Journal of Fluorine Chemistry 236 (2020) 109516

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Methyl-2,2-difluoro-2-(fluorosulfonyl) acetate (MDFA)/copper (I) iodide mediated and tetrabutylammonium iodide promoted trifluoromethylation of 1-aryl-4-iodo-1,2,3-triazoles

Chiradeep Panja[a,*], Jayashankara Vaderapura Puttaramu[a], Thirumurugan Kothandarama Chandran[a], Roshan Y. Nimje[a], Hemantha Kumar[a], Anuradha Gupta[a], Pirama Nayagam Arunachalam[a], James R. Corte[b], Arvind Mathur[b]

[a] Department of Discovery Synthesis, Biocon Bristol-Myers Squibb Research Center, Biocon Park, Bommasandra IV Phase, Jigani Link Road, Bangalore, 560100, India
[b] Discovery Chemistry, Bristol-Myers Squibb, P.O. Box 5400, Princeton, NJ, 08543-4000, United States

ARTICLE INFO

Keywords:
1-Aryl-4-(trimethylsilyl)-1*H*-1,2,3-triazole
1-Aryl-4-iodo-1,2,3-triazole
Trifluoromethylation
Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate
Tetrabutylammonium iodide
1-Aryl-4-(trifluoromethyl)-1*H*-1, 2, 3-triazole

ABSTRACT

While several methods are available for the synthesis of a host of trifluoromethylated heterocycles, very few of them have been applied to access 4-trifluoromethylated 1,2,3-triazoles. We report herein a general methodology for the trifluoromethylation of 1-aryl-4-iodo-1, 2, 3-triazoles. Tetrabutylammonium iodide (TBAI) has been shown to provide enhanced conversion in these CuI-mediated reaction using methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (MDFA). The method exhibited broad functional group tolerance and was applied to the synthesis of a library of 1-aryl-4-trifluoromethyl-1,2,3-triazoles on the multi-gram scale.

1. Introduction

The 1,2,3-triazole is a common moiety, which can be found in many biologically active compounds (Fig. 1) [1–3]. Some unique properties of 1,2,3-triazole are i) stability towards oxidation and reduction (ii) stability towards acidic and basic hydrolysis (iii) it can participate in hydrogen bonding interactions (iv) it can involve in π-stacking interaction and dipole-dipole interactions [3]. The trifluoromethyl group (CF_3) is an important functional group, which is present in a various important class of molecules, such as agrochemicals, pharmaceuticals, liquid crystals, etc. [4a–c]. Considering the Van der Waals radii of 1.47 Å and 1.2 Å for fluorine and hydrogen respectively, the volume of a trifluoromethyl group is about two times that of a methyl group [4d]. The trifluoromethyl moiety can be considered as the bioisostere [4e] for the isopropyl group. Adding a strong electron-withdrawing group like CF_3 to a 1,2,3-triazole moiety can significantly make favorable changes to the chemical and biological properties of the parent triazoles [4f].

In the last few decades, organic chemists have put substantial efforts to develop new methodologies for the trifluoromethylation of aromatic and heteroaromatic compounds [5a,b]. Among these methods, the coupling of the aromatic or heteroaromatic halides with a trifluoromethyl copper species is one of the most widely used methodologies in organofluorine chemistry [5a,c].

To support our drug discovery program, we were interested in synthesizing several 1-aryl-4-trifluoromethyl-1,2,3-triazoles. While a plethora of methods are available for the synthesis of various trifluoromethylated heterocycles [4f,5–7], very few of them have been applied to access trifluoromethylated triazoles. Cao and coworkers used $TMSCF_3$ as the trifluoromethyl source in the presence of CuI/KF/Phen/Ag_2CO_3 for trifluoromethylation of 5-iodo triazoles [7a]. Ma et al. has reported [8a] a silver-catalyzed [3 + 2] cycloaddition of isocyanides with diazo compounds to access trifluoromethylated triazoles. Very recently, Mohanan et al. has reported [8b] synthesis of trifluoromethylated triazoles *via* cyclization of trifluorodiazoethane. However, the lack of commercial availability of several substituted isocyanides and gaseous nature of trifluorodiazoethane precluded the use of these approaches for our SAR work. Other attractive approaches to achieve this would be either a Cu-mediated Alkyne-Azide Click reaction (CuAAC) using the appropriate azide and 3,3,3-trifluoroprop-1-yne [5d] or by substituting a halogen group of a suitable precursor molecule, using a CF_3 source via metal catalysis [5e]. We envisioned that the use of 3,3,3-trifluoroprop-1-yne [5f] could be problematic for our SAR study due to the gaseous and flammable nature of this reagent, and hence rationalized that the trifluoromethylation of the appropriate iodo precursor would be the most expeditious route to the compounds of interest. Herein, we describe such a strategy and development of the

* Corresponding author.
E-mail address: chiradeep.panja@syngeneintl.com (C. Panja).

https://doi.org/10.1016/j.jfluchem.2020.109516
Received 5 January 2020; Received in revised form 18 March 2020; Accepted 19 March 2020
Available online 15 May 2020
0022-1139/

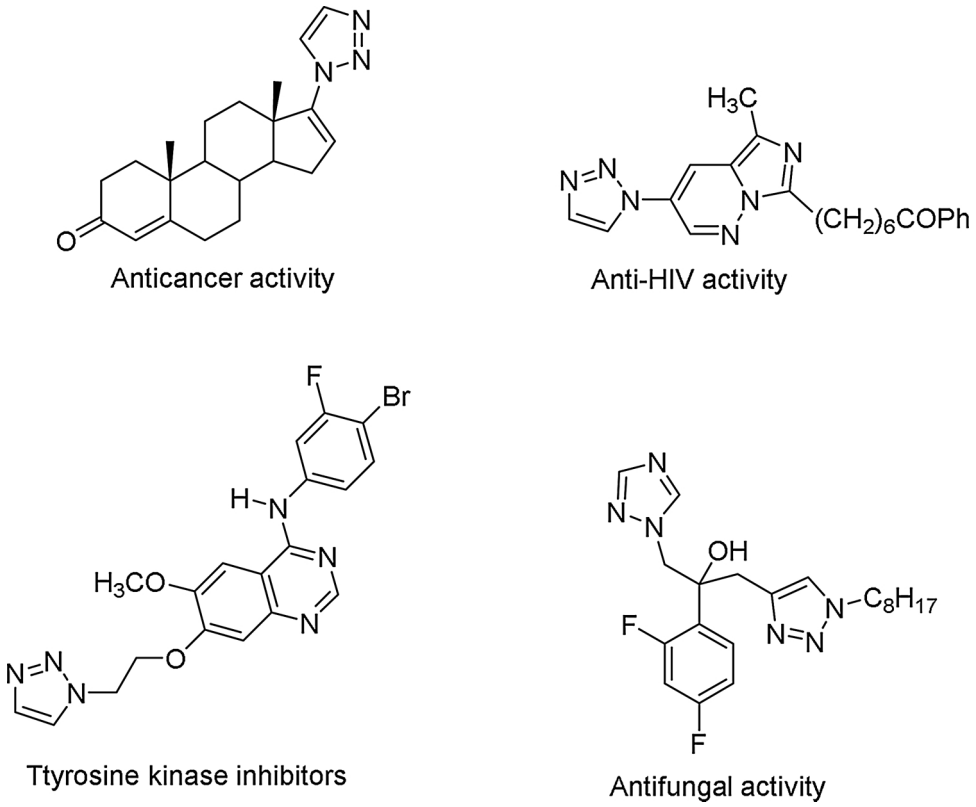


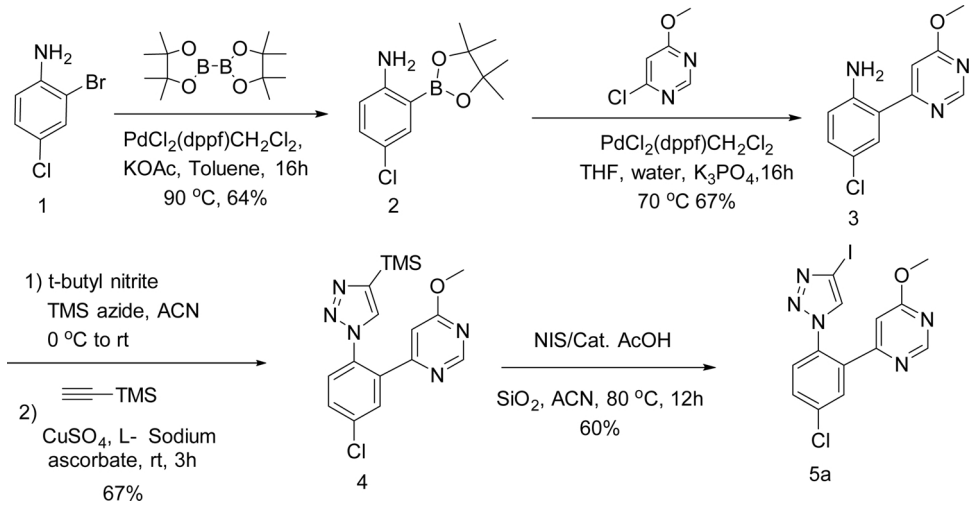
Fig. 1. Examples of biologically active triazole compounds.

trifluoromethylation reaction to effect this transformation on 1,2,3-triazole system.

2. Results and discussion

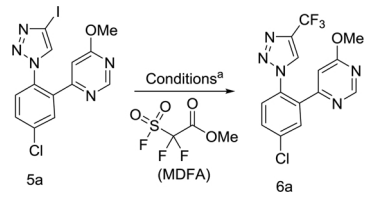
2.1. Synthesis of 4-iodo-substituted 1, 2, 3-triazole *5a* as a model precursor

Trifluoromethylated triazole **6a** was our initial target molecule and would arise from the corresponding iodotriazole **5a** (Scheme 1). The iodotriazole **5a** was synthesized in four steps starting from 2-bromo-4-chloroaniline **1**, which was converted to the pyrimidine intermediate **3** via Suzuki–Miyaura coupling [9a]. Following standard copper-catalyzed click chemistry with t-butyl nitrite, TMS azide, and TMS-acetylene, the TMS substituted triazolo intermediate **4** was synthesized [9b]. Our next goal was to convert the TMS triazole intermediate **4** to the corresponding iodo intermediate **5a**. Chlorination methodology on such substrates using silica and NCS [9b] has been reported, however, we did not find many references for the iodination [10,11]. Following the same NCS/silica mediated chlorination procedure, iodination reaction on intermediate **4** using NIS/silica was found to be extremely sluggish, taking 3 days for completion. We rationalized that the rate of the reaction could be enhanced by fine-tuning the acidity of the reaction medium. A quick screening of acid additives revealed that the addition of a catalytic amount of acetic acid to the reaction led to complete conversion to **5a** within 16 h. This methodology was later applied to synthesize 1-aryl-4-iodotriazoles (**5b–l**). These compounds could be coupled with a variety of partners leading to a large number of substituted analogs.



Scheme 1. Synthesis of iodo-substituted 1, 2, 3-triazole **5a** as a model precursor.

Table 1
Optimization of trifluoromethylation reaction of **5a** using MDFA as the trifluoromethylating agent.



Entry	Cu-Source/Additives	Solvent	Temp. °C	Conversion (%)[b]
1	CuI	DMF	80	18
2	CuI	HMPA	80	26
3	CuI/Complex-A	HMPA	80	62
4	CuI/TBAI	HMPA	80	62
5	CuI/TBAI	DMPU	80	42
6	CuI/KI	DMF/HMPA(1:1)	80	37
7	CuI/KI	HMPA	80	46
8	CuI/NaI	HMPA	80	45
9	CuI/KF	HMPA	80	45
10	CuI/CsF	HMPA	80	44
11	$CuSO_4$/TBAI	HMPA	80	26
12	$Cu(OTf)_2$/TBAI	HMPA	80	32

[a]Conditions: Solvent (15 vol.), methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$) (5 equiv.), Cu-salts (0.86 equiv.) and iodide salts (0.33 equiv.), 2h.
[b] By LCMS.

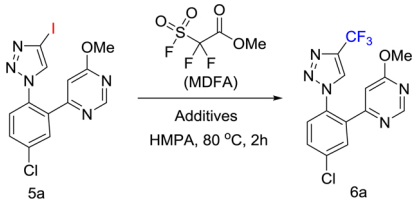
2.2. Optimization of the trifluoromethylation reaction of *5a*

The iodo-compound **5a** was used as a model precursor to screen various conditions for the trifluoromethylation reaction. While most of the known literature methods [5a] for the trifluoromethylation of aryl iodides such as using Ruppert-Prakash reagent [11b], chlorodifluoromethyl acetate [11c], sodium trifluoroacetate [11d], did not provide any desired product, it was gratifying to note that, ~18 % product formation (Table1, entry 1) was observed in presence of CuI and MDFA – Chen's reagent, which was first reported by Chen et al. [11e]. The ability of MDFA to be an efficient source of difluorocarbene [11f, g] at a higher temperature, may be helpful for this transformation, which required the addition of the MDFA under hot condition.

This initial result was encouraging; however, the low conversion prompted further exploration of the reaction parameters including solvent, Cu source, and additives. It is well documented in the review article by Roy [5a] et al. that DMF and HMPA are the best solvent systems for the trifluoromethylation reaction using MDFA as the reagent. While the reaction was sluggish in DMF, the use of HMPA as solvent provided a marginal increase in the conversion (Table 1, entry 2). Next, additives, such as TBAI, KI, NaI, KF [12a], that have previously been used to provide rate enhancements of thio-trifluoromethylation (SCF_3) [12a] reactions were considered. It is known in the literature [12b] that the addition of tetrabutylammonium iodide (TBAI) to CuI increases the solubility of the Cu species by forming a stable double salt. The use of this complex has been shown to significantly improve the rates of Carbon—Nitrogen, Carbon—Oxygen, bond formation [12b] and alkyne-azide Click reactions [12c].

Indeed, trifluoromethylation reaction with MDFA showed enhanced conversion to **6a** (62 %) (Table 1, entry 3) when the pre-formed Complex-**A** [12b] was used with HMPA. Further, the reaction was just as efficient when the complex was formed in situ by adding TBAI to the reaction mixture (Table 1, entry 4). Attempts to substitute HMPA with DMPU, did not improve the conversion (Table 1, Entry 5). Next, the influence of other additives, such as KI, NaI, CsF, and KF (Table 1, entries 6–10), were studied, but none of them resulted in further improvement. Other copper salts such as $CuSO_4$, $Cu(OTf)_2$ were not as effective as CuI (Table 1, entries 11 & 12). Similarly, no added advantage over TBAI was observed using other alkyl ammonium iodides (Table 2, entries 2–5). In summary, the best conversion (62 %) and yield (43.6 %) were observed using 5–7 equiv. of MDFA in the presence of CuI and TBAI in HMPA on a 30 g scale.

Table 2
Screening of alkyl ammonium additives for the trifluoromethylation reaction.



Entry	Additives	Cu-Regaent	Conversion (%)[b]
1	[a]$Bu_4N^+I^-$	CuI	62
2	$C_6H_5CH_2N^+[(CH_2)_3CH_3]_3I^-$	CuI	42
3	$(CH_3CH_2CH_2)_4N^+I^-$	CuI	37
4	$[CH_3(CH_2)_6]_4N^+I^-$	CuI	42
5	$Et_4N^+I^-$	CuI	40

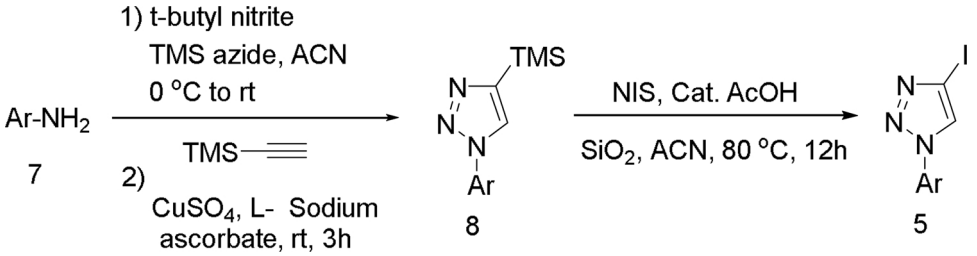
[a]Conditions: HMPA (15 vol.), methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$) (5 equiv.), CuI (0.86 equiv.) and iodide salts (0.33 equiv.).
[b] Monitored by LCMS.

2.3. ^{19}F NMR studies to understand the effect of additive TBAI

The CuI-mediated trifluoromethylation reaction using MDFA is believed to proceed *via in situ* formation of '$CuCF_3$' species [5,13,14]. To understand the role of the added TBAI and the nature of the $CuCF_3$ species responsible for the trifluoromethylation reaction, two different ^{19}F NMR experiments [15] were performed. In the first experiment ^{19}F NMR data was recorded. at 90 °C, mimicking the optimized reaction conditions with and without added TBAI. The ^{19}F NMR spectra with added TBAI (0.4 equiv.) led to a significant increase in the intensity of the peak at −34.5 ppm, which correlated with our experimental observation of improved conversions with added TBAI. Next, a variable temperature ^{19}F experiment (30 °C–90 °C) using CuI, MDFA, and TBAI in HMPA was performed to find out the existence of various $CuCF_3$ species at various temperatures. Results indicated the existence of two prominent $CuCF_3$ peaks at −28.8 and −32.3 ppm respectively, which slowly disappeared at elevated temperature, while the peak at −34.5 ppm was found to gradually increase as the NMR tube was heated from 30 °C to 90 °C. These results indicated that the $CuCF_3$ species (peak at −34.5 ppm) plays a key role in the trifluoromethylation reaction using TBAI as additive.

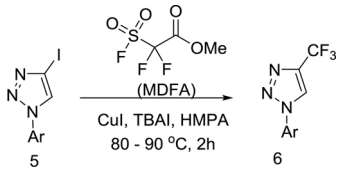
2.4. General substrate scope for the trifluoromethylation reaction of 1-aryl 4-iodo-1, 2, 3-triazoles *5*

Having established the optimized reaction conditions on the model substrate **5a**, we sought to explore the substrate scope of this reaction with various 1-aryl-4-iodotriazoles. Once various 4-iodo-1-aryl-1,2,3-triazoles **5b-l** were in hand (Scheme 2), they were subjected to the optimized trifluoromethylation condition and the results are shown in (Table 3). It was observed that the reaction was not dependent on the electronic nature of the substituent present in the aryl ring, and good to moderate yield was obtained. Several sensitive functional groups such as a ketone (Table 3, entry 8), ester (Table 3, entry 9) and nitrile (Table 3, entry 10), were well-tolerated. More importantly, the reactions were chemoselective, with bromo and chloro substituents staying intact during the transformation. In most of these cases, the reactions proceeded to > 60 % conversion; however, the isolated yields were lower due to un-optimized isolation protocols on a small scale. Thus this method was found to be generally applicable for the synthesis of a



Scheme 2. Synthesis of 4-Iodo-1, 2, 3-triazoles from anilines.

Table 3
General substrate scope for the trifluoromethylation reaction of 1-aryl 4-iodo-1, 2, 3-triazoles.



Entry	Ar	Product	Yield (%)
1	4-Cl-C_6H_4	6b	62
2	4-Br-C_6H_4	6c	51
3	3-Cl-C_6H_4	6d	63
4	4-F-C_6H_4	6e	43
5	4-CH_3-C_6H_4	6f	37
6	C_6H_5	6g	60
7	3,5-$(CF_3)_2$-C_6H_3	6h	38
8	4-$COCH_3$-C_6H_4	6i	36
9	4-$CO_2CH_2CH_3$-C_6H_4	6j	36
10	4-CN-C_6H_4	6k	25
11	4-OCF_3-C_6H_4	6l	48

variety of 1-aryl-4-trifluoromethyltriazoles from the corresponding iodo-precursors.

3. Conclusions

In summary, while several methods are available for the synthesis of trifluoromethylated aromatic and heteroaromatic compounds from their halo precursors, these were not amenable to the synthesis of trifluoromethyl triazoles. We demonstrated that the combination of MDFA with CuI and TBAI provided the trifluoromethyl triazoles. Tetrabutylammonium iodide is believed to play a key role in affecting better conversion, presumably by solubilizing the Cu and making it available in the solution for the reaction. This methodology was scaled up to multi-gram scale and enabled us to synthesize a host of 1-aryl-4-trifluoromethyltriazoles, and rapidly expand the structure-activity relationship (SAR) in the Discovery space for the program. Very recently, this methodology has been successfully scaled up using continuous flow chemistry to synthesize larger quantities of the target compound **6a**, and the results were communicated [16] by our Process Chemistry Department.

4. Experimental

4.1. General

All solvents and reagents were commercially available and were used as such without further purification. All LCMS experiments were done using Agilent 1200 coupled with Agilent 6140 Single Quad MS, and Agilent 6330 single quad MS using ES-APCI method with an Ascentis Express C18 (2.1 × 50 mm, 2.7 µm) column at ambient temperature. A gradient of acetonitrile and 10 mM ammonium formate in Milli-Q Water were used. To measure the absorbance 220 nm wavelength was used. HPLC data were recorded using Agilent 1200 series using Triart C-8 (150 × 4.6 mm, 5µ) column and 10 mM ammonium acetate: Acetonitrile; XBridge phenyl (150 × 4.6 mm, 3.5µ) sc/749 using 0.05 % TFA in water: acetonitrile; and Sunfire C18 (150 × 4.6 mm, 3.5µ) columns. ^{1}H NMR. ^{13}C NMR and ^{19}F NMR spectra were acquired on Bruker 300 MHz and 400 MHz instruments at temperature 300 K. Column chromatography was done using pre-packed silica columns of 40–60 µ of Redisep® Rf200 (Teledyne ISCO) for < 50 g scale and Torrent (Teledyne ISCO) for > 50 g batch size. LTQ Velos Orbitrap mass spectrometer (Thermo Fisher Scientific, Bremen, Germany) fitted with a heated electrospray ionization source and operated in positive-ion mode was used to capture all HRMS data. The data were recorded in a similar way as described in the literature [17]. To record electrospray mass spectrometry data, nitrogen was used both as sheath gas and auxiliary gas, and helium was used for collision-induced dissociation. The concentration of the compound was maintained as 1 µM, with a flow rate of 5 µL/min, using gradient solvent acetonitrile: water (50 %–50 %) and the stock solution was made in DMSO. Fourier transform mass spectrometry mode was used to operate the Orbitrap to enable the acquisition of both full-scan mass spectra and product-ion MS/MS spectra with mass accuracies within 5 ppm.

4.2. Experimental procedures

4.2.1. 4-Chloro-2-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) aniline (2)

A mixture of 2-bromo-4-chloroaniline (**1**) (20 g, 97 mmol), bis (pinacolato) diboron (27.1 g, 107 mmol), potassium acetate (24.72 g, 252 mmol), and $PdCl_2$(dppf) − CH_2Cl_2 adduct (2.373 g, 2.91 mmol) was taken in toluene (350 mL) at room temperature and the solution was deoxygenated by purging nitrogen gas for 15 min. The reaction mass was stirred at 90 °C for 16 h and the completion of the reaction was determined by TLC (Ethyl acetate: petroleum ether; 3:7). The reaction mixture was diluted with dichloromethane (400 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuo to get the crude material, which was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate as the eluent) to afford the pure compound **2** as a white solid, 23 g, yield 64 %. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 7.53 (d, J = 2.6 Hz, 1 H), 7.12 (dd, J = 2.6, 8.7 Hz, 1 H), 6.52 (d, J = 8.7 Hz, 1 H), 5.06 − 4.39 (m, 2 H), 1.34 (s, 12 H).

4.2.2. 4-Chloro-2-(6-methoxypyrimidin-4-yl) aniline (3)

A mixture of 4-chloro-2-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) aniline (**2**) (65 g, 256 mmol), 4-chloro-6-methoxypyrimidine (37.1 g, 256 mmol) was taken in tetrahydrofuran (1.2 L) and the solution was deoxygenated by purging nitrogen gas for 15 min. In another 500 mL conical flask, tripotassium phosphate (136 g, 641 mmol) was dissolved in water (300 mL), and was deoxygenated by purging nitrogen gas for 15 min. This aqueous solution was added to the above reaction mixture, and purging of nitrogen was continued for another 15 min, followed by the addition of $PdCl_2$(dppf) − CH_2Cl_2 adduct (6.28 g, 7.69 mmol). The reaction mixture was stirred at 70 °C for 16 h.

The mixture was cooled to room temperature and diluted with ethyl acetate (700 mL), filtered through a pad of celite, washed with 400 mL ethyl acetate. The combined filtrate was washed with brine solution (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to get the crude material, which was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate as the eluent) to afford pure compound **3** as a white solid, 72.8 g, yield 67.1 %. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 8.7 (s, 1 H), 7.48 (d, J = 2.4 Hz,1 H), 7.16 (dd, J = 2.4 Hz, 8.7 Hz,1 H), 6.98 (s,1 H), 6.65 (d, J = 8.7 Hz,1 H),5.90 (bs, 2 H), 4.02 (s, 3 H). ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 170.6, 165.7, 157.3, 146.3, 131.3, 128.67, 122.1, 120.0, 118.9, 104.27, 54.0. LCMS *m/z* (ESI); $[M^+H]^+$ 236.0.

4.2.3. 4-(5-Chloro-2-(4-(trimethylsilyl)-1H-1, 2, 3-triazol-1-yl) phenyl)-6-methoxypyrimidine (4)

4-Chloro-2-(6-methoxy pyrimidin-4-yl) aniline (**3**) (22.5 g, 95 mmol) was taken in acetonitrile (900 mL) and cooled to 0 °C. *t*-Butyl nitrite (19.30 mL, 162 mmol) and trimethylsilyl azide (19.01 mL, 143 mmol) were added dropwise to it. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Trimethylsilylacetylene (53.6 mL, 382 mmol) was added dropwise to the reaction mixture followed by the addition of copper (II) sulphate pentahydrate (2.384 g, 9.55 mmol) and a solution of L-sodium ascorbate (9.46 g, 47.7 mmol) in water (270 mL). This mixture was stirred at room temperature for 30 min, then warmed to 30 °C and stirred for one hour. It was again cooled to room temperature (22 °C), diluted with ethyl acetate (1 L) and water (500 mL). Organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 500 mL). The combined organic layer was washed with brine solution (500 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give a brown liquid, which was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate as the eluent) to afford the pure compound **4** as a yellow-orange solid, 34 g, yield: 67.1 %. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.70 (s, 1 H), 7.81 (d, J = 2.4 Hz, 1 H), 7.58 (dd, J = 2.4 Hz, 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 7.49 (s, 1 H), 6.2 (s, 1 H), 3.92 (s, 3 H), 0.3 (s, 9 H). ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 170.1, 161.9, 158.4, 147.2, 136.2, 135.80, 133.9, 131.2, 130.9, 130.7, 128.2, 107.3, 54.2, -1.1. LCMS *m/z* (ESI); $[M+H]^+$ 360.1.

4.2.4. 4-(5-Chloro-2-(4-iodo-1H-1, 2, 3-triazol-1-yl) phenyl)-6-methoxypyrimidine (5a)

A mixture of 4-(5-chloro-2-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl) phenyl)-6-methoxy pyrimidine (**4**) (100 g, 208 mmol), N-iodosuccinimide (281 g, 1250 mmol), silicon dioxide (288 g, 4793 mmol) (Silica gel 230–400 Mesh), acetic acid (2.386 mL, 41.7 mmol) was taken in acetonitrile (2000 mL) at room temperature. The heterogeneous reaction mixture was vigorously stirred at 80 °C (pre-heated oil bath) for 12 h. The heterogeneous mixture was cooled to room temperature, filtered through a pad of Celite, and washed with ethyl acetate (2 × 1000 mL). The combined filtrate and washing was concentrated in vacuum, diluted with ethyl acetate (1000 mL), washed with 10 % sodium thiosulphate solution (2 × 1000 mL), washed with brine solution (500 mL), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The resulting crude material was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate (8:2) as the eluent to afford the pure compound **5a** as a white solid, 45 g, yield 60 %. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 8.68 (d, J = 1.1 Hz, 1 H), 7.75 (d, J = 2.3 Hz, 1 H), 7.71 (s, 1 H), 7.60 (dd, J = 2.3 Hz, 8.7 Hz, 1 H), 7.47 (d, J = 8.7 Hz,1 H), 6.48 (d, J = 1.1 Hz, 1 H), 3.96 (s, 3 H). LCMS *m/z* (ESI); $[M+H]^+$ 412.0.

4.2.5. 4-(5-Chloro-2-(4-(trifluoromethyl)-1H-1, 2, 3-triazol-1-yl) phenyl) -6-methoxypyrimidine (6a)

To a solution of 4-(5-chloro-2-(4-iodo-1H-1, 2, 3-triazol-1-yl) phenyl)-6-methoxypyrimidine (**5a**) (30 g, 72.5 mmol) in hexamethylphosphoramide (240 mL, 1379 mmol), at 80 °C were added copper (I) iodide (18 g, 95.0 mmol), and tetrabutylammonium iodide (18 g, 48.7 mmol) followed by dropwise addition of methyl 2, 2-difluoro-2-(fluorosulfonyl) acetate (MDFA) (64.6 mL, 508 mmol) from a dropping funnel. The reaction was continued for 2 h at 90 °C and the progress of the reaction was monitored by TLC (ethyl acetate: petroleum ether; 3:7). After completion, the reaction mixture was cooled to room temperature and water (450 mL) was poured into it. The reaction mixture was filtered through a celite bed and washed with ethyl acetate (250 mL). Layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 250 mL). The combined organic layer was washed with brine solution (1 × 250 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to get the crude material, which was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate (8:2) as the eluent to afford the pure compound (**6a**) as a white solid, 11.2 g, yield 43.6 %. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.94 (s, 3 H), 7.09 (d, J = 1.2 Hz, 1 H), 7.84–7.91 (m, 2 H), 8.01 (d, J = 2.8 Hz, 1 H), 8.56 (d, J = 1.2 Hz, 1 H), 9.27 (s, 1 H). ^{19}F NMR (376.5 MHz, DMSO-d_6): δ -59.65. ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7, 161.9, 157.7, 136.8 (q, J = 38.1 Hz), 135.6, 135.5, 132.7, 130.8, 130.7, 129.0, 127.9, 120.7 (q, J = 265.5 Hz), 107.4, 54.0. HRMS (ESI) (*m/z*): calcd for $C_{14}H_{10}ClF_3N_5O$, 356.0520 $[M+H]^+$, found 356.0517.

4.3. General procedure for the synthesis of 1-aryll-4-(trimethylsilyl)-1H-1, 2, 3-triazole (8)

A solution of substituted aniline **7** (1.0 mmol) in acetonitrile (40 mL), was cooled to 0 °C and t-butyl nitrite (1.69 mmol), and trimethylsilyl azide (1.4 mmol) were added dropwise to it. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Trimethylsilylacetylene (3.7 mmol) was added dropwise followed by addition of Copper (II) sulfate pentahydrate (0.1 mmol) and a solution of L-sodium ascorbate (0.5 mmol) in water (150 mL). This mixture was stirred at room temperature for 30 min, then warmed to 30 °C and stirred for one hour. It was again cooled to room temperature (22 °C), diluted with ethyl acetate (250 mL), washed with brine solution (100 mL), dried over sodium sulfate, filtered and the filtrate was concentrated to get the crude product. The resulting crude material was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate as the eluent) to afford the desired compound of substituted phenyl-4-(trimethylsilyl)-1H-1, 2, 3-triazole **8**.

4.4. General procedure for the synthesis 1-aryl-4-iodo-1H-1, 2, 3-triazole (5)

A mixture of aryl-4-(trimethylsilyl)-1H-1,2,3-triazole (1.0 mmol), N-iodosuccinimide (6.0 mmol), silicon dioxide (20.0 mmol) (Silica gel, 230–400 mesh), acetic acid (0.02 mmol) was taken in acetonitrile (20 mL) and stirred at 80 °C (oil bath temperature) for 12 h. The reaction mixture was cooled to room temperature, filtered through a celite bed, washed with ethyl acetate (20 mL). The filtrate was washed with 10 % sodium thiosulfate solution (2 × 10 mL), brine solution (10 mL), dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to get the crude product. The resulting crude material was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate as the eluent) to afford the pure desired compound 4-iodo-substituted-aryl-1H-1, 2, 3-triazole **5**.

4.5. Copper (I) iodide tetra-n-butylammonium iodide dimeric complex (n-$Bu_4N^+)_2(Cu_2I_4)^{2-}$ (complex A)

Complex A was prepared following the reported literature procedure with slight modification [12a].

In a 100 mL three-neck round-bottom flask, fitted with a mechanical stirrer, CuI (2.55 g, 1.0 equivalent), n-Bu_4NI (4.95 g, 1.0 equivalent), and anhydrous THF (20 mL) were added under nitrogen atmosphere.

Nitrogen gas was bubbled into the solution for 5 min. The mixture was warmed to 48 °C. Once a homogeneous pale yellow solution was obtained the reaction mixture was cooled to 10 °C and methyl tert-butyl ether (25 mL) was added over 10 min. at 10 °C. The reaction mixture was stirred at 10 °C for 30 min and the crystalline solid appeared was filtered off and washed with 2:1 v/v t-BuOMe/THF (20 mL). The solid was dried under nitrogen to provide $(n\text{-}Bu_4N^+)_2(Cu_2I_4)^{2-}$ (5.0 g) of quantitative yield as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 3.33–3.28 (m, 16 H), 1.71–1.67 (m, 16 H), 1.52–1.46 (J = 7.3 Hz, 16 H), 1.05–1.01 (t, J = 7.3 Hz, 24 H).

4.6. Synthesis of 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl) phenyl)-6-methoxypyrimidine (**6a**) using dimeric Complex ($n\text{-}Bu_4N^+)_2(Cu_2I_4)^{2-}$ (**Complex A**)

To a solution of 4-(5-chloro-2-(4-iodo-1H-1,2,3-triazol-1-yl)phenyl)-6-methoxypyrimidine (**5a**) (1 g, 2.418 mmol) in hexamethylphosphoramide (2.103 mL, 12.09 mmol), was added dimeric complex $(nBu_4N^+)_2(Cu_2I_4)^{2-}$ (Complex A) (0.089 g, 0.242 mmol). This solution was stirred at 80 °C (pre-heated oil bath), and methyl 2,2-difluoro-2-(fluorosulfonyl) acetate (0.616 mL, 4.84 mmol) was added dropwise from a syringe. The reaction was continued for 2 h at 90 °C, with continuous monitoring of the reaction by TLC (ethyl acetate: petroleum ether; 3:7). The reaction mixture was cooled to room temperature, quenched with ice-cold water (6 mL) and filtered through celite bed. The bed was washed with ethyl acetate (25 mL). Layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the crude material, which was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate (8:2) as the eluent to afford the pure compound **6c** as a white solid, 0.370 g, yield 43 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.94 (s, 3 H), 7.09 (d, J = 1.2 Hz, 1 H), 7.84–7.91 (m, 2 H), 8.01 (d, J = 2.8 Hz, 1 H), 8.56 (d, J = 1.2 Hz, 1 H), 9.27 (s, 1 H). ^{19}F NMR (376.5 MHz, DMSO-d_6): δ-59.65. ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7, 161.9, 157.7, 136.8 (q, J = 38.1 Hz), 135.6, 135.5, 132.7, 130.8, 130.7, 129.0, 127.9, 120.7 (q, J = 265.5 Hz), 107.4, 54.0. HRMS (ESI) (m/z): calcd for $C_{14}H_{10}ClF_3N_5O$, 356.0520 $[M+H]^+$, found 356.0517.

4.7. General procedure for the 1-aryl-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6**)

To a solution of 4-iodo-substituted-aryl-1H-1,2,3-triazole **5** (1.5 mmol) in hexamethylphosphoramide (HMPA) (15 mL) at 80 °C, Cu (I)I (1.95 mmol), and tetrabutylammonium iodide (0.75 mmol) were added, followed by dropwise addition of Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (10.5 mmol) (MDFA) over 5 min. The reaction mixture was stirred at 90 °C for 2 h and the progress of the reaction was monitored by TLC (8:2; Petroleum ether: EtOAc). Reaction mixture was cooled to room temperature, quenched with ice-cold water (15 mL), diluted with ethyl acetate (15 mL) and filtered through celite bed. The bed was washed with ethyl acetate (7.5 mL). The layers were separated and the organic layer was washed with water (7.5 mL), brine solution (7.5 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to get the crude product. The resulting crude material was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate (8:2) as the eluent to afford the pure 1-aryl-4-(trifluoromethyl)-1H-1, 2, 3-triazole **6**.

4.7.1. 1-(4-Chlorophenyl)-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6b**) white solid

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.63 (s, 1 H), 8.00 (d, J = 9.0 Hz, 2 H), 7.73 (d, J = 9.0 Hz, 2 H).^{19}F NMR (400 MHz, CHLOROFORM-d) δ –61.26. ^{13}C NMR (101 MHz, DMSO-d_6) δ = 138.2 (q, J = 38.3 Hz, 1C), 134.7, 134.0, 129.9, 124.5 (q, J = 2.5 Hz, 1C), 122.5,121.1 (q, J = 265.75 Hz, 1C). HRMS: m/z calcd for $C_9H_5ClF_3N_3$ $[M+H]^+$ 248.0197, found 248.0186.

4.7.2. 1-(4-Bromophenyl)-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6c**) off white solid

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 8.26 (s, 1 H), 7.77 − 7.70 (m, 2 H), 7.70 − 7.60 (m, 2 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –61.26. ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 139.7 (q, J = 39.5 Hz, 1C), 135.1, 133.2, 123.7, 122.3, 121.4, 120.2 (q, J = 268.4 Hz, 1C). HRMS: m/z calcd for $C_9H_5BrF_3N_3$ $[M+H]^+$ 291.9692, found 291.9684.

4.7.3. 1-(3-Chlorophenyl)-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6d**) white solid

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.28 (s, 1 H), 7.85 − 7.77 (m, 1 H), 7.66 (td, J = 2.3, 6.6 Hz, 1 H), 7.57 − 7.47 (m, 2 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –61.30. ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 139.7 (q, J = 39.8 Hz, 1C), 136.9, 135.9, 131.1, 129.9, 124.2, 121.5 (q, J = 3.7 Hz), 120.2 (q, J = 265 Hz), 121.2, 118.9, 118.9. HRMS: m/z calcd for $C_9H_5ClF_3N_3$ $[M+H]^+$ 248.0197, found 248.0192.

4.7.4. 1-(4-Fluorophenyl)-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6e**) white solid

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 8.26 (s, 1 H), 7.80 − 7.71 (m, 2 H), 7.32 − 7.22 (m, 2 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –110.22, –61.24. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 162.7 (d, J = 247.3 Hz, 1C), 138.1 (q, J = 38.4 Hz, 1C), 132.9 (d, J = 2.7 Hz, 1C), 124.9 (q, J = 2.7 Hz, 1C), 123.7 (d, J = 9.5 Hz, 1C), 121.1 (q, J = 267.3 Hz, 1C),117.3 (d, J = 23.2 Hz, 1C). HRMS: m/z calcd for $C_9H_5F_4N_3$ $[M^+H]^+$ 232.0492 found 232.0487.

4.7.5. 1-(p-Tolyl)-4-(trifluoromethyl)-1H-1,2,3-triazole (**6f**) white solid

^{1} H NMR (300 MHz, CHLOROFORM-d) δ = 8.23 (s, 1 H), 7.61 (d, J = 8.7 Hz, 2 H), 7.36 (d, J = 8.7 Hz, 2 H), 2.45 (s, 3 H). ^{19}F NMR (400 MHz, DMSO-d_6) δ –61.16. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 139.8, 138.1 (q, J = 38.8 Hz, 1C), 134.1, 130.7, 124.5 (q, J = 3.2 Hz, 1C), 121.1, 121.2 (q, J = 267.0 Hz, 1C), 21.0. HRMS: m/z calcd for $C_{10}H_8F_3N_3$ $[M^+H]^+$ 228.0743 found 228.0737.

4.7.6. 1-(Phenyl)-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6g**) white solid

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.30 (s, 1 H), 7.83 − 7.70 (m, 2 H), 7.65 − 7.52 (m, 3 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –61.2. ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 139.6 (q, J = 42 Hz),136.2, 130.00, 129.8, 121.7, 121.45121.0, 120.9, 120.4 (q, J = 265 Hz), 100. HRMS: m/z calcd for $C_{11}H_{10}F_3N_3O_2$ $[M^+H]^+$ 214.0587 found 214.058.

4.7.7. 1-(3, 5-Bis (trifluoromethyl) phenyl)-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6 h**) white solid

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.44 (d, J = 1.0 Hz, 1 H), 8.28 (d, J = 1.5 Hz, 2 H), 8.07 − 8.03 (m, 1 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –63.05, –61.40. ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 140.4 (q, J = 39.8 Hz, 1C), 137.2, 134.0 (q, J = 34.7 Hz, 1C), 123.3(q, J = 3.0 Hz, 1C), 122.3 (q, J = 273.2 Hz, 1C), 121.7, 121.0, 116.4 (q, J = 267.2 Hz, 1C). HRMS: m/z calcd for $C_{11}H_4F_9N_3$ $[M^+H]^+$ 350.0334 found 350.0323.

4.7.8. 1-(4-Acetylphenyl)-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6i**) white solid

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.36 (s, 1 H), 8.17 (d, J = 9.0 Hz, 2 H), 7.90 (d, J = 9.0 Hz, 2 H), 2.68 (s, 3 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –61.30. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 197.4, 139.3, 137.6, 138.3 (q, J = 38.8 Hz, 1C), 130.5, 125.1 (q, J = 2.7 Hz, 1C), 121.1, 121.1 (q, J = 267.5 Hz, 1C), 27.3. HRMS: m/z calcld for $C_{11}H_4F_9N_3$ $[M+H]^+$ 256.0692 found 256.0688.

*4.7.9. 1-(4-Ethoxycarbonylphenyl)-4-(trifluoromethyl)-1H-1, 2, 3-triazole (**6j**) white solid*

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.35 − 8.34 (m, 1 H), 8.26 (d, J = 8.5 Hz, 2 H), 7.86 (d, J = 9.0 Hz, 2 H), 4.44 (q, J = 8.0 Hz, 2 H), 1.46 − 1.41 (t, J = 8.0 Hz, 3 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –61.29. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 165.1, 139.5, 138.4 (q, J = 38.6 Hz, 1C), 131.3, 1301.0, 124.9 (q, J = 2.7 Hz, 1C), 121.0, 121.0 (q, J = 267.7 Hz, 1C), 61.6, 14.5. HRMS: m/z calcd for $C_{11}H_4F_9N_3$ $[M+H]^+$ 286.0798 found 286.0789.·

*4.7.10. 4-(4-(Trifluoromethyl)-1H-1, 2, 3-triazol-1-yl) benzonitrile (**6k**) white solid*

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.39 − 8.35 (m, 1 H), 7.99 − 7.87 (m, 4 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –61.45. ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 140.2 (q, J = 40.2 Hz, 1C), 138.9, 134.1, 121.4, 121.1, 120.2 (q, J = 267.7 Hz, 1C), 117.3, 113.7. HRMS: m/z calcd for $C_{10}H_5F_3N_4$ $[M+H]^+$ 239.0539 found 239.0534·

*4.7.11. 1-(4-(Trifluoromethoxy)phenyl)-4-(trifluoromethyl)-1H-1,2,3-triazole (**6l**) white solid*

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 8.26 (s, 1 H), 7.82 − 7.77 (m, 2 H), 7.44 − 7.40 (m, 2 H). ^{19}F NMR (400 MHz, CHLOROFORM-d) δ –66.03, –62.73. ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 149.8 (q, J = 2.25 Hz, 1C),139.8 (q, J = 40.0 Hz, 1C), 134.4, 122.5, 122.5, 121.6, 120.3 (q, J = 258.9 Hz, 1C), 120.2 (q, J = 267.7 Hz, 1C). HRMS: m/z calcd for $C_{10}H_5F_6N_3O$ $[M+H]^+$ 298.0410 found 298.0402.

Declaration of Competing Interest

I hereby declare that there is no conflict of interest associated with the submitted manuscript.

Acknowledgments

Authors are thankful to Discovery Analytical Department, Biocon Bristol-Myers Squibb Research Centre (BBRC), Syngene, Bangalore (India) for analytical support. We wish to thank Drs. Rajappa Vaidyanathan, and James Kempson for their insights and review of this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2020.109516.

References

[1] D.K. Dalvie, A.S. Kalgutkar, S.C. Khojasteh-Bakht, R.S. Obach, J.P. Donnell, Biotransformation reactions of five-membered aromatic heterocyclic rings, Chem. Res. Toxicol. 15 (2002) 269–299.

[2] (a) S.G. Agalave, S.R. Maujan, V.S. Pore, Click chemistry: 1,2,3-triazoles as pharmacophores, Chem. Asian J. 6 (2011) 2696–2718;
(b) N. Boechat, V.F. Ferreira, S.B. Ferreira, M.L.G. Ferreira, F.C. da Silva, M.M. Bastos, M.S. Costa, M.C.S. Lourenco, A.C. Pinto, A.U. Krettli, A.C. Aguiar, B.M. Teixeira, N.V. da Silva, P.R.C. Martins, F.A.F.M. Bezerra, A.L.S. Camilo, G.P. da Silva, C.C.P. Costa, Novel 1,2,3-triazole derivatives for use against Mycobacterium tuberculosis H37Rv (ATCC 27294) strain, J. Med. Chem. 54 (2011) 5988–5999.

[3] S. Haider, M.S. Alam, H. Hamid, 1, 2, 3-Triazoles: scaffold with medicinal significance, Inflamm. Cell Signal. 1 (2014) 1–10 e95.

[4] (a) D. Cartwright, R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry, Plenum, New York, 1994, pp. 237–262;
(b) P. Kirsch, Modern Fluoro-Organic Chemistry, Wiley-VCH, Weinheim, Germny, 2004;
(c) K. Müller, C. Faeh, F. Diederich, Fluorine in pharmaceuticals: looking beyond intuition, Science, (2007), pp. 1881–1886;
(d) H.-J. Bohm, D. Banner, S. Bendels, M. Kan-sy, B. Kuhn, K. Muller, U.-O. Sander, M. Stahl, Fluorine in medicinal chemistry, Chem-BioChem, (2004), pp. 637–643;
(e) N.A. Meanwell, Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design, J. Med. Chem. (2018), pp. 5822–5880;
(f) Fluorine in Hetreocyclic Chemistry, Valentine Nenajdenko (Ed.), Volume-1; 5-Membered Heterocylces and Macrocyles, Springer, 2014.

[5] (a) S. Roy, B.T. Gregg, G.W. Gribble, V.-D. Le, S. Roy, Trifluoromethylation of aryl and heteroaryl halides, Tetrahedron 67 (2011) 2161–2195 and references there in; 3, 3, 3-Trifluoroprop-1-yne is a highly flammable and irritant gas.
(b) O.A. Tomashenko, V.V. Grushin, Aromatic trifluoromethylation with metal complexes, Chem. Rev. 111 (2011) 4475–4521;
(c) G.-b. Li, C. Zhang, C. Song, Y.-d. Ma, Progress in copper-catalyzed trifluoromethylation, Beilstein J. Org. Chem. 14 (2018) 155–181;
(d) V.D. Bock, H. Hiemstra, J.H. van Maarseveen, Cu^I-catalyzed alkyne-azide "Click" cycloadditions from a mechanistic and synthetic perspective, Eur. J. Org. Chem. (2006) 51–68;
(e) T. Liu, Q. Shen, Progress in copper-mediated formation of trifluoromethylated arenes, Eur. J. Org. Chem. (2012) 6679–6687

[6] (a) J. Wei, J. Chen, J. Xu, L. Cao, H. Deng, W. Sheng, H. Zhang, W. Cao, Scope and regioselectivity of the 1,3-dipolar cycloaddtion of azides with methyl-2-perfluoroalkylnoates for an easy, metal free route to perfluoroalkylated 1,2,3-triazoles, J. Fluor. Chem. 133 (2012) 146–154;
(b) Y. Kobayashi, H. Hamana, S. Fujino, A. Ohsawa, I. Kumadaki, Studies of organic fluorine compounds. 29. Cycloaddition reactions of hexakis(trifluoromethyl)-1,4-diphosphabarrelene, J. Org. Chem. 44 (1979) 4930–4933;
(c) G. Meazza, G. Zanardi, Aryl trifluoromethyl-1,2,3-triazoles, J. Fluor. Chem. 55 (1991) 199–206;
(d) T. Hanamoto, Y. Hakoshima, M. Egashira, Tributyl(3,3,3-trifluoro-1-propynyl) stannane as an efficient reagent for the preparation of various trifluoromethylated heterocyclic compounds, Tetrahedron Lett. 45 (2004) 7573–7576;
(e) F. Wei, T. Zhou, Y. Ma, C.-H. Tung, Z. Xu, Bench stable5-stannyl triazoles by a copper(I) catalyzed interrupted click reaction: bridge to trifluoromethyltriazoles and trifluoromethylthiotriazoles, Org. Lett. 19 (2017) 2098–2101;
(f) A. Pace, S. Buscemi, N. Vivona, Org. Prep. Proced. Int. 37 (5) (2005) 447–506;
(g) W. Carpenter, A. Haymaker, D.W. Moore, Fluorinated 1,2,3-triazolines, J. Org. Chem. 31 (1966) 789–792.

[7] (a) D. Fu, J. Zhang, S. Cao, Copper mediated trifluoromethylation of 5-iodotriazole with (trifluoromethyl)trimethylsilane promoted by silver carbonate, J. Fluor. Chem. 156 (2013) 170–176;
(b) C. Hager, R. Miethchen, H. Reinke, New trifluoromethyl substituted 1,2,3-triazoles linked to D-galactose and D-gulose, J. Prakt. Chem. 342 (2000) 414–420.

[8] (a) S. Wang, L.-J. Yang, J.-L. Zeng, Y. Zheng, J.-A. Ma, Silver-catalyzed [3 + 2] cycloaddition of isocyanides with diazo compounds: new regioselective access to 1,4-disubstituted-1,2,3-triazoles, Org. Chem. Front. 2 (2015) 1468–1474;
(b) A. Kumar, S. Ahamad, R. Kant, K. Mohanan, Silver-catalyzed three-component route to trifluoromethylated 1,2,3-triazolines using aldehydes, amines and trifluorodiazoethane, Org. Lett. 21 (2019) 2962–2965.

[9] (a) K. Barral, A.D. Moorhouse, J.E. Moses, Efficient conversion of aromatic amines into azides: a one-pot synthesis of triazole linkages, Org. Lett. 9 (2007) 1809–1811; K.T. Mark, J. Rong, S. Xinyi, L. Phillip, C.M. Darin, Substituted Pyrimidinyl-Amines as Protein Kinase Inhibitors, WO2009032861A1 (2009).

[10] M.B. Avory, H.J. Wadsworth, R.J. Domett Nairne, Radioiodinated Fatty Acids, US20130272960A1 (2013).

[11] (a) A. Darwish, M. Blacker, N. Janzen, S.M. Rathmann, S. Czorny, S.M. Hillier, J.L. Joyal, J.W. Babich, J.F. Valliant, Triazole appending agent (TAAG): a new synthon for preparing iodine-based molecular imaging and radiotherapy agents, ACS Med. Chem. Lett. 3 (2012) 313–316;
(b) G.K.S. Prakash, M. Mandal, Nucleophilic trifluoromethylation tamed, J. Fluor. Chem. 112 (2001) 123–131;
(c) J.J. Van Veldhuizen, D.G. Gil-lingham, S.B. Garber, O. Kataoka, A.H. Hoveyda, Chiral Ru-based complexes for asymmetric olefin metathesis: enhancement of catalyst activity through steric and electronic modifications, J. Am. Chem. Soc. 125 (2003) 12502–12508;
(d) S. Hunig, R. Bau, M. Kemmer, H. Meixner, T. Metzenthin, K. Peters, K. Sinzger, J. Gulbis, 2,5-Disubstituted N,N'-dicyanoquinone diimines (DCNQIs)—syntheses, and redox properties, J. Eur. J. Org. Chem. (1998) 335–348;
(e) Q.-Y. Chen, S.-W. Wu, Methyl fluorosulphonyldifluoroacetate; a new trifluoromethylating agent, J. Chem. Soc. Chem. Commun. (1989) 705–706;
(f) A.J. Mulder, R.P. Frutos, N.D. Patel, B. Qu, X. Sun, T.G. Tampone, J. Gao, M. Sarvestani, M.C. Eriksson, N. Haddad, S. Shen, J.J. Song, C.H. Senanayake, Development of a safe and economical synthesis of methyl 6-chloro-5-(trifluoromethyl)nicotinate: trifluoromethylation on kilogram scale, Org. Process Res. Dev. 17 (2013) 940–945;
(g) S. Eusterwiemann, H. Martinez, W.R. Dolbier Jr, Methyl 2.,2-difluoro-2-(fluorosulfonyl) acetate, a difluorocarbene reagent with reactivity comparable to that of trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl) acetate (TFDA), J. Org. Chem. 77 (2012) 5461–5464;
(h) Q. Xie, J. Hu, Chen's reagent: a versatile reagent for trifluoromethylation, difluoromethylation, and difluoroalkylation in organic synthesis, Chin. J. Chem. 38 (2) (2020) 202–212.

[12] (a) J.D. Adams, J.H. Clark, Preparation of trifluoromethyl aryl sulfides using silver (I) trifluoromethanethiolate and an inorganic iodide, J. Org. Chem. 65 (2000) 1456–1460;
(b) P.E. Maligres, S.W. Krska, P.G. Dormer, A soluble copper(I) source and stable salts of volatile ligands for copper-catalyzed C − X couplings, J. Org. Chem. 77 (2012) 7646–7651;
(c) S. Ramasamy, C. Petha, S. Tendulkar, P. Maity, M.D. Eastgate, R. Vaidyanathan, Synergistic effect of copper and ruthenium on regioselectivity in the alkyne-azide click reaction of internal alkynes, Org. Process Res. Dev. 22 (2018) 880–887.

[13] (a) C.P. Zhang, Z.L. Wang, Q.Y. Chen, C.T. Zhang, Y.C. Gu, J.C. Xiao, Copper

mediated trifluoromethylation of heteroaromatic compounds by trifluoromethyl sulfonium salts, Angew. Chem. Int. Ed. 50 (2011) 1896–1900;
(b) O.A. Tomashenko, E.C. Escudero-Adán, M. Martínez Belmonte, V.V. Grushin, Simple, stable and easily accessible well-defined CuCF3 aromatic trifluoromethylating agents, Angew. Chem. Int. Ed. 50 (2011) 7655–7659;
(c) H. Serizawa, K. Aikawa, K. Mikami, Direct synthesis of a trifluoromethyl copper reagent from trifluoromethyl ketones: application to trifluoromethylation, Chem. Eur. J. 19 (2013) 17692–17697;
(d) Y. Nakamura, M. Fujiu, T. Murase, Y. Itoh, H. Serizawa, K. Aikawa, K. Mikami, Cu-catalyzed trifluoromethylation of aryl iodides with trifluoromethylzinc reagent prepared in situ from trifluoromethyl iodide, Beilstein J. Org. Chem. 9 (2013) 2404–2709.

[14] (a) D.M. Wiemers, D.J. Burton, Pregeneration, spectroscopic detection, and chemical reactivity of (trifluoromethyl)copper, an elusive and complex species, J. Am. Chem. Soc. 108 (1986) 832–834;
(b) J.G. MacNeil, D.J. Burton, Generation of trifluoromethylcopper from chlorodifluoroacetate, J. Fluor. Chem. 55 (1991) 225–227;
(c) H. Liu, Q. Shen, Bistrifluoromethylated organocuprate $[Ph_4P]^+[Cu(CF_3)_2]^-$: synthesis, characterization, and its application for trifluoromethylation of activated heteroaryl bromides, chlorides and iodides, Org. Chem. Front. 6 (2019) 2334–2338.

[15] Please refer to the supporting information for the ^{19}F NMR experiment data.

[16] R. Ayothiraman, A.S. Gangu, D. Bandaru, S.K. Guturi, T. Lakshminarasimhan, M. Jaleel, K. Kanagavel, S. Rangaswamy, N.L. Cuniere, S. Zaretsky, K. Camacho, M.D. Eastgate, R. Vaidyanathan, Two approaches to a trifluoromethyl triazole: a fit-for-purpose trifluoromethylation in flow-mode and a long-term decarboxylative click approach, Org. Process Res. Dev. 24 (2020) 207–215.

[17] S. Sinha, D. Ahire, S. Wagh, D. Mullick, R. Sistla, K. Selvakumar, J.C. Cortes, S.P. Putlur, S. Mandlekar, B.M. Johnson, Electrophilicity of pyridazine-3-carbonitrile, pyrimidine-2-carbonitrile, and pyridine-carbonitrile derivatives: a chemical model to describe the formation of thiazoline derivatives in human liver microsomes, Chem. Res. Toxicol. 27 (2014) 2052–2061.