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PII: S0040-4020(18)31232-8

DOI: https://doi.org/10.1016/j.tet.2018.10.026

Reference: TET 29859

To appear in: *Tetrahedron*

Received Date: 17 August 2018

Revised Date: 10 October 2018

Accepted Date: 14 October 2018

Please cite this article as: Han J, Ran J-X, Chen X-P, Wang Z-H, Wu F-H, Study on the green click-chemistry synthesis of 4-trifluoroacetyl-1,2,3-triazoles, *Tetrahedron* (2018), doi: https://doi.org/10.1016/j.tet.2018.10.026.

## Graphical Abstract

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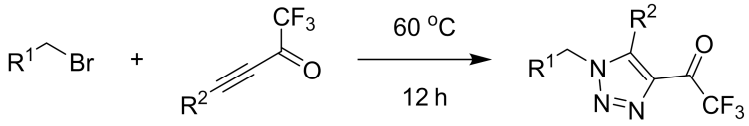
*School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai, People's Republic of China*



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# Study on the green click-chemistry synthesis of 4-trifluoroacetyl-1,2,3-triazoles

Jie Han [a], Jian-Xiong Ran [a], Xiu-Ping Chen [a], Zhong-Hua Wang [a, b, *], Fan-Hong Wu [a, **]

[a]*School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai, People's Republic of China*
[b]*Shanghai Engineering Research Center of Pharmaceutical Progress, Shanghai, 201203, China*

ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Click-chemistry
Metal-free
Solvent free
Anti-cancer activities

ABSTRACT

A metal-free and solvent free click-chemistry procedure has been revealed for the synthesis of 4-trifluoroacetyl-1,2,3-triazoles from corresponding azides and alkyne with high yield and selectivity. The pure products could be easily obtained via crystallization of the reaction mixture (standing for 1 day). Among the 4-trifluoroacetyl-1,2,3-triazoles, **3ba** showed the best anticancer activity against HepG2 cell with $IC_{50}$ of 0.0267μmol/ml. This method has the advantages of less pollution, low cost, simple treatment and more efficiency.

## 1. Introduction

Click chemistry, a term coined by K. Barry Sharpless is a way to generate substances rapidly and reliably by joining small modular units together, and become ubiquitous in a plethora of fields such as drug design, sensors, catalysis, materials chemistry, and bioconjugations.[1] The most accepted click reaction was found to be 1,3-dipolar cycloaddition reaction also known as Husigen cycloaddition between azides and a terminal alkynes affording 1,2,3-triazole, which was first reported by Dimorth in 1902,[7] and then its mechanism was not fully realized till 1965 by Husigen.[8] This reaction was flourished since 2001 because Sharpless and Meldal independently reported that copper catalyst strategy with 10 million times acceleration and excellent region-selection.

However, the addition of a metal catalyst (such as copper and ruthenium) have some limitation within biological systems and some materials applications.[9] Thus, some metal-free conditions had been developed such as: heterogeneous reactions employing an immobilized catalyst,[10] non-transition metal catalyzed reactions have been explored,[11] microwave irradiation.[12]

Trifluoroacetyl containing heterocycles are an integral part of many biologically active compounds in the pharmaceutical and agro chemistry.[13] Additionally, trifluoroacetyl group is a kind of most useful synthetic building block. For example, via simple reduction, trifluoroacetyl group could be converted to corresponding trifluoroethanol skeleton, which is a potent pharmacophoric group in many drugs or candidates.[15]

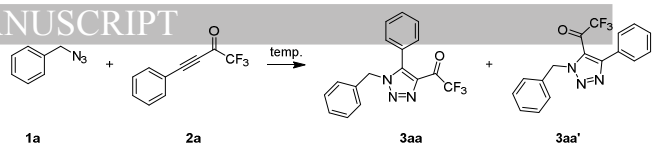
Owing to the rising environmental awareness, dual-free (metal-free and solvent-free) systems have been popular in pharmaceutical industry. Here, a systematic investigation of cycloaddition of trifluoroacetyl-acetylenes with azides under dual-free condition with high yield and selectivity is reported. 4-trifluoroacetyl-1,2,3-triazoles owning potential biological activity have been obtained after the easy crystallization via standing the reaction mixture for 1 day. Fortunately **3ba** was screened out with potent anticancer activity against HepG2 cells with $IC_{50}$ of 0.0267 μmol/ml. This system could reduce the amount of metal and solvent, reduce contaminayion and costs, simplify the treatment, improve the efficiency, and coincided with the requirements of green chemistry during the screening of new drug candidates and subsequent large scale process.

## 2. Results and discussion

**1a** and **2a** were selected for the optimization study of the dual-free click reaction conditions. As expected, the corresponding products **3aa** and **3aa'** were obtained after 12 hours reaction at room temperature with 27% conversion and high regioselectivity (Table 1, entry 1), and the conversion rate would not increase even the reaction time was extended. While increasing the reaction temperature, it was found that the reaction was accelerated, starting materials were completely converted, the regioselectivity was decrease slightly and the yield was first increased from rt to 60°C then decreased from 60°C to 100°C. The optimum reaction temperature was 60°C in view of conversion, regioselectivity and yield. A series of 4-trifluoroacetyl-1,2,3-triazoles were synthesized by this very simple method.

**Table 1**

Optimization of the reaction temperature for click chemistry.[a]




1a 2a 3aa 3aa'

| Entry | *T*(°C) | Time (h) | Conversion rate(%)[b] | **3aa/3aa'** ratio[b] | Yield(%)[b,c] |
|---|---|---|---|---|---|
| 1 | rt | 12h | 27% | 95:5 | 23% |
| 2 | 40 | 12h | 77% | 94:6 | 72% |
| 3 | 60 | 12h | 100% | 92:8 | 91% |
| 4 | 70 | 10h | 100% | 90:10 | 90% |
| 5 | 80 | 8h | 100% | 89:1 | 89% |
| 6 | 100 | 6h | 100% | 88:12 | 87% |

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol);

[b] Determined by F-NMR of the crude mixture;

[c] Yield of **3aa**.

The reaction mixtures were purified by column separation or crystallization at room temperature for 1 day to obtain a more pure compound **3aa** for analysis. The structure of **3aa** was confirmed by $^{1}$H-NMR, $^{13}$C-NMR, HRMS and X-ray diffraction crystallography spectrum. According to the $^{1}$H-NMR spectrum, the chemical shift range of 7.58-7.00 ppm is 10 hydrogen atoms on the benzene ring, and the chemical shift 5.47 ppm is the 2 hydrogen atoms of the benzyl site (Fig.1). While the C=O group (δ174.2 (q, $^{2}J_{C\text{-}F}$ = 36.7Hz)) and $CF_3$ group (δ116.2 (q, $^{1}J_{C\text{-}F}$ = 289.2Hz)) were assisted by $^{13}$C-NMR (Fig.2). The HRMS spectrum (EI-TOF) of [M]+ for **3aa** was found as 331.0930 (calculated as 331.0932 ). Moreover, the structure of **3aa** was confirmed by X-ray diffraction crystallography data (Fig.3), which clearly and unambiguously demonstrates that the trifluoroacetyl substituted triazole cis-isomer was a more stable conformation, which was consistent with the results reported in the literature.[11] Interestingly, this result indicated that it is in the form of a monohydrate or dihydroxy group. Further infrared spectrum analysis elucidated that the monohydrate or dihydroxyl structure was in crystalline form, while the trifluoroacetyl structure was present as an oil or solution. There was a broad peak around 3199 $cm^{-1}$ in the infrared spectrum of its crystal form (Fig.4). Correspondingly, a characteristic peak of carbonyl at 1722 $cm^{-1}$ was found in the infrared spectrum of its DCM solution (Fig.5).

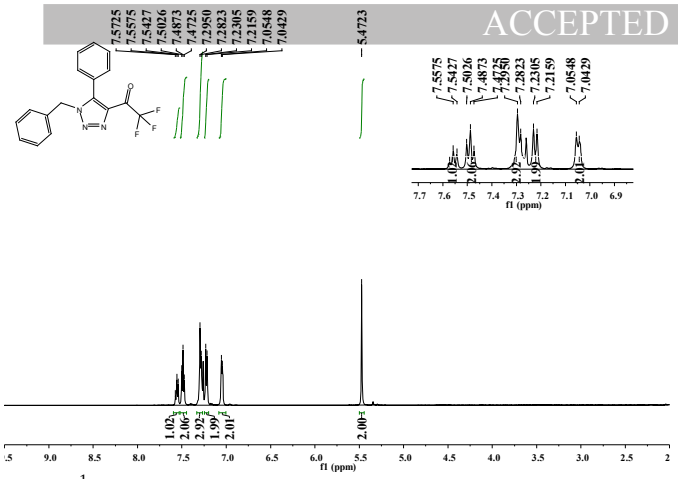


**Fig.1** $^{1}$H-NMR spectroscopy of **3aa**

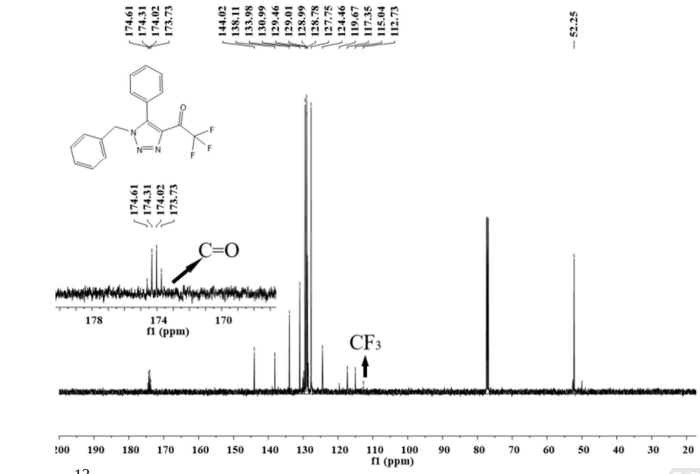


**Fig.2** $^{13}$C-NMR spectroscopy **3aa**

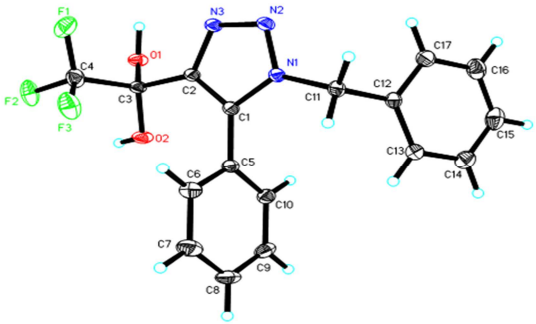


**Fig.3** X-ray structure of **3aa monohydrate**[16]

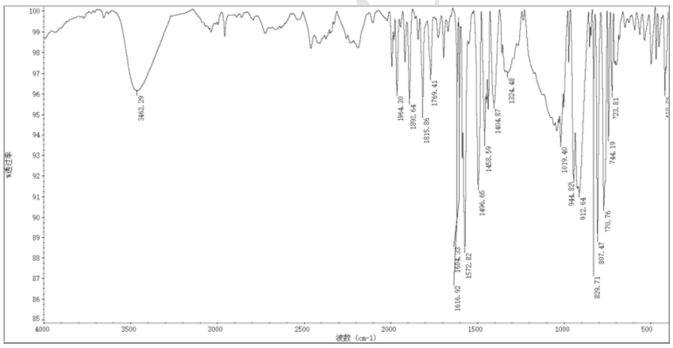


**Fig.4** The infrared spectrum of its crystal form

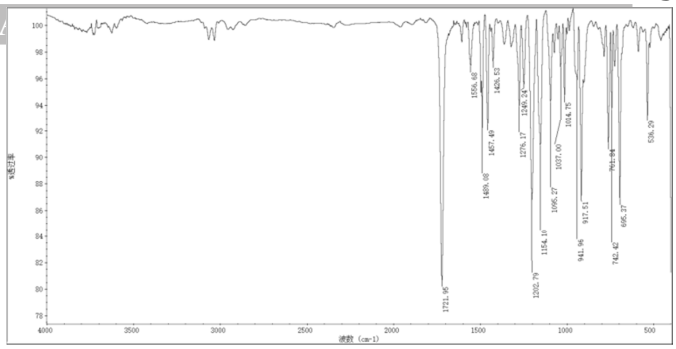
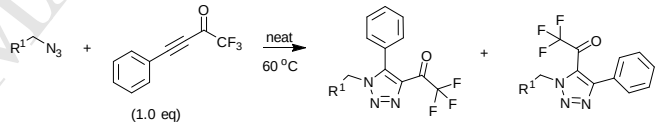


**Fig.5** The infrared spectrum of its DCM solution

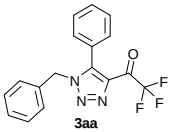
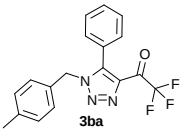
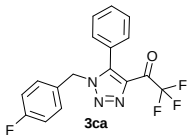
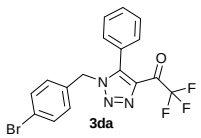
With the optimum conditions in hand, various 4-trifluoroacetyl-1,2,3-triazoles were synthesized. The scope of azide substrates was first examined. All benzyl azide compounds were reacted smoothly under mild conditions to give the corresponding triazoles, where electron donating groups or electron withdrawing groups in the para position include methyl, F, Cl substituted benzyl azide provides excellent yield and high regioselectivity (Table 2, **3ba**-**3da**). The substrates bearing two groups gave a lower yield than those with a group in the meta or para position (Table 2, **3ea**-**3ia**), where the yield of the substrate with the two substituents in the ortho position was the lowest (Table 2, **3ha**, **3ia**). For substrates with naphthyl substituents, the desired product was obtained in moderate yields (Table 2, **3ja**, **3ka**). It was worth noting that alkyl azide substrates also have good yields and good selectivity (**3la**).

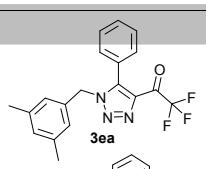
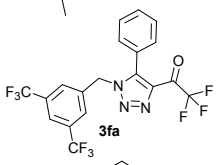
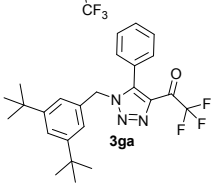
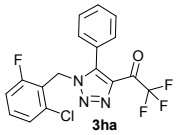
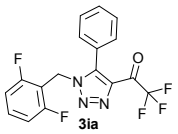
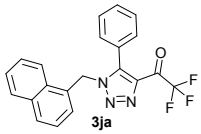
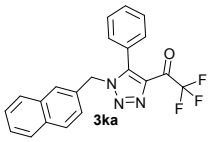
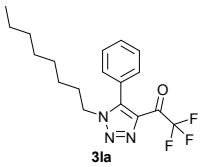
**Table 2**

Scope of Azide compounds[a]




**1** **2a** **3** **3'**

| entry | produnt **3** | yield %[b] | **3**:**3'** |
|---|---|---|---|
| 1 |  **3aa** | 84% | **3aa**:**3aa'**=92:8 |
| 2 |  **3ba** | 95% | **3ba**:**3ba'**=95:5 |
| 3 |  **3ca** | 95% | **3ca**:**3ca'**=96:4 |
| 4 |  **3da** | 94% | **3da**:**3da'**=96:4 |

| | | | |
|---|---|---|---|
| 5 |  **3ea** | 87% | **3ea**:**3ea'**=92:8 |
| 6 |  **3fa** | 80% | **3fa**:**3fa'**=92:8 |
| 7 |  **3ga** | 86% | **3aa**:**3aa'**=92:8 |
| 8 |  **3ha** | 80% | **3ba**:**3ba'**=87:13 |
| 9 |  **3ia** | 80% | **3ca**:**3ca'**=91:9 |
| 10 |  **3ja** | 88% | **3da**:**3da'**=89:11 |
| 11 |  **3ka** | 84% | **3ea**:**3ea'**=84:16 |
| 12 |  **3la** | 90% | **3fa**:**3fa'**=92:8 |

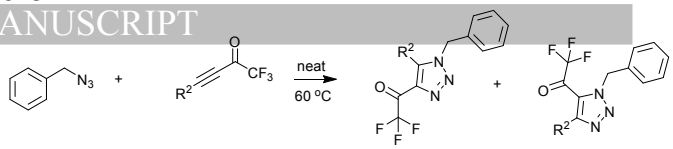
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), 60°C, 12 h;

[b] Isolated yield

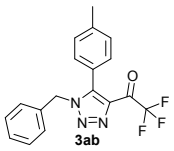
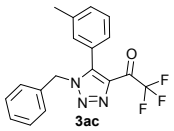
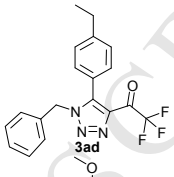
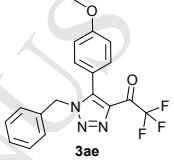
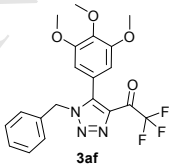
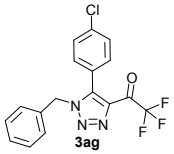
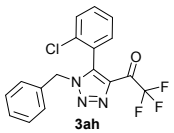
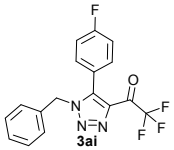
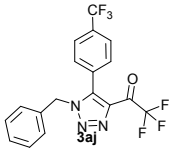
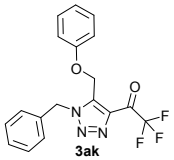
Next, the range of the alkyne was examined (Table 3). In Table 3, it was found that all the substrates were obtained in good yield (Table 3, **3ab-3ak**). Among them, the electron-donating substrate (Table 3, **3ab-3af**) has better regioselectivity than the halogen substrate (Table 3, **3ag-3ai**). Notably, the aliphatic alkynes may have better selectivity due to smaller steric hindrance (Table 3, **3ak**).

**Table 3**

Scope of Trifluoroacetyl modified acetylenic compounds[a]



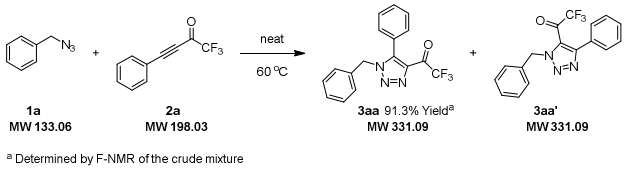

**1a** **2** **3** **3'**

| entry | produnt **3** | yield %[b] | **3**:**3'** |
|---|---|---|---|
| 1 |  **3ab** | 85% | **3aa**:**3aa'**=91:9 |
| 2 |  **3ac** | 82% | **3ba**:**3ba'**=90:10 |
| 3 |  **3ad** | 88% | **3ca**:**3ca'**=89:11 |
| 4 |  **3ae** | 82% | **3da**:**3da'**=92:8 |
| 5 |  **3af** | 87% | **3ea**:**3ea'**=92:8 |
| 6 |  **3ag** | 85% | **3fa**:**3fa'**=85:15 |
| 7 |  **3ah** | 90% | **3aa**:**3aa'**=90:10 |
| 8 |  **3ai** | 83% | **3ba**:**3ba'**=83:17 |
| 9 |  **3aj** | 85% | **3aa**:**3aa'**=91:9 |
| 10 |  **3ak** | 90% | **3ba**:**3ba'**=93:7 |

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), 60°C, 12 h;
[b] Isolated yield

To evaluate the synthesis of 4-trifluoroacetyl-1,2,3-triazoles as shown in Scheme 1, a series of green metrics calculations were

conducted which include atom economy (AE), atom efficiency (AEf), carbon efficiency (CE), reaction mass efficiency (RME), optimum efficiency (OE), process mass intensity (PMI) and E-factor (E).[17] AE is 100% (Table 4), and this result is in full accordance with the principles of atomic economics. The CE, RME and OE for the process were 95.6%, 91.2% and 91.2% (Table 4), RME is one of the most useful metric to determine the greenness of the process, since it takes into account the reactant mass, yield and atom economy. Product **3aa** could be obtained by crystallization at room temperature for 1 day. The optimum efficiency (OE) for the process was high (91.2%) (Table 4).




[a] Determined by F-NMR of the crude mixture

**Scheme 1** The synthesis of 4-trifluoroacetyl-1,2,3-triazoles for green metrics analysis

**Table 4**

Green metrics (AE, AEF, CE, RME, OE and MP) for synthesis process of 4-trifluoroacetyl-1,2,3-triazoles

| Yield (%) | AE (%) | AEf (%) | CE (%) | RME (%) | OE (%) |
|---|---|---|---|---|---|
| 91.3 | 100 | 91.3 | 95.6 | 91.2 | 91.2 |

The higher the value (closer to 100%), the greener the reaction process.

**Table 5**

Green metrics (PMI and E-factor, SI and WI) for synthesis process of 4-trifluoroacetyl-1,2,3-triazoles

| PMI ($g\ g^{-1}$) | E ($g\ g^{-1}$) | SI ($g\ g^{-1}$) | WI ($g\ g^{-1}$) |
|---|---|---|---|
| 1.1 | 0.1 | -- | -- |

The lower the value, the better the reaction process.

The lower the process mass intensity (PMI) the better the process. The PMI (1.1) for the process was low hence efficient (Table 5). No solvents and water were used in the reaction and treatment process, so solvent intensity (SI) and water intensity (WI) were not calculated.

### 3. Bioactivity test

The 1,2,3-triazoles has been studied mainly on their potential anti-cancer activities.[20] Meanwhile, the incorporation of fluorine into the molecule provides binding with target receptors, better membrane permeability, and blocking effect to metabolic decomposition.[21] We used the CCK-8 method to evaluate the anticancer activities of the 4-trifluoroacetyl-1,2,3-triazoles on A549, HTC-116, Hela, HepG2, MGC-803 and MKN45 cell. The results are summarized in Table 6, indicating that **3ba** possesses the best anticancer activity against HepG2 cell with $IC_{50}$ of 0.0267μmol/ml (Table 6). Further structure-activity relationship studies were under investigation.

**Table 6**

Inhibitory activities of selected compounds on cell proliferation.

| Compound | Cellular $IC_{50}$(μmol/ml) | | | | | |
|---|---|---|---|---|---|---|
| | A549 | HCT-116 | Hela | HepG2 | MGC-803 | MKN45 |
| **3ba** | -- | 82.59 | 72.53 | 0.0267 | 81.47 | 106.4 |
| **3da** | 33.78 | 30.07 | 124.4 | 10.36 | 18.90 | 50.28 |
| **3ga** | 37.95 | 84.43 | 369.5 | 43.55 | 26.13 | 49.53 |
| **3ac** | 1132 | 97.58 | 5418 | 0.5401 | -- | 115.1 |
| **CA-4** | 133.2 | 21.42 | 492.1 | 0.4521 | 6.493 | 28.0 |
| **Erianin** | 1.176 | 59.73 | 5192 | 0.0636 | 0.1837 | 26.83 |

### 4. Conclusions

In summary, an green click-chemistry procedure has been developed for the synthesis of 4-trifluoroacetyl-1,2,3-triazoles from corresponding azides and alkyne under copper-free and solvent-free conditions with high yield and selectivity, as well as easy crystallization. This method will play an important influence in the pharmaceutical industry, especially in drugs discovery, because of its less pollution, low cost, simple treatment and more efficiency. Among the 4-trifluoroacetyl-1,2,3-triazoles, **3ba** showed the best anticancer activity against HepG2 cell with $IC_{50}$ of 0.0267μmol/ml.

### 5. Experimental section

*5.1. General*

All reagents were commercially available and used without further purification unless indicated otherwise. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatorgraphy (TLC) carried out on GF254 plates (0.25 mm layer thickness) using UV light as visualizing agent. Flash chromatography was performed with 300-400 mesh silica gels. All NMR spectra were recorded on a Bruker Avance 500 (resonance frequencies 500 MHz for $^{1}H$ and 125 MHz for $^{13}C$) equipped with a 5 mm inverse broadband probe head with z-gradients at 295.8 K with standard Bruker pulse programs. The samples were dissolved in 0.6 mL $CDCl_3$ (99.8% D.TMS). Chemical shifts were given in valuesof δH and δC referenced to residual solvent signals (δH 7.26 for $^{1}H$, δC 77.0 for $^{13}C$ in $CDCl_3$). Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet of doublets (td), triplet (t), quartet (q), multiplet (m), broad singlet (bs). The $^{19}F$ NMR spectra were obtained using a 500 spectrometer (470 MHz) using trifluorotoluene as external standard. High resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument and recorded on a MicroMass LCTTM spectrometer. Melting points are uncorrected.

*5.2. General Synthetic Approach for Azide Compounds **1***

A mixture of benzyl halide (5 mmol) and aqueous solution of $NaN_3$ (6 mmol) in dimethyl formamide (DMF) was stirred at 80°C for 8 h. The reaction was monitored by thin layer chromatography (TLC) analysis. When the reaction was over, the reaction mixture was cooled down to room temperature followed by extraction with 20 mL of dichlorome-thane. The organic layer was washed with water for three times, dried over anhydrous $Na_2SO_4$, and concentrated under reduced. Then the target products were obtained **1a - 1m**, Yield from 90% to 100%.

*5.2.1. 2-(azidomethyl)-1-chloro-3-fluorobenzene (**1h**)*

colorless oil; Yield = 95%, $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.30 (dt, *J* = 15.7, 7.5 Hz, 2H), 7.08 (t, *J* = 8.3 Hz, 1H), 4.56 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 161.7 (d, $^{1}J_{C\text{-}F}$ = 250.0 Hz), 135.9 (d, $^{3}J_{C\text{-}F}$ = 5.0 Hz), 130.6 (d, $^{3''}J_{C\text{-}F}$ = 10.0 Hz), 125.6 (d, $^{2}J_{C\text{-}F}$ = 2.5 Hz), 121.6 (d, $^{4}J_{C\text{-}F}$ = 17.5 Hz), 114.4 (d, $^{2''}J_{C\text{-}F}$ = 22.5 Hz), 45.2 (d, $^{3'}J_{C\text{-}F}$ = 3.8 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$): δ -113.1 (s, 1F); HRMS (EI-TOF) calculated [M]+ for $C_7H_5ClFN_3$: 187.0127, found: 187.0125.

*5.3. General Synthetic Approach for the trifluoromethyl-α,β-ynones compounds **2***

A n-hexane solution of n-BuLi (15 mmol) was added to a solution of the alkyne derivatives (from a commercial source or synthesis of the literature 2 ) (15 mmol) in 22 mL of dry THF at -78°C. The solution was stirred for 30 min at -78°C, and ethyl trifluoroacetate (15 mmol, 2.13g) as a solution in THF (30 mL) and boron trifluoride etherate (2.25 mL) were added successively. The reaction mixture was stirred an additional 90 min at -78°C, saturated $NH_4Cl$ (aq) (8 mL) was the added, and the slurry was allowed to warm to ambient temperature. The THF was removed under reduced pressure, and the residue was diluted with ether (75 mL), washed with brine (25 mL, 2 times), and dried over anhydrous $Na_2SO_4$ and then evaporated. The residue was purified by column chromatography and Kugelrohr distillation under reduced pressure. Trifluoromethyl-α,β-ynone compounds was obtained. Yield from 83% to 90%.

*5.3.1. 1,1,1-trifluoro-4-(m-tolyl)but-3-yn-2-one (**2c**)*

pale yellow oil; Yield = 92%, $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 5.0 Hz, 2H), 7.39 - 7.30 (m, 2H); 2.39 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 167.3 (q, $^{2}J_{C\text{-}F}$ = 41.3 Hz), 139.0, 134.4, 133.5, 131.2, 128.9, 117.9, 114.9 (q, $^{1}J_{C\text{-}F}$ = 286.3 Hz ), 101.1, 83.2, 21.1; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -77.8 (s, 3F); HRMS (EI-TOF) calculated [M]+ for $C_{11}H_7F_3O$: 212.0449, found: 212.0451.

*5.3.2. 4-(4-ethylphenyl)-1,1,1-trifluorobut-3-yn-2-one (**2d**)*

pale yellow oil; Yield = 95%, $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 10.0 Hz, 2H), 7.30 (d, *J* = 5.0 Hz, 2H); 2.74 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 167.2 (q, $^{2}J_{C\text{-}F}$ = 41.7 Hz), 150.0, 134.2, 128.6, 115.2, 115.0 (q, $^{1}J_{C\text{-}F}$ = 285.8 Hz ), 101.6, 83.5, 29.2, 14.9; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -77.8 (s , 3F); HRMS (EI-TOF) calculated $[M]^+$ for $C_{12}H_9F_3O$: 226.0605, found: 226.0604.

*5.3.3. 1,1,1-trifluoro-4-(3,4,5-trimethoxyphenyl)but-3-yn-2-one (**2f**)*

pale yellow oil; Yield = 85%, $^{1}$H NMR (500 MHz, $CDCl_3$): δ 6.89 (s, 2H), 3.92 (s, 3H); 3.88 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 167.0 (q, $^{2}J_{C\text{-}F}$ = 42.0 Hz), 153.4, 142.8, 167.0 (q, $^{2}J_{C\text{-}F}$ = 286.7 Hz) 112.4, 111.4, 101.4, 83.3, 61.1, 56.4; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -77.6 (s , 3F); HRMS (EI-TOF) calculated $[M]^+$ for $C_{13}H_{11}F_3O_4$: 288.0609, found: 288.0608.

*5.3.4. 4-(2-chlorophenyl)-1,1,1-trifluorobut-3-yn-2-one (**2h**)*

pale yellow oil; Yield = 90%, $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 3.3 Hz, 2H), 7.32 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 167.1 (q, $^{2}J_{C\text{-}F}$ = 42.1 Hz), 138.6, 135.6, 133.5, 130.0, 127.0, 118.5, 114.9 (q, $^{1}J_{C\text{-}F}$ = 286.3 Hz ), 96.4, 86.9; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -77.8 (s, 3F); HRMS (EI-TOF) calculated $[M]^+$ for $C_{10}H_4ClF_3O$: 233.9873, found: 233.9875.

*5.3.5. 1,1,1-trifluoro-4-(4-fluorophenyl)but-3-yn-2-one (**2i**)*

pale yellow oil; Yield = 90%, $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.15 (t, *J* = 8.6 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 167.0 (q, $^{2}J_{C\text{-}F}$ = 42.1 Hz), 165.1 (d, $^{1}J_{C\text{-}F}$ = 255 Hz), 136.5 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz), 116.6 (d, $^{4}J_{C\text{-}F}$ = 22.5 Hz), 114.8 (q, $^{1}J_{C\text{-}F}$ = 286.3 Hz ), 114.2 (d, $^{2'}J_{C\text{-}F}$ = 3.75 Hz), 99.4, 83.4; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -77.8 (s, 3F), -102.5 (s, 1F); HRMS (EI-TOF) calculated $[M]^+$ for $C_{10}H_4F_4O$: 216.0198, found: 216.0197.

*5.3.6. 1,1,1-trifluoro-4-(4-(trifluoromethyl)phenyl)but-3-yn-2-one (**2j**)*

pale yellow oil; Yield = 85%, $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.8 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 167.1 (q, $^{2}J_{C\text{-}F}$ = 42.5 Hz), 134.0, 133.8 (q, $^{2'}J_{C\text{-}F}$ = 33.3 Hz), 125.8 (q, $^{3'}J_{C\text{-}F}$ = 3.8 Hz), 123.3 (q, $^{1'}J_{C\text{-}F}$ =270.8 Hz), 121.8, 114.7 (q, $^{1}J_{C\text{-}F}$ = 286.3 Hz), 97.2, 83.8; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -63.8 (s , 3F), -78.2 (s , 3F); HRMS (EI-TOF) calculated $[M]^+$ for $C_{11}H_4F_6O$: 266.0166, found: 266.0167.

*5.3.7. 1,1,1-trifluoro-5-phenoxypent-3-yn-2-one (**2k**):*

pale yellow oil; Yield = 89%, $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.3 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H); 7.01 (d, *J* = 7.9 Hz, 2H), 4.93 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 166.7 (q, $^{2}J_{C\text{-}F}$ = 43.8 Hz), 157.1, 129.8, 122.6, 115.1, 114.6 (q, $^{1}J_{C\text{-}F}$ = 286.3 Hz ), 96.2, 80.3, 55.6; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -78.2 (t, *J* = 4.7 Hz, 3F); HRMS (EI-TOF) calculated $[M]^+$ for $C_{11}H_7F_3O_2$: 228.0398, found: 228.0393.

*5.4. Synthesis Typical procedure for the 4-trifluoroacetyl-1,2,3-triazoles (**3aa-3la**;) in solvent-free and catalyst-free condition*

In a 10 mL sealed tube, 1 (1 equiv.) and 2 (1 equiv.) were added. The reaction mixture was then stirred at 60□ for 12 h, and the reaction was monitored by thin layer chromatography (TLC) analysis. When the reaction was over, the reaction mixture was cooled down to room temperature, then the crude products were purified by silica gel chromatography using petroleum ether/ethyl acetate (10:1 to 5:1, V:V) as eluent to give the corre-sponding products **3aa-3la**; **3ab-3ak**.

*5.4.1. 1-(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3aa**)[22]*

pale yellow oil; Yield = 83.8%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.60 - 7.42 (m, 3H), 7.31 - 7.21 (m, 5H), 7.07 (d, *J* = 6.0 Hz, 2H), 5.50 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz), 144.0, 138.1, 134.0, 131.0, 129.5, 129.0, 129.0, 128.8, 127.8, 124.5, 116.2 (q, $^{1}J_{C\text{-}F}$ = 289.2 Hz), 52.3; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.0 (s, 3F); IR (KBr) *v*: 3034, 1721, 1556, 1489, 1457, 1275, 1249, 1201, 1154, 917, 761, 695, 536 $cm^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{12}F_3N_3O$: 331.0932, found: 331.0930.

*5.4.2. 2,2,2-trifluoro-1-(1-(4-methylbenzyl)-4-phenyl-1H-1,2,3-triazol-5-yl)ethan-1-one (**3ba**)*

pale yellow oil; Yield = 94.5%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.60 - 7.50 (m, 3H), 7.09 - 7.28 (m, 4H), 6.97 (d, *J* = 7.9 Hz, 2H), 5.45 (s, 2H), 2.34 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 37.1 Hz), 143.9, 138.7, 138.1, 131.0, 130.9, 129.6, 129.5, 128.9, 127.7, 124.6, 116.2 (q, $^{1}J_{C\text{-}F}$ = 288.3 Hz), 52.1, 21.1; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F); IR (KBr) *v*: 3670, 3432, 3131, 2701, 1719, 1594, 1457, 1248, 1202, 1155, 936, 907, 774, 697, 477, 419 $cm^{-1}$;HRMS (EI-TOF) calculated $[M]^+$ for $C_{18}H_{14}F_3N_3O$:345.1089, found:345.1091.

*5.4.3. 2,2,2-trifluoro-1-(1-(4-fluorobenzyl)-4-phenyl-1H-1,2,3-triazol-5-yl)ethan-1-one (**3ca**)*

pale yellow oil; Yield = 94.4%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.59 - 7.46 (m, 3H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.06 - 6.94 (m, 4H), 5.44 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 162.8 (d, $^{1'}J_{C\text{-}F}$ = 247.5 Hz), 143.8, 138.2, 131.0, 129.8 (d, $^{4'}J_{C\text{-}F}$ = 8.75 Hz), 129.7 (d, $^{3'}J_{C\text{-}F}$ = 3.75 Hz), 129.4, 129.1, 124.5, 116.0 (d, $^{2'}J_{C\text{-}F}$ = 21.25 Hz), 116.1 (q, $^{1}J_{C\text{-}F}$ = 288.8 Hz), 51.6; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F), -112.4 (s, 1F); IR (KBr) *v*: 3670, 2927, 1720, 1607, 1558, 1513, 1488, 1458, 1276, 1155, 1096, 1014, 936, 907, 841, 792, 735, 697, 558, 523, 492 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{11}F_4N_3O$:349.0839, found:349.0837 .

*5.4.4. 1-(1-(4-bromobenzyl)-4-phenyl-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3da**)*

pale yellow oil; Yield = 93.9%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.59 - 7.39 (m, 5H), 7.23 (d, *J* = 7.5 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 5.42 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 37.5 Hz), 143.9, 138.2, 132.9, 132.2, 131.1, 129.5, 129.4, 129.1, 124.3, 123.0, 116.1 (q, $^{1}J_{C\text{-}F}$ = 288.3 Hz), 51.6; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.2 (s, 3F); IR (KBr) *v*: 3670, 3429, 3140, 2924, 2853, 1718, 1591, 1488, 1457, 1155, 1011, 937, 907, 697, 542 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{11}BrF_3N_3O$: 409.0038, found: 409.0036.

*5.4.5. 1-(1-(3,5-dimethylbenzyl)-4-phenyl-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ea**)*

pale yellow oil; Yield = 86.6%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.59 - 7.46 (m, 3H), 7.24 (d, *J* = 7.6 Hz, 2H), 6.92 (s, 1H), 6.63 (s, 2H), 5.39 (s, 2H), 2.23 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz), 143.9, 138.7, 138.1, 133.7, 130.9, 130.4, 129.5, 128.9, 125.6, 124.6, 116.2 (q, $^{1}J_{C\text{-}F}$ = 288.8 Hz), 52.3, 21.2; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F); IR (KBr) *v*: 3679, 3155, 2922, 1719, 1606, 1556, 1488, 1457, 1274, 1200, 1155, 1014, 911, 777, 696, 532, 419 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{19}H_{16}F_3N_3O$: 359.1245, found: 359.1244 .

*5.4.6. 1-(1-(3,5-bis(trifluoromethyl)benzyl)-4-phenyl-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3fa**)*

pale yellow oil; Yield = 79.7%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.63 - 7.46 (m, 5H), 7.24 - 7.21 (d, *J* = 7.3 Hz, 2H), 5.60 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.1 (q, $^{2}J_{C\text{-}F}$ = 37.1 Hz), 143.9, 138.4, 135.9, 132.5 (q, $^{1'}J_{C\text{-}F}$ = 33.75 Hz), 131.4, 129.3, 129.2, 128.6, 123.9 (d, $^{2'}J_{C\text{-}F}$ = 36.25 Hz), 123.0 (m), 121.6, 116.0 (q, $^{1}J_{C\text{-}F}$ = 288.8 Hz), 51.3; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -63.1 (s, 6F), -74.3 (s, 3F); IR (KBr) *v*: 3670, 3429, 3140, 1718, 1591, 1457, 1383, 1279, 1133, 911, 699, 682, 537 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{19}H_{10}F_9N_3O$: 467.0680, found: 467.0679.

*5.4.7. 1-(1-(3,5-di-tert-butylbenzyl)-4-phenyl-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ga**)*

pale yellow oil; Yield = 86.4%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.59 - 7.48 (m, 3H), 7.36 (s, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.92 (s, 2H), 5.47 (s, 2H), 1.30 (s, 2H), 1.25 (s, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.3 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz), 151.7, 143.7, 138.2, 133.1, 130.8, 129.6, 128.9, 124.9, 122.8, 122.4, 116.2 (q, $^{1}J_{C\text{-}F}$ = 288.8 Hz), 53.0, 34.8, 31.3; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F); IR (KBr) *v*: 3670, 3148, 2963, 1719, 1640, 1557, 1458, 1363, 1249, 1201, 1158, 1095, 949, 914, 778, 696, 526 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{25}H_{28}F_3N_3O$: 443.2184, found: 443.2182.

*5.4.8. 1-(1-(2-chloro-6-fluorobenzyl)-4-phenyl-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ha**)*

pale yellow oil; Yield = 79.5%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.60 - 7.48 (m, 3H), 7.38 (d, *J* = 6.8 Hz, 2H), 7.31 - 7.13 (m, 2H), 6.95 (t, *J* = 8.7 Hz, 1H), 5.57 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz), 161.7 (d, $^{1'}J_{C\text{-}F}$ = 251.25 Hz), 144.1, 137.7, 135.8 (d, $^{3'}J_{C\text{-}F}$ = 5.0 Hz), 131.4 (d, $^{3''}J_{C\text{-}F}$ = 10.0 Hz), 130.9, 129.4, 129.0, 125.7 (d, $^{2'}J_{C\text{-}F}$ = 3.75 Hz), 124.5, 119.6 (d, $^{4'}J_{C\text{-}F}$ = 11.25 Hz), 116.6 (q, $^{1}J_{C\text{-}F}$ = 292.5 Hz), 114.4 (d, $^{2''}J_{C\text{-}F}$ = 21.25 Hz), 44.0; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F), -111.9 (s, 1F); IR (KBr) *v*: 3426, 2926, 2853, 1720, 1608, 1582, 1488, 1456, 1359, 1274, 1154, 1092, 1013, 920, 861, 792, 741, 696, 565, 519 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{10}ClF_4N_3O$: 385.0419, found: 385.0417.

*5.4.9. 1-(1-(2,6-difluorobenzyl)-4-phenyl-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ia**)*

pale yellow oil; Yield = 79.7%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 5.0 Hz, 3H), 7.36 (d, *J* = 45.0 Hz, 3H), 6.86 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.1 (q, $^{2}J_{C\text{-}F}$ = 37.1 Hz), 161.3 (dd, $^{1'}J_{C\text{-}F}$ =252.0, 6.8Hz), 144.2, 137.8, 131.5 (t, $^{3'}J_{C\text{-}F}$ = 10.6Hz), 130.9, 129.3, 129.0, 124.3, 116.2 (q, $^{1}J_{C\text{-}F}$ = 288.8 Hz), 111.6 (dd, $^{2'}J_{C\text{-}F}$ =20.3,4.3 Hz), 109.8 (t, $^{2''}J_{C\text{-}F}$ = 18.1 Hz), 40.5; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F), -113.9 (s, 2F); IR (KBr) *v*: 3071, 1723, 1629, 1598, 1559, 1488, 1475, 1361, 1301, 1276, 1238, 1202, 1159, 1094, 1024, 929, 797, 697, 522 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{10}F_5N_3O$: 367.0744, found: 367.0745.

*5.4.10. 2,2,2-trifluoro-1-(1-(naphthalen-1-ylmethyl)-4-phenyl-1H-1,2,3-triazol-5-yl)ethan-1-one (**3ja**)*

pale yellow oil; Yield = 88.4%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.83 - 7.69 (m, 3H), 7.60 - 7.41 (m, 6H), 7.29 - 7.18 (m, 3H), 5.63 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz), 144.1, 138.2, 133.1, 133.1, 131.3, 131.0, 129.5, 129.1, 129.0, 128.0, 127.8, 127.2, 126.8, 126.8, 124.9, 124.6, 116.2 (q, $^{1}J_{C\text{-}F}$ = 288.8 Hz), 52.5; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.0 (s, 3F); IR (KBr) *v*: 3676, 3167, 2946, 1893, 1719, 1600, 1513, 1488, 1458, 1276, 1188, 939, 699, 528 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{21}H_{14}F_3N_3O$: 381.1089, found: 381.1090.

*5.4.11. 2,2,2-trifluoro-1-(1-(naphthalen-2-ylmethyl)-4-phenyl-1H-1,2,3-triazol-5-yl)ethan-1-one (**3ka**)*

pale yellow oil; Yield = 84.1%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.93 - 7.79 (m, 3H), 7.57 - 7.14 (m, 8H), 6.82 (d, *J* = 7.1 Hz, 1H), 5.97 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz), 144.3, 138.2, 133.7, 130.9, 130.5, 129.6, 129.4, 129.3, 129.0, 129.0, 127.1, 126.8, 126.3, 125.1, 124.6, 122.5, 116.2 (q, $^{1}J_{C\text{-}F}$ = 288.8 Hz), 50.3; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.0 (s, 3F); IR (KBr) *v*: 3623, 3051, 2960, 2927, 2855, 1696, 1614, 1568, 1490, 1456, 1322, 1182, 1158, 1132, 1105, 944, 774, 697, 545 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{21}H_{14}F_3N_3O$: 381.1089, found: 381.1090.

*5.4.12. 2,2,2-trifluoro-1-(1-octyl-4-phenyl-1H-1,2,3-triazol-5-yl)ethan-1-one (**3la**)*

pale yellow oil; Yield = 89.9%; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.57 (t, *J* = 7.5 Hz , 3H), 7.36 (d, *J* = 5.0 Hz , 2H), 5.28 (s, 2H), 4.27 (t, *J* = 5.0 Hz , 2H), 1.55 (s, 4H), 1.19 (s, 8H), 0.86 (t, *J* = 7.5 Hz , 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^{2}J_{C\text{-}F}$ = 36.3 Hz), 143.7, 137.9, 130.8, 129.7, 129.3, 129.1, 128.6, 124.8, 116.2 (q, $^{1}J_{C\text{-}F}$ = 289.2 Hz), 53.4, 48.5, 31.6, 29.8, 28.9, 28.7, 26.3, 22.5, 14.0; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F); IR (KBr) *v*: 3735, 2922, 2851, 1743, 1732, 1715, 1659, 1597, 1564, 1494, 1397, 1261, 1179, 1033, 763, 695, 503 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{18}H_{22}F_3N_3O$: 353.1715, found: 353.1713.

*5.4.13. 1-(1-benzyl-4-(p-tolyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ab**)*

pale yellow oil; Yield = 84.6%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H), 7.40 - 7.18 (m, 6H), 5.57 (s, 2H), 2.36 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^2J_{C\text{-}F}$ = 37.08 Hz), 144.2, 141.4, 138.0, 134.2, 129.7, 129.4, 129.0, 128.7, 127.7, 121.4, 116.2 (q, $^1J_{C\text{-}F}$ = 288.8 Hz), 52.1, 21.5; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F); IR (KBr) *v*: 3416, 3033, 1716, 1615, 1564, 1502, 1456, 1362, 1323, 1090, 1030, 1012, 916, 823, 784, 744, 693, 587, 536, 454 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{18}H_{14}F_3N_3O$: 345.1089, found: 345.1088.

*5.4.14. 1-(1-benzyl-4-(m-tolyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one(**3ac**)*

pale yellow oil; Yield = 81.7%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.45 - 7.35 (m, 2H), 7.32 - 7.25 (m, 3H) 7.10 - 7.05 (m, 2H), 7.01 (s, 1H), 5.48 (s, 2H), 2.38 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.1 (q, $^1J_{C\text{-}F}$ = 36.7 Hz), 144.3, 138.9, 138.1, 134.2, 131.7, 130.0, 129.0, 128.9, 128.7, 127.8, 126.5, 124.3, 116.2 (q, $^1J_{C\text{-}F}$ = 288.3 Hz), 52.3, 21.3; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.0 (s, 3F); IR (KBr) *v*: 3034, 2925, 1720, 1589, 1555, 1456, 1258, 1275, 1205, 1155, 1098, 943, 922, 744, 694 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{18}H_{14}F_3N_3O$: 345.1089, found: 345.1088.

*5.4.15. 1-(1-benzyl-4-(4-ethylphenyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one(**3ad**)*

pale yellow oil; Yield = 88.1%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.37 - 7.25 (m, 5H), 7.25 - 7.20 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 3.5 Hz, 2H), 5.50 (s, 2H), 2.77 (dd, *J*= 15.1, 7.5 Hz, 2H), 1.32 (t, *J*= 7.6 Hz, 3H ); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^2J_{C\text{-}F}$ = 36.7 Hz), 147.6, 144.3, 138.0, 134.2, 129.5, 129.0, 128.7, 128.5, 127.7, 121.5, 116.3 (q, $^1J_{C\text{-}F}$ = 288.8 Hz), 52.1, 28,8, 15,1; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -73.9 (s, 3F); IR (KBr) *v*: 3033, 2968, 1720, 1614, 1497, 1454, 1276, 1201, 1156, 1091, 1011, 939, 917, 833, 844, 694 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{19}H_{16}F_3N_3O$: 359.1245, found: 359.1246.

*5.4.16. 1-(1-benzyl-4-(4-methoxyphenyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ae**)*

pale yellow oil; Yield = 81.7%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.35 - 7.25 (m, 3H), 7.19 (d, *J* = 10.0, 1H), 7.09 (d, *J* = 5.0, 1H), 6.99 (d, *J* = 10.0, 1H), 5.47 (s, 2H), 3.86 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^2J_{C\text{-}F}$ = 36.7 Hz), 161.6, 144.1, 137.9, 134.2, 131.1, 129.0, 128.7, 127.6, 116.3 (q, $^1J_{C\text{-}F}$ = 288.8 Hz), 116.1, 114.5, 114.0, 55.4, 52.1; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.0 (s, 3F); IR (KBr) *v*: 2957, 1719, 1612, 1577, 1503, 1455, 1301, 1256, 1200, 1155, 1090, 1035, 917, 836, 745, 694, 545 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{18}H_{14}F_3N_3O_2$: 361.1038, found: 361.1039.

*5.4.17. 1-(1-benzyl-4-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one(**3af**)*

pale yellow oil; Yield = 87.1%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 3H), 7.09 (d, *J* = 5.0 Hz, 2H), 6.36 (s, 2H), 5.49 (s, 2H), 3.91 (s, 3H), 3.67 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.3 (q, $^2J_{C\text{-}F}$ = 37.1 Hz), 153.5, 144.0, 140.0, 138.0, 124.6, 129.1, 128.7, 127.4, 119.2, 116.2 (q, $^1J_{C\text{-}F}$ = 288.8 Hz), 106.8, 61.0, 56.1, 52.4; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.0 (s, 3F); IR (KBr) *v*: 3671, 2940, 1720, 1586, 1499, 1464, 1413, 1372, 1336, 1245, 1127, 954, 925, 860, 744, 695, 526, 419 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{20}H_{18}F_3N_3O_4$: 421.1249, found: 421.1248.

*5.4.18. 1-(1-benzyl-4-(4-chlorophenyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ag**)*

pale yellow oil; Yield = 84.4%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 5.0 Hz, 2H), 7.35 - 7.25 (m, 9H), 7.17 (d, *J* = 5.0 Hz, 2H), 7.10 - 7.00 (m, 2H), 5.47 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.2 (q, $^2J_{C\text{-}F}$ = 37.1 Hz), 142.9, 138.2, 137.4, 133.8, 130.9, 129.4, 129.1, 128.9, 127.6, 122.9, 116.1 (q, $^1J_{C\text{-}F}$ = 288.8 Hz), 52.4; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F); IR (KBr) *v*: 3726, 3704, 3625, 3600, 3035, 2924, 1721, 1605, 1483, 1455, 1251, 1202, 1156, 1093, 1011, 939, 918, 746, 694, 538 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{11}ClF_3N_3O$: 365.0543, found: 365.0544.

*5.4.19. 1-(1-benzyl-4-(2-chlorophenyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ah**)*

pale yellow oil; Yield = 90.1%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.55 - 7.45 (m, 2H), 7.35 - 7.30 (m, 1H), 7.26 - 7.10 (m, 3H), 7.04 (d, *J* = 7.5, 1H), 6.96 (d, *J* = 7.5, 2H), 5.43 (dd, , *J* = 109.8, 14.9, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 173.9 (q, $^2J_{C\text{-}F}$ = 38.3 Hz), 140.9, 139.2, 133.8, 133.2, 132.3, 131.0, 130.1, 128.9, 128.9, 128.1, 127.3, 124.3, 116.0 (q, $^1J_{C\text{-}F}$ = 288.8 Hz), 52.9; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.3 (s, 3F); IR (KBr) *v*: 3068, 3034, 1723, 1605, 1561, 1475, 1456, 1281, 1244, 1204, 1155, 1097, 1013, 942, 919, 759, 694, 657, 545 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{11}ClF_3N_3O$: 365.0543, found: 365.0544.

*5.4.20. 1-(1-benzyl-4-(4-fluorophenyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ai**)*

pale yellow oil; Yield = 82.9%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.35 - 7.28 (m, 3H), 7.25 - 7.20 (m, 2H), 7.20 - 7.10 (m, 2H), 7.10 - 7.00 (m, 2H), 5.48 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.3 (q, $^2J_{C\text{-}F}$ = 37.1 Hz), 164.1 (d, $^{1'}J_{C\text{-}F}$ = 251.3 Hz), 143.1, 138.2, 133.9, 131.7 (d, $^{3'}J_{C\text{-}F}$ = 8.8 Hz), 129.1, 128.9, 127.6, 120.4, 116.4 (d, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 116.2 (q, $^1J_{C\text{-}F}$ = 288.8 Hz), 52.3; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.1 (s, 3F), -108.1 (s, 1F); IR (KBr) *v*: 2926, 1722, 1609, 1501, 1456, 1276, 1238, 1201, 1160, 1102, 1025, 918, 842, 745, 694, 541 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{11}F_4N_3O$: 349.0838, found: 349.0839.

*5.4.21. 1-(1-benzyl-4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3aj**)*

pale yellow oil; Yield = 85.3%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 10.0 Hz; 2H), 7.32 (d, *J* = 20.8, 7.2 Hz; 5H), 7.03 (d, *J* = 5.0 Hz; 2H), 5.48 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.3 (q, $^2J_{C\text{-}F}$ = 37.5 Hz), 142.4, 138.5, 133.6, 133.0 (q, $^{2'}J_{C\text{-}F}$ = 32.9 Hz), 130.1, 129.2, 129.0, 128.4, 127.6, 125.9 (q, $^{3'}J_{C\text{-}F}$ = 3.3 Hz), 123.5 (q, $^{1'}J_{C\text{-}F}$ = 271.3 Hz), 116.0 (q, $^1J_{C\text{-}F}$ = 288.8 Hz), 52.6; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -63.1 (s, 1F), -74.2 (s, 3F); HRMS (EI-TOF) calculated $[M]^+$ for $C_{17}H_{11}F_4N_3O$: 349.0838, found: 349.0839.

*5.4.22. 1-(1-benzyl-4-(phenoxymethyl)-1H-1,2,3-triazol-5-yl)-2,2,2-trifluoroethan-1-one (**3ak**)*

pale yellow oil; Yield = 90.2%; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.40 - 7.27 (m, 5H), 7.27 - 7.20 (m, 2H), 7.05 (d, *J* = 7.5, 1H), 6.89 (d, *J* = 10.0, 2H), 5.79 (s, 2H), 5.36 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 175.6 (q, $^2J_{C\text{-}F}$ = 37.5 Hz), 157.0, 139.6, 138.7, 133.1, 129.9, 129.2, 129.0, 128.0, 122.5, 116.1 (q, $^1J_{C\text{-}F}$ = 288.3 Hz), 114.5, 57.7, 53.7; $^{19}$F NMR (470 MHz, $CDCl_3$): δ -74.2 (s, 3F); IR (KBr) *v*: 3725, 3026, 2924, 1720, 1599, 1496, 1352, 1289, 1201, 1200, 1161, 1116, 947, 925, 848, 753, 691 cm$^{-1}$; HRMS (EI-TOF) calculated $[M]^+$ for $C_{18}H_{14}F_3N_3O_2$: 361.1038, found: 361.1036.

**Acknowledgements**

We were grateful for financial support from the National Natural Science Foundation of China (21472126, 21672151 and 21602136) and Shanghai Municipal Education Commission (Plateau Discipline Construction Program).

**Appendix A. Supplementary data**

Supplementary data related to this article can be found at

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