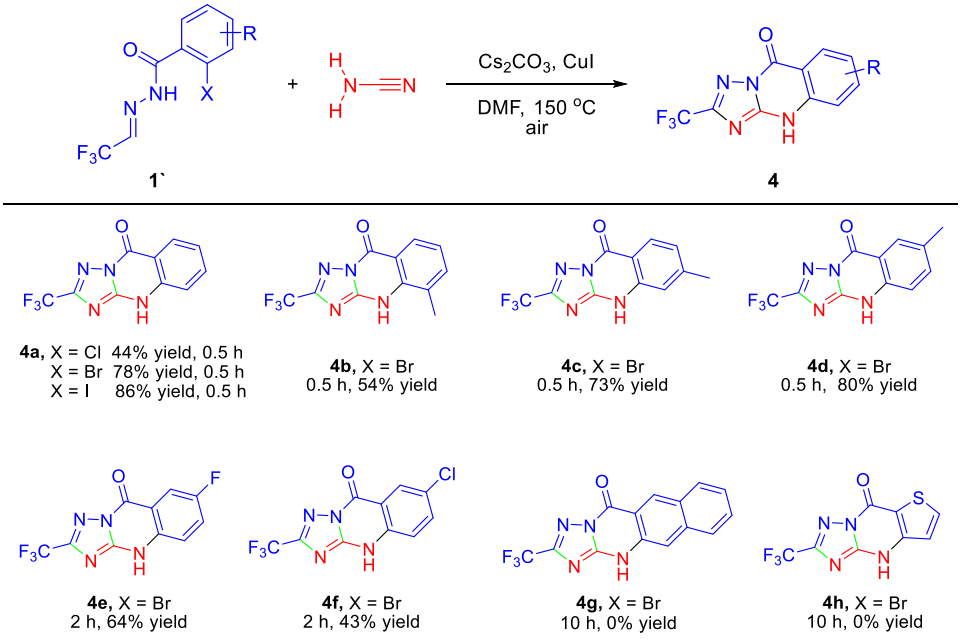
Table 3. Further Transformation of 3-Trifluoromethyl-1,2,4-triazolines[a]



[a]Reaction conditions: All reactions were carried out by using 0.2 mmol **2** and 1.5 equiv of NBS in 2 mL of CH_2Cl_2 at 40 °C. [b]Isolated yields.

Table 4. Synthesis of 3-Trifluoromethyl-[1,2,4]triazolo[1,5-*a*]pyrimidines[a]



[a]Reaction conditions: All reactions were carried out by using 0.2 mmol **1**, 2.5 equiv of cyanamide, 2.5 equiv of Cs_2CO_3, and 0.15 equiv of CuI in 2 mL of DMF at 150 °C under an air atmosphere. [b]Isolated yields.

produced in 20% yield (Supporting Information, Table S2, entry 1). After brief optimization of the reaction conditions, the suitable reaction condition was used to carry out the reaction by using **1a′**, cyanamide, Cs_2CO_3, and CuI in a molar ratio of 1:2.5:2.5:0.15 in dimethylformamide (DMF) at 150 °C under an air atmosphere to give **4a** in 78% yield (Supporting Information, Table S2).

Next, the substrate scopes were examined (Table 4). First, the influence of a different halogen atom at the ortho-position of the phenyl ring of aromatic trifluoromethyl *N*-acylhydrazones was examined. It was found that when the halogen is an iodine or bromine atom, the target product **4a** was obtained in good yields. However, when the halogen is a chlorine atom, product **4a** can only be obtained with a yield of 44% (Table 4, **4a**). The steric hindrance of the substituents on the phenyl ring of *N*-acylhydrazones **1′** was also investigated. The results showed that when the R group was the methyl group, 5-methyl-substituted trifluoromethyl *N*-acylhydrazones gave

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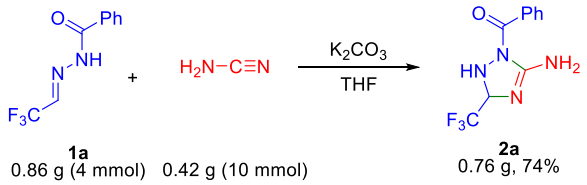
product **4d** in the highest yield compared to those of 3-methyl- and 4-methyl-substituted ones (Table 4, **4b**–**4d**). Finally, it was found that the trifluoromethyl *N*-acylhydrazone derived from naphthalene hydrazide and thiophene hydrazide did not give the corresponding products **4g** and **4h**.

To demonstrate the synthetic utility of this methodology, gram-scale reactions were performed by using *N*′-(2,2,2-trifluoroethylene)benzohydrazide **1a** and cyanamide under the standard reaction conditions (Scheme 3). The reactions proceeded well to give product **2a** in 74% yields.

Scheme 3. Gram-Scale Reaction



Based on the literature reports[14] and our experimental results, a possible reaction mechanism was tentatively proposed in Scheme 4. At first, nucleophilic addition of cyanamide to trifluoromethylhydrazone produced anionic intermediate **I**, which undergoes 1,2-hydrogen migration to afford intermediate **II**. Anion **II** underwent an intramolecular nucleophilic addition reaction to give intermediate **III**, which was protonated to give **IV**. Isomerization of intermediate **IV** produce products **2**.

CONCLUSIONS

In summary, a novel and efficient protocol for the synthesis of polysubstituted 5-amino-3-trifluoromethyl-1,2,4-triazolines and their derivatives, such as 5-amino-3-trifluoromethyl-1,2,4-triazoles and trifluoromethylated [1,2,4]triazolo[1,5-*a*]-pyrimidin-7(4*H*)-one derivatives, has been developed from the tandem addition/cyclization reaction of trifluoromethyl *N*-acylhydrazones and cyanamide. The method features atom economy, mild reaction conditionss, a broad substrate scope, and good product yields. This further demonstrates that trifluoromethylated *N*-acylhydrazones are versatile trifluoromethyl building blocks for the construction of trifluoromethylated nitrogen heterocycles.

EXPERIMENTAL SECTION

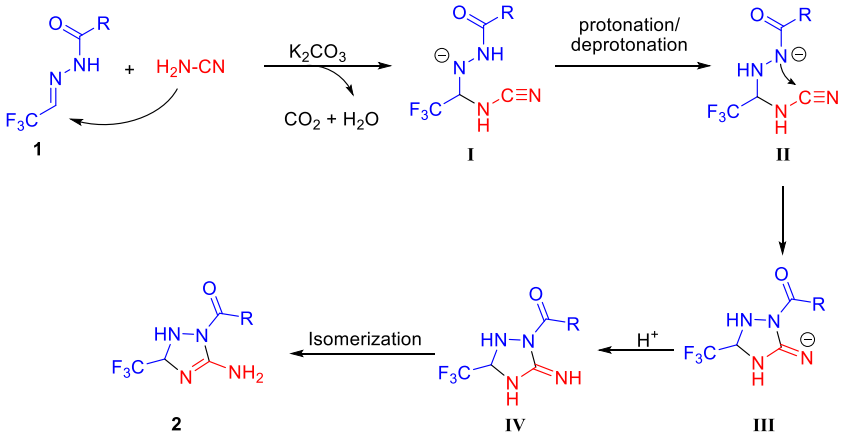
General Methods. The solvents were distilled using standard methods. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Silica gel column chromatography was carried out using silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed using silica gel (silica gel 60 GF254). TLC plates were analyzed via exposure to ultraviolet (UV) light and/or submersion in phosphomolybdic acid solution, in $KMnO_4$ solution, or in iodine vapor. NMR experiments were carried out in deuterated chloroform ($CDCl_3$-*d*) or deuterated DMSO (DMSO-d_6). ^{1}H NMR, ^{13}C{^{1}H} NMR, and ^{19}F NMR spectra were recorded using 400 or 600 MHz, 100 or 150 MHz, and 376 MHz spectrometers, respectively. Chemical shifts are reported as δ values relative to internal tetramethylsilane (δ 0.00 ppm for ^{1}H NMR), chloroform (δ 7.26 ppm for ^{1}H NMR), and chloroform (δ 77.00 ppm for ^{13}C{^{1}H} NMR) in parts per million (ppm). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; and m, multiplet. Coupling constants (J) are reported in hertz (Hz). Melting points were uncorrected. High-resolution mass spectroscopy (HRMS) spectra were recorded on a Micro TOF-QII mass instrument [electrospray ionization (ESI)]. Single-crystal X-ray data were collected using an ROD, Synergy Custom system, HyPix diffractometer.

General Procedure for the Synthesis of Trifluoromethyl *N*-Acylhydrazones 1.[15] A mixture of benzoyl hydrazides (1.0 equiv), trifluoroacetaldehyde methyl hemiacetal (1.7 equiv), TsOH·H_2O (0.1 equiv), and ethanol was added into a round-bottom flask and stirred under reflux conditions in a metal bath. The reaction was monitored using TLC. After the reaction was completed, it was cooled to room temperature. The product was precipitated from the reaction mixture and recrystallized in ethanol to obtain pure trifluoromethyl *N*-acylhydrazones **1**.

General Procedure for the Synthesis of Trifluoromethyl 1,2,4-Triazolines 2. The mixture of *N*′-(2,2,2-trifluoroethylene)-benzohydrazides **1** (0.2 mmol, 1 equiv), cyanamide (0.5 mmol, 2.5 equiv), and K_2CO_3 (0.5 mmol, 2.5 equiv) in 2 mL of THF was sequentially added into a 15 mL Schleck tube. The reaction mixture was stirred at 25 °C until the reaction was completed (monitored via TLC). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl solution (2 mL), and extracted with ethyl acetate (EA) (3 × 5 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (30:1) as the eluent to afford the pure products **2**.

*(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-(phenyl)methanone (**2a**).* Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (47 mg, 92%), mp 171–173

Scheme 4. Proposed Reaction Mechanism



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°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.30 (br, 2H), 7.14 (d, J = 7.6 Hz, 1H), 5.18−5.13 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 167.7, 156.2, 134.6, 131.9, 128.9, 128.34, 124.3 (q, J = 282.0 Hz), 77.2 (q, J = 31.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.14 (d, J = 6.0 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_{10}F_3N_4O$, 259.0801; found, 259.0802.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)(o-tolyl)methanone (**2b**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (38 mg, 70%), mp 236−238 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37−7.25 (m, 6H), 6.90 (d, J = 8.0 Hz, 1H), 5.11−5.04 (m, 1H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 168.3, 155.4, 136.0, 134.5, 130.5, 129.9, 126.7, 125.7, 124.2 (q, J = 282.0 Hz), 77.2 (q, J = 31.5 Hz), 19.02; ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.08 (d, J = 6.0 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{12}F_3N_4O$, 273.0958; found, 273.0969.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)(m-tolyl)methanone (**2c**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (48 mg, 88%), mp 172−174 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (s, 2H), 7.37−7.35 (m, 2H), 7.30 (br, 2H), 7.14 (d, J = 7.6 Hz, 1H), 5.19−5.13 (m, 1H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 167.8, 156.4, 137.6, 134.6, 132.4, 129.4, 128.2, 126.0, 124.3 (q, J = 282.0 Hz), 77.3 (q, J = 30.0 Hz), 21.3; ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.09 (d, J = 5.6 Hz); HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{11}H_{11}F_3N_4NaO$, 295.0777; found, 295.0789.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)(p-tolyl)methanone (**2d**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (51 mg, 94%), mp 165−167 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.47 (d, J = 8.0 Hz, 2H), 6.06−6.04 (m, 4H), 5.93 (d, J = 8.0 Hz, 1H), 3.97−3.90 (m, 1H), 1.13 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 167.6, 156.5, 142.1, 131.7, 129.2, 128.8, 124.3 (q, J = 282.0 Hz), 77.3 (q, J = 30.0 Hz), 21.5; ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.16 (d, J = 5.6 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{12}F_3N_4O$, 273.0958; found, 273.0971.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)(4-methoxyphenyl)methanone (**2e**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (44 mg, 76%), mp 184−186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (d, J = 8.8 Hz, 2H), 7.31 (br, 2H), 7.18 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 5.21−5.15 (m, 1H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 166.9, 162.3, 156.7, 131.6, 126.3, 124.4 (q, J = 283.5 Hz), 113.6, 77.3 (q, J = 30.0 Hz), 55.9; ^{19}F NMR (376 MHz, DMSO-d_6): δ −80.94 (d, J = 4.9 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{12}F_3N_4O_2$, 289.0907; found, 289.0906.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-(3,5-dimethylphenyl)methanone (**2f**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (50 mg, 88%), mp 191−192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37 (s, 2H), 7.29 (br, 2H), 7.18 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 5.19−5.13 (m, 1H), 2.31 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 168.0, 156.4, 137.4, 134.7, 133.1, 126.5, 124.2 (q, J = 283.5 Hz), 77.2 (q, J = 30.0 Hz), 21.2; ^{19}F NMR (376 MHz, DMSO-d_6): δ −80.89 (d, J = 5.6 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{12}H_{14}F_3N_4O$, 287.1114; found, 287.1109.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-(3,5-dimethoxyphenyl)methanone (**2g**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (57 mg, 90%), mp 188−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (br, 2H), 7.14 (d, J = 7.6 Hz, 1H), 6.90 (s, 2H), 6.68 (s, 1H), 5.19−5.14 (m, 1H), 3.77 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 167.2, 160.3, 156.2, 136.4, 124.2 (q, J = 283.5 Hz), 106.9, 103.5, 77.2 (q, J = 33.0 Hz), 55.8; ^{19}F NMR (376 MHz, DMSO-d_6): δ −80.89 (d, J = 6.0 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{12}H_{14}F_3N_4O_3$, 319.1013; found, 319.1012.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-(benzo[d][1,3]dioxol-5-yl)methanone (**2h**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (56 mg, 93%), mp 211−213 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (m, 1H), 7.38 (s, 1H), 7.28 (br, 2H), 7.16 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.12 (s, 2H), 5.20−5.15 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 166.6, 156.6, 150.5, 147.1, 127.9, 125.0, 124.3 (q, J = 282.0 Hz), 109.5, 108.1, 102.3, 77.23 (q, J = 31.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −80.90 (d, J = 5.3 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{10}F_3N_4O_3$, 303.0700; found, 303.0698.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)(4-fluorophenyl)methanone (**2i**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (41 mg, 75%), mp 176−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90−7.87 (m, 2H), 7.33 (t, J = 8.6 Hz, 4H), 7.18 (d, J = 7.6 Hz, 1H), 5.23−5.17 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 166.4, 164.2 (d, J = 248.3 Hz), 156.2, 131.9 (d, J = 9.0 Hz), 131.0 (d, J = 3.2 Hz), 124.3 (q, J = 282.0 Hz), 115.4 (d, J = 21.8 Hz), 77.2 (q, J = 30.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.12 (d, J = 4.9 Hz), −103.65 (m); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_9F_4N_4O$, 277.0707; found, 277.0704.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)(4-chlorophenyl)methanone (**2j**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (43 mg, 74%), mp 166−168 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.33 (br, 2H), 7.17 (d, J = 7.2 Hz, 1H), 5.22−5.17 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 166.5, 156.1, 136.7, 133.3, 130.9, 128.5, 125.3 (q, J = 285.0 Hz), 77.3 (q, J = 31.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.08 (d, J = 6.0 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_{10}H_9ClF_3N_4O$, 293.0411; found, 293.0426.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)(4-bromophenyl)methanone (**2k**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (50 mg, 74%), mp 200−201 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (s, 4H), 7.33 (br, 2H), 7.17 (d, J = 7.6 Hz, 1H), 5.24−5.17 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 166.6, 156.1, 133.7, 131.5, 131.0, 125.6, 124.3 (q, J = 282.0 Hz), 77.3 (q, J = 28.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −80.85 (d, J = 6.0 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_{10}H_9BrF_3N_4O$, 336.9906; found, 336.9915.

1-(2-Naphthoyl)-5-amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazole (**2o**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (53 mg, 87%), mp 201−203 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18 (s, 1H), 6.80−6.76 (m, 3H), 6.61 (d, J = 8.6 Hz, 1H), 6.45−6.37 (m, 2H), 6.14 (br, 2H), 6.02 (d, J = 8.0 Hz, 1H), 4.01−3.96 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 167.7, 156.4, 134.5, 132.1, 132.0, 129.6, 129.3, 128.5, 128.1, 127.7, 127.3, 125.4, 124.4 (q, J = 282.0 Hz), 77.3 (q, J = 30.0 Hz); ^{19}F NMR (400 MHz, DMSO-d_6): δ −80.82 (d, J = 6.0 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_{14}H_{12}F_3N_4O$, 309.0958; found, 309.0961.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-(furan-2-yl)methanone (**2p**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (31 mg, 63%), mp 134−136 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03−8.02 (m, 1H), 7.60 (d, J = 2.8 Hz, 1H), 7.27 (br, 2H), 7.21 (d, J = 8.0 Hz, 1H), 6.73 (dd, J = 3.6, 1.6 Hz, 1H), 5.32−5.26 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 156.1, 148.1, 145.1, 124.2 (q, J = 282.0 Hz), 120.8, 116.9, 112.6, 77.6 (q, J = 30.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.09 (d, J = 5.6 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_8H_8F_3N_4O_2$, 249.0594; found, 249.0604.

(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-(thiophen-2-yl)methanone (**2q**). Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (37 mg, 71%), mp 182−184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (d, J = 3.6 Hz, 1H), 7.98 (d, J = 4.8 Hz, 1H), 7.36−7.34 (m, 3H), 7.24−7.22 (m, 1H), 5.36−5.30 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 159.8, 156.1, 136.2, 136.1, 134.7, 127.8, 124.2 (q, J = 282.5 Hz), 77.5 (q, J = 30.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −81.07 (d, J = 5.6 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_8H_8F_3N_4OS$, 265.0365; found, 265.0376.

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*(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-(thieno[3,2-b]thiophen-2-yl)methanone (**2r**).* Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (36 mg, 54%), mp 206−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 7.96 (d, J = 5.2 Hz, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.39 (br, 2H), 5.39−5.33 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 160.0, 156.1, 146.5, 138.6, 136.0, 134.1, 128.9, 124.3 (q, J = 282.0 Hz), 120.7, 77.7 (q, J = 31.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −80.94 (d, J = 4.9 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_{10}H_8F_3N_4OS_2$, 321.0086; found, 321.0100.

*1-(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-2-phenylethanone (**2t**).* Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (50 mg, 92%), mp 141−143 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34−7.31 (m, 2H), 7.28−7.24 (m, 3H), 7.15 (br, 2H), 7.07 (d, J = 8.0 Hz, 1H), 5.23−5.18 (m, 1H), 3.92 (d, J = 15.6 Hz, 1H), 3.84 (d, J = 15.6 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 170.4, 155.4, 134.6, 130.1, 128.7, 127.2, 124.3 (q, J = 282.0 Hz), 77.0 (q, J = 30.0 Hz), 41.7; ^{19}F NMR (376 MHz, DMSO-d_6): δ −81.18 (d, J = 5.64 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula $C_{11}H_{12}F_3N_4O$, 273.0958; found, 273.0966.

*1-(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)ethan-1-one (**2u**).* Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (33 mg, 84%), mp 142−144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.12 (br, 2H), 8.98 (d, J = 8.0 Hz, 1H), 5.20−5.13 (m, 1H), 2.16 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 169.8, 155.3, 124.3 (q, J = 282.0 Hz), 76.8 (d, J = 30.0 Hz), 23.7; ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.69 (d, J = 5.6 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_5H_8F_3N_4O$, 197.0645; found, 197.0644.

*(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-(cyclohexyl)methanone (**2v**).* Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (49 mg, 93%), mp 171−173 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16 (br, 2H), 7.00 (d, J = 8.0 Hz, 1H), 5.18−5.11 (m, 1H), 2.81−2.75 (m, 1H), 1.83−1.62 (m, 5H), 1.37−1.15 (m, 5H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 175.0, 155.8, 124.4 (q, J = 283.5 Hz), 76.9 (q, J = 30.0 Hz), 42.6, 28.4, 27.9, 25.8, 25.5, 25.4; ^{19}F NMR (376 MHz, DMSO-d_6): δ −81.14 (d, J = 5.6 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_{10}H_{16}F_3N_4O$, 265.1271; found, 265.1280.

*1-(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one (**2w**).* Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (44 mg, 98%), mp 163−165 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (br, 2H), 7.02 (d, J = 8.0 Hz, 1H), 5.20−5.13 (m, 1H), 3.07−3.00 (m, 1H), 1.07 (d, J = 2.4 Hz, 3H), 1.05 (d, J = 2.4 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 176.1, 155.8, 124.4 (q, J = 282.0 Hz), 77.9 (q, J = 31.5 Hz), 33.0, 18.7, 18.3; ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.46 (d, J = 6.0 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_7H_{12}F_3N_4O$, 225.0958; found, 225.0967.

*1-(5-Amino-3-(trifluoromethyl)-2,3-dihydro-1H-1,2,4-triazol-1-yl)dodecan-1-one (**2x**).* Purified by column chromatography (CH_2Cl_2/MeOH, 30:1). White solid (53 mg, 80%), mp 141−144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13 (s, 2H), 6.94 (d, J = 8.0 Hz, 1H), 5.19−5.12 (m, 1H), 2.60−2.38 (m, 4H), 1.56−1.50 (m, 2H), 1.24 (s, 14 H), 0.86 (t, J = 5.4 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 172.3, 155.5, 124.3 (q, J = 282.0 Hz), 76.9 (q, J = 30.0 Hz), 35.1, 31.7, 29.4, 29.4, 29.3, 29.2, 29.1, 28.9, 23.8, 22.5, 14.3; ^{19}F NMR (376 MHz, DMSO-d_6): δ −76.69 (d, J = 5.6 Hz); HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_{15}H_{28}F_3N_4O$, 337.2210; found, 337.2213.

General Procedure for the Synthesis of Trifluoromethyl 1,2,4-Triazoles 3. The mixture of 3-trifluoromethyl-1,2,4-triazoles **2** (0.2 mmol, 1 equiv), NBS (0.3 mmol, 1.5 equiv), and CH_2Cl_2 (2 mL) was sequentially added into a 15 mL Schleck tube. The reaction mixture was stirred at 40 °C in a metal bath until the reaction was completed (monitored via TLC). The reaction mixture was cooled to room temperature, quenched with $Na_2S_2O_3$ (aq, 2 mL), and extracted with EA (3 × 5 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with EA/petroleum ether (1:5) as the eluent to afford pure products **3**.

*(5-Amino-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)(phenyl)-methanone (**3a**).* Purified by column chromatography (EA/petroleum ether, 1:5). White solid (43 mg, 84%), mp 177−179 °C; ^{1}H NMR (400 MHz, chloroform-d): δ 8.20 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 8.0 Hz, 2H), 7.27 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, chloroform-d): δ 168.3, 159.4, 152.2 (q, J = 40.5 Hz), 134.1, 131.5, 130.4, 128.4, 118.7 (q, J = 268.5 Hz); ^{19}F NMR (376 MHz, chloroform-d): δ −67.61; HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_{10}H_8F_3N_4O$, 257.0645; found, 257.0645.

*(5-Amino-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)(o-tolyl)-methanone (**3b**).* Purified by column chromatography (EA/petroleum ether, 1:5). White solid (48 mg, 88%), mp 193−193 °C; ^{1}H NMR (400 MHz, chloroform-d): δ 7.59−7.57 (m, 1H), 7.49−7.46 (m, 1H), 7.33−7.29 (m, 2H), 7.15 (br, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, chloroform-d): δ 170.2, 158.7, 152.3 (q, J = 39.0 Hz), 137.8, 132.1, 131.1, 130.9, 129.6, 125.4, 118.6 (q, J = 268.5 Hz), 20.0; ^{19}F NMR (376 MHz, DMSO-d_6): δ −80.90; HRMS (ESI) m/z: [M + Na]$^+$ calcd for chemical formula: $C_{11}H_9F_3N_4ONa$, 293.0621; found, 293.0628.

*(5-Amino-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)(m-tolyl)-methanone (**3c**).* Purified by column chromatography (EA/petroleum ether, 1:5). White solid (47 mg, 87%), mp 201−203 °C; ^{1}H NMR (400 MHz, chloroform-d): δ 8.00 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 6.77 (br, 2H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, chloroform-d): δ 168.5, 159.4, 152.2 (q, J = 39.0 Hz), 138.3, 134.9, 131.7, 130.3, 128.7, 128.2, 118.7 (q, J = 270.0 Hz), 21.3; ^{19}F NMR (376 MHz, chloroform-d): δ −67.63; HRMS (ESI) m/z: [M + Na]$^+$ calcd for chemical formula: $C_{11}H_9F_3N_4ONa$, 293.0621; found, 293.0632.

*5-Amino-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)(4-chlorophenyl)methanone (**3d**).* Purified by column chromatography (EA/petroleum ether, 1:5). White solid (48 mg, 83%), mp 207−209 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (s, 2H), 8.00 (d, J = 5.6 Hz, 2H), 7.63 (d, J = 6.0 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 167.3, 159.7, 151.8 (q, J = 37.5 Hz), 133.1, 131.7, 130.9, 127.8, 119.4 (q, J = 268.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −65.66; HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_{10}H_7ClF_3N_4O$, 291.0255; found, 291.0260.

*(5-Amino-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)(naphthalen-2-yl)methanone (**3e**).* Purified by column chromatography (EA/petroleum ether, 1:5). White solid (51 mg, 84%), mp 223−225 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 8.21 (s, 2H), 8.14−8.01 (m, 4H), 7.74−7.66 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 168.1, 159.8, 151.8 (q, J = 37.5 Hz), 135.3, 132.8, 131.9, 129.9, 129.5, 129.1, 128.1, 128.0, 127.6, 126.5, 119.4 (q, J = 268.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −65.98; HRMS (ESI) m/z: [M − H]$^+$ calcd for chemical formula: $C_{14}H_8F_3N_4O$, 305.0656; found, 305.0657.

*(5-Amino-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)(thiophen-2-yl)methanone (**3f**).* Purified by column chromatography (EA/petroleum ether, 1:5). White solid (38 mg, 73%), mp 186−188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37−8.36 (m, 1H), 8.23−8.22 (m, 1H), 8.19 (s, 2H), 7.36−7.33 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 160.2, 159.6, 151.8 (q, J = 39.0 Hz), 139.4, 139.0, 132.3, 128.7, 119.0 (q, J = 268.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ −66.86; HRMS (ESI) m/z: [M + H]$^+$ calcd for chemical formula: $C_8H_6F_3N_4OS$, 263.0209; found, 263.0210.

*1-(5-Amino-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)-2-methyl-propan-1-one (**3g**).* Purified by column chromatography (EA/petroleum ether, 1:5). White solid (45 mg, 97%), mp 174−176 °C; ^{1}H NMR (400 MHz, Chloroform-d): δ 7.16 (s, 2H), 3.62−3.52 (m, 1H), 1.23 (d, J = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (150 MHz, chloroform-d): δ 178.9, 158.0, 151.9 (q, J = 40.5 Hz), 118.6 (q, J = 270.0 Hz), 33.5, 18.4; ^{19}F NMR (376 MHz, chloroform-d): δ −67.74; HRMS (ESI) m/z: [M + Na]$^+$ calcd for chemical formula: $C_7H_9F_3N_4ONa$, 245.0621; found, 245.0630.

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*1-(5-Amino-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)dodecan-1-one (**3h**).* Purified by column chromatography (EA/petroleum ether, 1:5). White solid (65 mg, 97%), mp 171−173 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.27 (s, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 1.79−1.71 (m, 2H), 1.27 (s, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, chloroform-*d*): δ 174.9, 157.8, 151.9 (q, *J* = 39.0 Hz), 118.6 (q, *J* = 268.5 Hz), 35.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 23.6, 22.6, 14.1; ^{19}F NMR (376 MHz, chloroform-*d*): δ −67.71; HRMS (ESI) *m*/*z*: [M − H]$^+$ calcd for chemical formula: $C_{15}H_{24}F_3N_4O$, 333.1908; found, 333.1909.

General Procedure for the Synthesis of 3-Trifluoromethyl-[1,2,4]triazolo[1,5-*a*]pyrimidines 4. The mixture of *N*′-(2,2,2-trifluoroethylene)-*ortho*-bromobenzohydrazide **1a**′ (0.2 mmol, 1 equiv), cyanamide (0.5 mmol, 2.5 equiv), Cs_2CO_3 (0.5 mmol, 2.5 equiv), CuI (0.03 mmol, 0.15 equiv), and DMF (2 mL) was sequentially added into a 15 mL Schleck tube. The reaction mixture was stirred at 150 °C in a metal bath until the reaction was completed (monitored via TLC). The reaction solution was cooled to room temperature, quenched with NH_4Cl (aq, 2 mL), and extracted with EA (3 × 5 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (50:1) as the eluent to afford pure products **4**.

*2-(Trifluoromethyl)-[1,2,4]triazolo[5,1-b]quinazolin-9(4H)-one (**4a**).* Purified by column chromatography (CH_2Cl_2/MeOH, 50:1). White solid (40 mg, 78%), m.p: 213−215 °C; ^{1}H NMR (400 MHz, DMSO-*dz*$_6$): δ 13.6 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.90 (t, *J* = 9.2 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$): δ 156.0, 153.3 (q, *J* = 39.0 Hz), 152.3, 139.9, 136.2, 128.0, 124.0, 119.7 (q, *J* = 268.5 Hz), 117.6, 114.2; ^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ −65.63; HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for chemical formula: $C_{10}H_6F_3N_4O$, 255.0488; found, 255.0488.

*5-Methyl-2-(trifluoromethyl)-[1,2,4]triazolo[5,1-b]quinazolin-9(4H)-one (**4b**).* Purified by column chromatography (CH_2Cl_2/MeOH, 50:1). White solid (29 mg, 54%), mp 207−209 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 12.88 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$): δ 156.1, 153.4 (q, *J* = 39.0 Hz), 152.6, 138.5, 136.9, 126.5, 125.8, 123.7, 119.7 (q, *J* = 270.0 Hz), 114.4, 18.1; ^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ −65.72; HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for chemical formula: $C_{11}H_7F_3N_4ONa$, 291.0464; found, 291.0468.

*6-Methyl-2-(trifluoromethyl)-[1,2,4]triazolo[5,1-b]quinazolin-9(4H)-one (**4c**).* Purified by column chromatography (CH_2Cl_2/MeOH, 50:1). White solid (39 mg, 73%), mp 216−218 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 13.51 (br, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$): δ 155.8, 153.3 (q, *J* = 37.5 Hz), 152.2, 147.2, 140.0, 127.9, 125.5, 119.7 (q, *J* = 270.0 Hz), 117.0, 111.9, 20.0; ^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ −65.65; HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for chemical formula: $C_{11}H_7F_3N_4ONa$, 291.0464; found, 291.0475.

*7-Methyl-2-(trifluoromethyl)-[1,2,4]triazolo[5,1-b]quinazolin-9(4H)-one (**4d**).* Purified by column chromatography (CH_2Cl_2/MeOH, 50:1). White solid (43 mg, 80%), mp 303−305 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 13.52 (s, 1H), 8.05 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$): δ 155.9, 153.4 (q, *J* = 37.5 Hz), 152.1, 137.8, 137.4, 133.4, 127.0, 119.7 (q, *J* = 268.5 Hz), 117.5, 113.9, 20.8; ^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ −65.63; HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for chemical formula: $C_{11}H_7F_3N_4ONa$, 291.0464; found, 291.0475.

*7-Fluoro-2-(trifluoromethyl)-[1,2,4]triazolo[5,1-b]quinazolin-9(4H)-one (**4e**).* Purified by column chromatography (CH_2Cl_2/MeOH, 50:1). White solid (35 mg, 64%) mp 274−276 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 13.74 (1s, H), 7.97 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.83 (td, *J* = 8.4, 2.8 Hz, 1H), 7.61 (dd, *J* = 9.2, 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$): δ 158.0 (d, *J* = 240.0 Hz), 155.4 (d, *J* = 3.0 Hz), 153.4 (q, *J* = 39.0 Hz), 152.2, 136.9, 136.0, 124.7 (d, *J* = 24.0 Hz), 120.3 (d, *J* = 7.5 Hz), 119.6 (q, *J* = 268.5 Hz), 112.4 (d, *J* = 21.0 Hz); ^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ −65.29, −117.93 (m); HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for chemical formula: $C_{10}H_4F_4N_4ONa$, 295.0213; found, 295.0213.

*7-Chloro-2-(trifluoromethyl)-[1,2,4]triazolo[5,1-b]quinazolin-9(4H)-one (**4f**).* Purified by column chromatography (CH_2Cl_2/MeOH, 50:1). White solid (25 mg, 43%), mp 312−315 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 13.80 (s, 1H), 8.19 (d, *J* = 2.4 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$): δ 155.1, 153.5 (q, *J* = 39.0 Hz), 152.3, 138.8, 136.0, 127.9, 126.7, 120.0, 119.6 (q, *J* = 268.5 Hz), 115.6; ^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ −60.93; HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for chemical formula: $C_{10}H_4ClF_3N_4ONa$, 310.9918; found, 310.9925.

Gram-Scale Reaction. The mixture of *N*′-(2,2,2-trifluoroethylene)benzohydrazide **1a** (4 mmol), cyanamide (10 mmol), and K_2CO_3 (10 mmol) in THF (30 mL) was stirred at 25 °C for 6 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EA (3 × 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (30:1) as the eluent to afford pure products **2a** (0.76 g, 74% yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00176.

Copies of the ^{1}H NMR, ^{13}C{^{1}H} NMR, ^{19}F NMR, and HRMS spectra for compounds **2**, **3**, and **4** and crystallography data of **2w** (PDF)

Accession Codes

CCDC 2090350 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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