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Metal-Free Synthesis of 5-Trifluoromethyl-1,2,4-Triazoles from Iodine-Mediated Annulation of Trifluoroacetimidoyl Chlorides and Hydrazones

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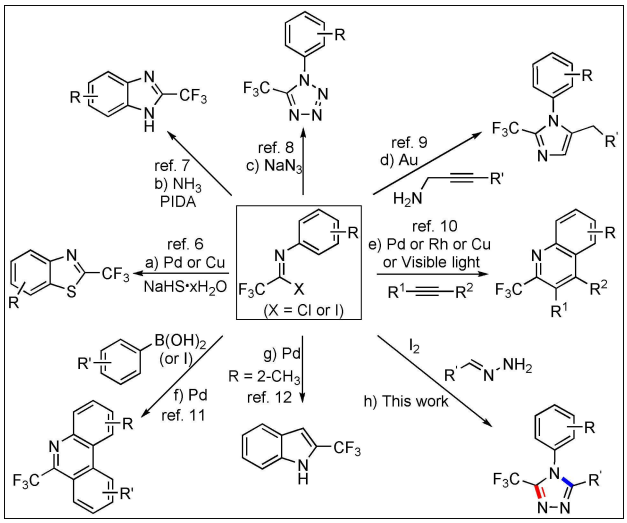
Abstract: A metal-free approach for the synthesis of 5-trifluoromethyl-1,2,4-triazoles from trifluoroacetimidoyl chlorides and hydrazones has been achieved under aerobic oxidative conditions. The reaction proceeds through a cascade base-promoted intermolecular C–N bond formation and iodine-mediated intramolecular C–N bond oxidative coupling sequence. The protocol features broad substrate scope and can be scaled up to gram scale.

Keywords: trifluoroacetimidoyl chlorides; 5-trifluoromethyl-1,2,4-triazoles; metal-free; C–N bond formation; *N*-heterocyclic compounds

The trifluoromethyl-substituted nitrogen-containing heterocycles have found wide applications in the fields of pharmaceuticals, agrochemicals, and materials science, due to the unique properties of fluorine atoms, including improving the electronegativity, bioavailability, metabolic stability and lipophilicity of the compounds.[1] Considering the excellent properties of the trifluoromethyl group, the exploration of efficient methods for the incorporation of trifluoromethyl group into the functionalized *N*-heterocyclic molecules has emerged as an attractive research area over the past decades.[2] In general, there are two mainstream pathways to access to versatile trifluoromethyl-substituted *N*-heterocycles: 1[st]) trifluoromethylation of pre-synthesized *N*-heterocycles by the employment of diverse trifluoromethyl reagents;[3] 2[ed]) direct construction of trifluoromethyl-substituted *N*-heterocycles through the reaction of different trifluoromethyl-containing synthons with suitable coupling substrates.[4] In this context, in contrast to the frequent application of 2,2,2-trifluorodiazoethane (CF_3CHN_2) as an appealing trifluoromethyl-containing 1,3-dipole to build numerous trifluoromethyl-substituted *N*-heterocycles,[5] the using of trifluoroacetimidoyl halide as trifluoromethyl synthon is proven to be exceptional in many cases.[6–12]

Trifluoroacetimidoyl halides were usually applied as useful building blocks for the assembly of trifluoromethyl-substituted *N*-heterocycles in synthetic organofluorine chemistry. In 2010, the research groups of Wu[6a] and Zhang[6b] reported palladium- or copper-catalyzed cyclization of trifluoroacetimidoyl chlorides with sodium hydrosulfide hydrate to synthesize 2-trifluoromethylbenzothiazoles, respectively (Scheme 1a). In 2012, Wu and coworkers described a PIDA (phenyliodine (III) diacetate)-mediated oxidative intramolecular cyclization of the trifluoromethyl amidine for the formation of 2-trifluoromethylbenzimidazoles (Scheme 1b).[7] Two years later, Darehkordi's group

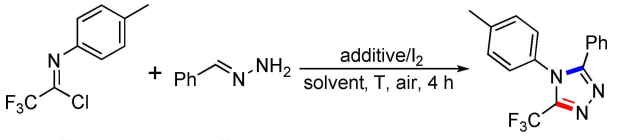


Scheme 1. The Reactions of Trifluoroacetimidoyl Halides for the Synthesis of Trifluoromethyl-substituted *N*-Heterocycles.

explored a convenient approach for the preparation of 5-trifluoromethyl-tetrazoles via microwave-assisted [2 + 3] cycloaddition reaction of trifluoroacetimidoyl chloride and sodium azide. (Scheme 1c).[8] The Wu's group developed an novel Au-catalyzed protocol for the synthesis of 2-fluoroalkyl imidazole derivatives from trifluoroacetimidoyl chloride and propargyl amines (Scheme 1d).[9] Additionally, transition-metal-catalyzed transformations of trifluoroacetimidoyl halides with alkynes for the construction of 2-trifluoromethyl quinolones have also been extensively investigated (Scheme 1e).[10] The 2-trifluoromethyl quinolone could also be obtained through palladium-catalyzed tandem Suzuki/C–H arylation reaction of trifluoroacetimidoyl chlorides with arylboronic acids[11a–c] or norbornene-mediated intermolecular dehydrogenative annulation with aryl iodides[11d] (Scheme 1f). Recently, a Pd(0)-catalyzed C(sp^3)–H functionalization of trifluoroacetimidoyl chlorides to lead to 2-(trifluoromethyl)indoles was reported by Cramer and co-workers. (Scheme 1g).[12] Encouraged by the above fruitful works and our continuous endeavors on the synthesis of structurally diverse nitrogen-containing heterocycles,[13] we present herein an efficient metal-free multistep coupling reaction of trifluoroacetimidoyl chlorides and hydrazones for the rapid preparation of 5-trifluoromethyl-1,2,4-triazoles (Scheme 1h). Noteworthy was that the reports about the synthesis of perfluoroalkyl-1,2,4-triazoles were quite rare, which involved the hydrazinolysis reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles or the conversion of the 2-chloro-1,1,1-trifluoro-2-propyl azo compound.[14] Notably, 1,2,4-triazoles are highly privileged heterocyclic scaffolds and have been broadly applied in biological and pharmaceutical fields as well as materials science.[15]

Initially, we chose 2,2,2-trifluoro-*N*-(*p*-tolyl)acetimidoyl chloride **1b** and hydrazone **2a** as the model substrates for our investigation. The corresponding trifluoroacetimidoyl chlorides could be readily prepared by simply mixing the parent amine with trifluoroacetic acid, CCl_4, and PPh_3.[16] It is enough stable to be isolated by silica gel chromatography. The reaction proceeded with **1b** and **2a** in DCE at 80 °C for 3 h, and then 1.0 equiv. I_2 was added to the reaction. Molecular iodine has been known as good catalyst or mediator in the C–N bond formation. To our delight, the 5-trifluoromethyl-1,2,4-triazole product **3b** was formed in 62% yield (Table 1, entry 1). The exact structure of the obtained 5-trifluoromethyl 1,2,4-triazole **3b** was unambiguously confirmed by single X-ray diffraction analysis (CCDC: 1940424).[17] Then, different basic additives were added into the first step of the reaction, and NaOAc could give the best outcome (Table 1, entries 2–5). The solvent effect was examined by the employment of various solvents, and the highest yield was observed with respect to DCE (Table 1, entries 6–11). Further optimization towards

Table 1. Optimization of reaction conditions.[a]



1b **2a** **3b**

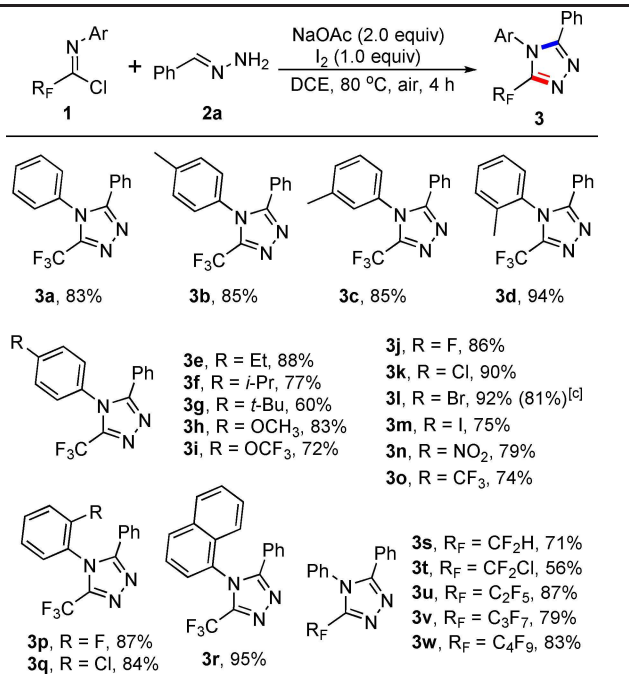
Entry	Additive. (equiv.)	Solvent (mL)	Temperature (°C)	Yield[b] (%)
1	–	DCE	80	62
2	Cs_2CO_3	DCE	80	69
3	K_2CO_3	DCE	80	74
4	**NaOAc**	**DCE**	**80**	**85**
5	NEt_3	DCE	80	trace
6	NaOAc	DMSO	80	48
7	NaOAc	toluene	80	ND
8	NaOAc	CH_3CN	80	trace
9	NaOAc	Dioxane	80	59
10	NaOAc	DMF	80	trace
11	NaOAc	MeOH	80	82
12	NaOAc	DCE	rt	47
13	NaOAc	DCE	60	71
14	NaOAc	DCE	100	55
15	NaOAc	DCE	80	45[c]
16	NaOAc	DCE	80	86[d]
17	NaOAc	DCE	80	0–45[e]

[a] Reaction conditions: **1b** (0.2 mmol), **2a** (0.4 mmol), and additive (2.0 equiv.) in solvent (2.0 mL) in seal tube under air at specified temperature for 3 h, then adding I_2 (0.2 mmol) for another 1 h.
[b] Isolated yields.
[c] 0.5 equiv. of I_2 was used.
[d] 1.5 equiv. of I_2 was used.
[e] The iodine was replaced with Lewis acids $FeCl_3$, CuI or Cu$(OTf)_2$. ND = No detection of the product.

the reaction temperature was implemented and the reaction was carried out at room temperature, 60 °C and 100 °C, respectively. The inferior results were obtained compared with that of 80 °C (Table 1, entries 12–14). Decreasing the amount of I_2 to 0.5 equivalent resulted in the decrease of reaction yield and a slight increase of the reaction efficiency could be achieved when 1.5 equivalents of I_2 was used in the second step (Table 1, entries 15–16). Given that the iodine could be served as Lewis acid to promote the reaction, we also investigated other Lewis acids ($FeCl_3$, CuI and Cu$(OTf)_2$) to replace iodine in the reaction. The results indicated that $FeCl_3$ or Cu$(OTf)_2$ could give the product in 37% or 45% yield and no reaction occurred in the presence of CuI (Table 1, entry 17).

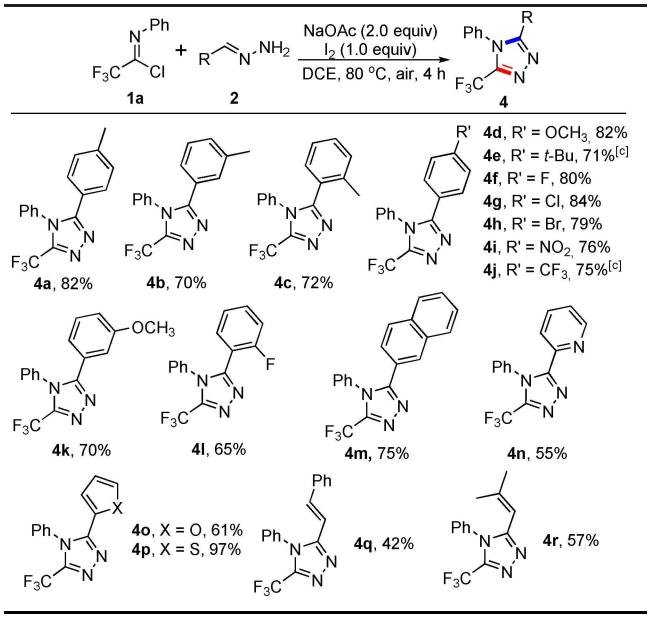
Having established the optimal reaction conditions, the generality and limitation of the protocol were examined (Table 2). In general, a range of *N*-aryl-trifluoroacetimidoyl chlorides bearing electron-donating or -withdrawing groups were subjected into the

Table 2. Scope of Fluorinated Imidoyl Chlorides.[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), and NaOAc (2.0 equiv.) in DCE (2.0 mL) under air at 80 °C for 3 h, and then adding I_2 (0.2 mmol) for another 1 h.
[b] Isolated yields.
[c] The reaction was performed on 3.5 mmol scale.

Table 3. Scope of Hydrazones Derived from Diverse Aldehydes.[a,b]

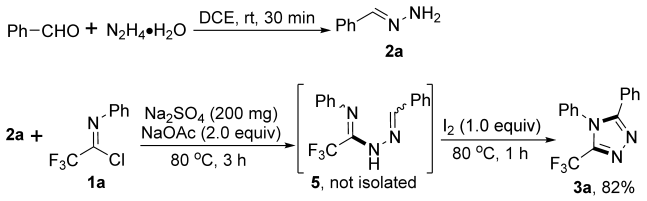


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), and NaOAc (2.0 equiv.) in DCE (2.0 mL) under air at 80 °C for 3 h, and then adding I_2 (0.2 mmol) for another 1 h.
[b] Isolated yields.
[c] MeOH was used as solvent.

standard conditions and good yields could be obtained in most cases (**3a–p**). Noteworthy was that steric hindrance (**3b–d**) and electronic factors (**3a–p**) of trifluoroacetimidoyl chlorides seemingly had a little influence on the transformation. The smooth tolerance of halogen atom (F, Cl, Br and I) at different substituted positions on the aryl ring provides the possibility for further derivatization through various coupling reactions (**3j–m**, **3p–q**). The transformation could be readily reproducible on a gram scale in 81% yield for product **3l**. More importantly, strong electron-withdrawing groups, such as $-NO_2$ and CF_3, were compatible with the reaction system to deliver the corresponding products (**3n–o**) with decent efficiency. Furthermore, the naphthalene group could be successfully incorporated into the 1,2,4-triazole product **3r** in excellent yield as well. It should be noted that other fluoroalkyl-1,2,4-triazoles (**3s–w**) could also be produced under the current reaction conditions by using the corresponding fluorinated imidoyl chlorides. Perhaps due to the unique properties of the CF_2X groups, the reaction failed to occur when the CF_2X groups were replaced with other groups. Unfortunately, the trifluoroacetimidoyl chlorides from heteroaryl amines could not be obtained and the trifluoroacetimidoyl chlorides from aliphatic amines did not participate in the reaction.

The scope of this transformation was further examined by the employment of a variety of hydrazones derived from different aldehyde (Table 3). Hydrazones attaching electron-donating and -withdrawing groups on the phenyl ring reacted smoothly with trifluoroacetimidoyl chloride **1a** to afford the relevant 5-trifluoromethyl-1,2,4-triazole products in moderate to good yields (**4a–l**). The orientation of substituents on the aromatic ring exerted a marginal effect on the reaction, as illustrated by the slightly decreased efficiency of *ortho* methyl substituted hydrazone (**4c**). Diverse halogenated substituents could be well tolerated, as well as several strong electron-withdrawing groups (**4f–j**). Notably, better results could be afforded by using MeOH as the solvent as for product **4e** and **4j**. The naphthalene attached 1,2,4-triazole **4m** could be furnished in 75% yield under the standard conditions.

Furthermore, hydrazone possessing heterocyclic skeletons, including pyridine, furan and thiophene, were also viable substrates to provide the target 1,2,4-triazoles in moderate to excellent yields (**4n–p**). It is worth mentioning that the obtained 1,2,4-triazole products **4n–p** have the great potential to be applied as bidentate ligands.[18] To our delight, 3-alkenyl substituted 1,2,4-triazole **4q** and **4r** could also be afforded in acceptable yield by the use of hydrazone from cinnamaldehyde and 3-methylbut-2-enal as the reac-

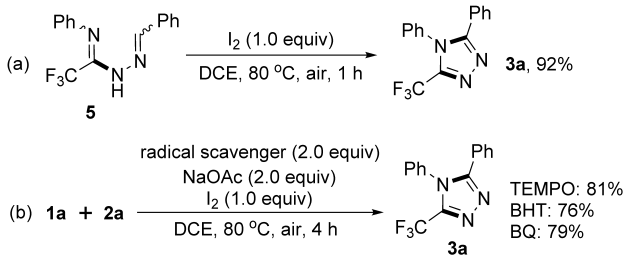


Scheme 2. One-pot Reaction.

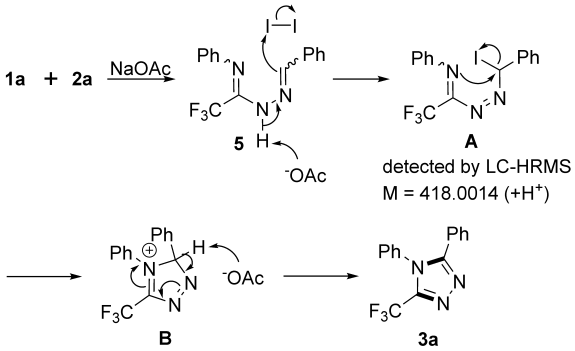
tant. Unfortunately, the hydrazones from aliphatic aldehydes failed to participate in the reaction, presumably due to their instability and tendency to be discomposed under the reaction conditions.

The protocol could be operated in a consecutive one-pot manner (Scheme 2). Initially, the reaction of benzaldehyde and hydrazine hydrate proceeded in DCE at room temperature for 30 minutes. Then, trifluoroacetimidoyl chloride **1a** was added to the mixture in the presence of anhydrous Na_2SO_4 and 2.0 equiv. of NaOAc. The reaction was conducted at 80 °C for 3 hours whereas the isolation of the coupling product **5** was not necessary due to the operation as one-pot reaction. Finally, 1.0 equiv. of I_2 was subjected into the reaction for another 1 hour and the target product **3a** could be attained in 82% overall yield.

The intermediate **5** was successfully isolated as a mixture of *cis*- and *trans*-isomer and subjected into the reaction in the presence of 1.0 equiv. of I_2 (Scheme 3a). Not surprisingly, the product **3a** could be delivered in 92% yield. The intermediate **5** could not be transformed into **3a** in the absence of iodine even though the reaction was conducted at elevated temperature. The result demonstrated the plausible intermediacy of compound **5**. In addition, a series of radical trapping experiments were conducted by the addition of radical scavenger of 2.0 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl), BHT (2,4-di-*tert*-butyl-4-methylphenol) and BQ (1,4-benzoquinone) into the second step of the standard conditions (Scheme 3b), but the reaction yield was not sharply decreased. Therefore, a single electron transfer (SET) process might not be involved in the reaction.



Scheme 3. Mechanistic Investigations.



Scheme 4. Plausible Reaction Mechanism.

On the basis of the results from the preliminary mechanistic investigations and in previous literatures,[19] a plausible reaction mechanism was proposed as depicted in Scheme 4. At first, the base-mediated C–N bond coupling of trifluoroacetimidoyl chloride **1a** and hydrazone **2a** gave the trifluoroacetamidine derivative **5**. This step could also occur in the absence of base.[7] Then, the base-promoted oxidative iodination of **5** led to an iodo species **A**, which was successfully detected by LC-HRMS. The intramolecular nucleophilic attack of nitrogen to the iodo-substituted carbon could generate intermediate **B**. Finally, the base-promoted deprotonation and rearomatization of **B** delivered the 5-trifluoromethyl-1,2,4-triazole product **3a**.

In conclusion, we have developed an expeditious and practical metal-free strategy for the assembly of 5-trifluoromethyl-1,2,4-triazole through C–N bond formation from readily available trifluoroacetimidoyl chlorides and hydrazones. Compared with the conventional multistep and tedious methods to access to perfluoroalkyl-1,2,4-triazoles, the current transformation features mild reaction conditions, simple operation, broad substrate scope and high efficiency, and can be easily scaled up to gram scale. The methodology provides a straightforward and environmentally benign pathway for the synthesis of trifluoromethyl-substituted *N*-heterocycles. Further studies toward extending the application of trifluoroacetimidoyl halides to construct more structurally diversified trifluoromethyl-substituted *N*-heterocycles are underway.

Experimental Section

Typical Procedure for the Synthesis of 5-Trifluoromethyl-1,2,4-Triazoles

NaOAc (32.8 mg, 0.4 mmol) were added to a solution of trifluoroacetimidoyl chloride **1** (0.2 mmol) and hydrazone **2** (0.4 mmol) in DCE (2 mL). The mixture was stirred at 80 °C

under air for 3 h. Then, I_2 (50.8 mg, 0.2 mmol) was added into the reaction for another 1 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature, quenched by water and extracted with ethyl acetate (3 × 15 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w) (2 × 15 mL), dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to provide a crude product, which was purified by column chromatography on silica gel with petroleum ether/EtOAc as eluent to afford the product 5-trifluoromethyl-1,2,4-triazoles.

Acknowledgements

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