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A Convenient $FeCl_3$-Mediated Synthesis of 5-Trifluoromethyl-1,2,4-triazoles from Trifluoroacetimidoyl Chlorides and Hydrazides

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Abstract. A low cost $FeCl_3$-mediated cascade annulation of trifluoroacetimidoyl chlorides and hydrazides for the efficient synthesis of 5-trifluoromethyl-1,2,4-triazoles has been developed. The transformation proceeds through a cascade base-promoted intermolecular C-N bond formation and $FeCl_3$-mediated intramolecular dehydration sequence under mild conditions. The protocol exhibits many notable features and can be readily scaled up to gram scale.

Keywords: trifluoroacetimidoyl chlorides; hydrazides; 5-trifluoromethyl-1,2,4-triazoles; cascade annulation reaction; *N*-heterocyclic compounds

1,2,4-Triazoles are identified as important heterocyclic scaffolds and have been widely applied in the biological and pharmaceutical fields, ligand chemistry as well as materials science.[1] Several commercial drugs contain 1,2,4-triazole motifs, such as maraviroc, trizaolam, sitagliptin, and deferasirox (Figure 1).[2] Considering the unique properties of fluorine atoms, the existence of trifluoromethyl or perfluoroalkyl groups could evidently improve the electronegaivity, bioavailability, metabolic stability and lipophilicity of the parent molecules.[3] Consequently, the exploration of efficient methods to the synthesis of trifluoromethyl-substituted 1,2,4-triazoles are of great significance and a series of synthetic approaches regarding these frameworks have been developed.

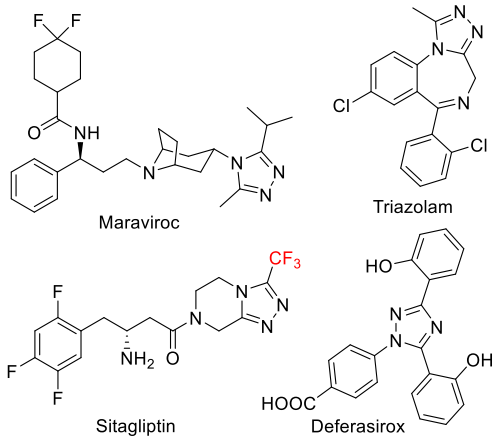

Figure 1. Selected Examples of Drugs Containing 1,2,4-Triazole Cores.

For instance, the reaction of 2,5-dichloro-1,1,1,6,6,6-hexafluoro-3,4-diazahexa-2,4-dienes or 3,5-bis(trifluoromethyl)-1,3,4-oxadiazoles with primary amines under diverse reaction conditions could afford 3,5-bis(trifluoromethyl)-1,2,4-triazoles which were reported by Tipping and Reitz (Scheme 1a).[4] Funabiki described a synthetic method of trifluoromethyl-substituted 1,2,4-triazoles, which involved the *in-situ* generation of 2,2,2-trifluoroacetohydrazide from the reaction of ethyl 2,2,2-trifluoroacetate with hydrazine hydrate and the subsequent cyclization with amidines (Scheme 1b).[5] The 5-trifluoromethylated 1,2,4-triazolium salts were obtained by multistep reactions of ethyl-(1,1,1-trifluoro-2-propylidene)carbazate with nitriles (Scheme 1c).[6] In addition, Vivona and Buscemi disclosed a hydrazinolysis reaction of 5-trifluoromethyl-1,2,4-oxadiazoles to prepare fluorinated 1,2,4-triazoles (Scheme 1d).[7] Several other synthetic pathways were also reported.[8] Although much progress had been gained in this field, most existing methods suffered from relatively harsh reaction conditions, tedious synthetic procedures, and narrow substrate scope. Pertinent to the present research, the development of general and convenient approach for the assembly of trifluoromethyl-decorated 1,2,4-triazoles is still highly desirable.

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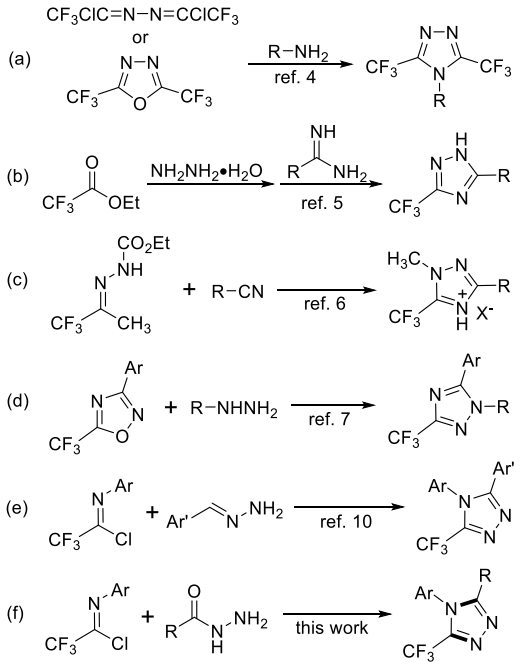
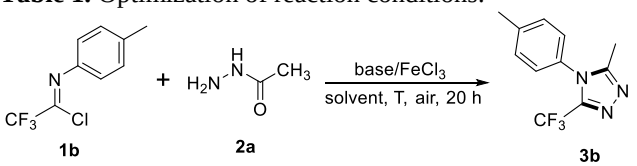


Scheme 1. Synthesis of Trifluoromethyl-Substituted 1,2,4-Triazole Derivatives.

In recent years, the synthetic protocol employing different trifluoromethyl synthons and suitable reactive partners has been emerged as a mainstream and attractive pathway to build trifluoromethyl-containing heterocyclic compounds. In this context, trifluoroacetimidoyl halides have been frequently applied as versatile building blocks in synthetic organofluorine chemistry.[9] Very recently, our group reported an iodine-mediated annulation reaction of trifluoroacetimidoyl chlorides and hydrazones to prepare a variety of 5-trifluoromethyl-1,2,4-triazoles in good yields (Scheme 1e).[10] Nevertheless, the hydrazones derived from aliphatic aldehydes were not applicable to the reaction, so 3-alkyl-fluorinated 1,2,4-triazoles could not be furnished. As a continuation of our ongoing research on the synthesis of trifluoromethyl-containing *N*-heterocycles,[10,11] we herein present an $FeCl_3$-mediated cascade annulation of trifluoroacetimidoyl chlorides and hydrazides to produce structurally diverse 5-trifluoromethyl-1,2,4-triazoles under mild conditions (Scheme 1f).

Table 1. Optimization of reaction conditions.[a]



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

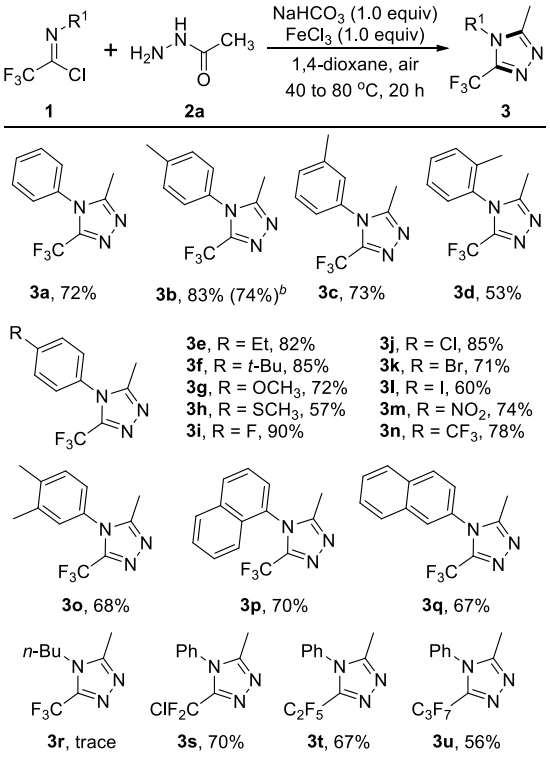
Entry	Base (equiv)	Solvent (mL)	Temperature (°C)	Yield[b] (%)
1	K_2CO_3	CH_3CN	80	45
2	K_2CO_3	THF	80	34
3	K_2CO_3	DCE	80	trace
4	K_2CO_3	DMF	80	ND
5	K_2CO_3	1,4-dioxane	80	59
6	NaOAc	1,4-dioxane	80	64
7	Na_2CO_3	1,4-dioxane	80	23
8	**$NaHCO_3$**	**1,4-dioxane**	**80**	**83**
9	K_3PO_4	1,4-dioxane	80	67
10	NEt_3	1,4-dioxane	80	44
11	$NaHCO_3$	1,4-dioxane	40	47
12	$NaHCO_3$	1,4-dioxane	100	79
13	$NaHCO_3$	1,4-dioxane	120	80
14	$NaHCO_3$	1,4-dioxane	80	trace-64[c]
15	$NaHCO_3$	1,4-dioxane	80	46[d]
16	$NaHCO_3$	1,4-dioxane	80	68[e]

[a] Reaction conditions: **1b** (0.3 mmol), **2a** (0.45 mmol), 4 Å MS (40 mg) and base (1.0 equiv) in solvent (2.0 mL) under air at 40 °C for 12 h, and then adding $FeCl_3$ (0.3 mmol) at specified temperature for 8 h.
[b] Isolated yields.
[c] The $FeCl_3$ was replaced with $Fe(OTf)_3$ (53%), $Cu(OTf)_2$ (64%), $Sc(OTf)_3$ (trace) or I_2 (15%), respectively.
[d] 0.5 equiv of $FeCl_3$ was used.
[e] 1.5 equiv of $FeCl_3$ was used. ND = No detection of the product.

Initially, 2,2,2-trifluoro-*N*-(*p*-tolyl)acetimidoyl chloride **1b** and acetohydrazide **2a** were used as the model substrates to optimize the reaction conditions. Noteworthy was that the trifluoroacetimidoyl chlorides could be easily obtained from the reaction of the parent amine with trifluoroacetic acid, CCl_4 and PPh_3.[12] The reaction proceeded smoothly with **1b** and **2a** in the presence of 1.0 equiv. of K_2CO_3 and 4 Å MS in CH_3CN at 40 °C for 12 h, and then 1.0 equiv $FeCl_3$ was added to the reaction at elevated 80 °C for another 8 h. To our delight, the desired product **3b** was delivered in 45% yield (Table 1, entry 1). Then, a range of solvents were surveyed in the transformation and 1,4-dioxane could afford the highest yield (Table 1, entries 2-5). The choice of additive was important for the transformation, and different basic additives were added into the reaction, including NaOAc, Na_2CO_3, $NaHCO_3$, K_3PO_4, and NEt_3. The result showed $NaHCO_3$ could render the best reactivity (Table 1, entries 6-10). Further examination towards reaction temperature demonstrated that the low temperature was detrimental to the reaction and the elevated temperature had a marginal influence on the reaction with the slight decrease of the reaction efficiency (Table 1, entries 11-13). Other Lewis acids, such as $Fe(OTf)_3$, $Cu(OTf)_2$, $Sc(OTf)_3$, and molecular iodine, were also tested in the transformation and their reactivity was all inferior to that of $FeCl_3$ (Table 1, entry 14). Notably, reducing or increasing the amount loading of $FeCl_3$ in the second step could result in the decline of the reaction yield (Table 1, entries 15-16).

With the optimized conditions in hand, we began to investigate the scope and limitation of the annulation reaction using a wide range of trifluoroacetimidoyl chlorides (Table 2). Diverse *N*-aryltrifluoroacetimidoyl chlorides bearing electron-donating or -withdrawing groups could react smoothly with acetohydrazide **2a** to give rise to the corresponding 5-trifluoromethyl-1,2,4-triazole products in good to excellent yields in most cases (**3a-o**). Of note, the steric hindrance of trifluoroacetimidoyl chlorides exerted an obvious effect on the reaction, as demonstrated by the gradually decrease of the reaction yields of products **3b-d**. Meanwhile, the electron factors seemingly had a marginal impact on the transformation (**3a-o**). The protocol could be easily scaled up to 2 mmol scale for product **3b** without any difficulty. The compatibility of the protocol was further proved by the good tolerance of halogen atoms and strong electron-withdrawing groups (**3i-l**). The trifluoroacetimidoyl chlorides bearing naphthalene ring were also suitable for the current reaction conditions to furnish the desired 1,2,4-triazole products in 67-70% yields (**3p-q**) Unfortunately, the trifluoroacetimidoyl chloride from aliphatic amine was not applicable to the reaction system and only trace of product **3r** was observed, probably due to the instability of the *N*-arylltrifluoroacetimidoyl chloride. The reaction was amendable to several other fluorinated imidoyl chlorides, as illustrated that diverse fluoroalkyl groups, including CF_2Cl, C_2F_5 and C_3F_7, could be successfully incorporated into the 1,2,4-triazole core in moderate to good yields (**3s-u**).

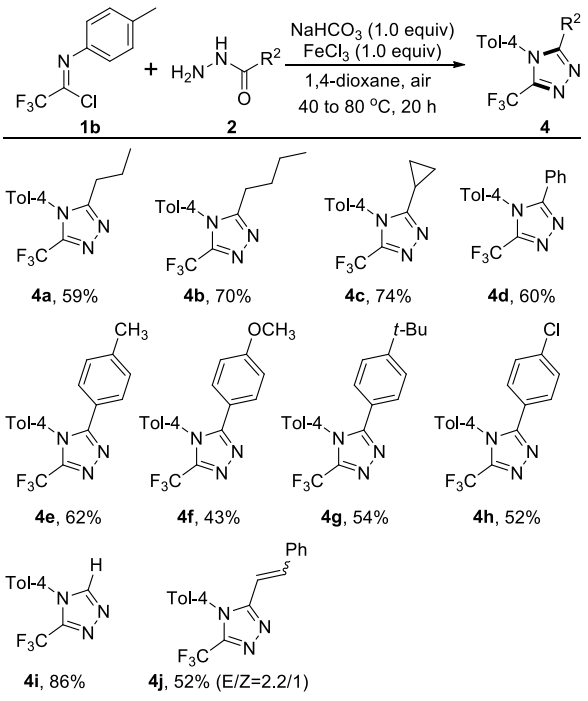
Table 2. Scope of Trifluoroacetimidoyl Chlorides.[a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), 4 Å MS (40 mg) and $NaHCO_3$ (1.0 equiv) in 1,4-dioxane (2.0 mL) under air at 40 °C for 12 h, and then adding $FeCl_3$ (0.3 mmol) at 80 °C for another 8 h, isolated yields.
[b] The reaction was performed on 2 mmol scale.

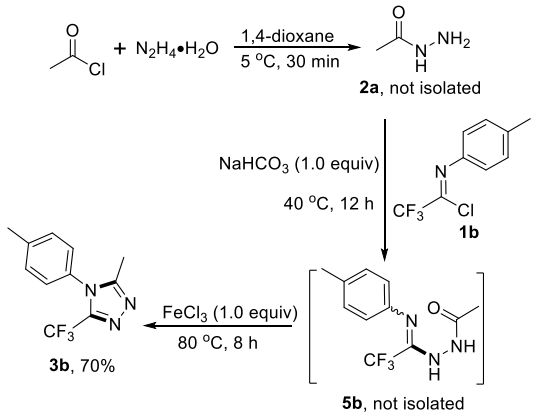
After examination of the scope of fluorinated imidoyl chlorides, the generality of the protocol was further evaluated by surveying diverse hydrazides (Table 3). Different alkyl substituted hydrazides reacted smoothly with trifluoroacetimidoyl chloride **1b** to build the desired 1,2,4-triazole products in moderate to good yields (**4a-c**). With respect to arylhydrazides, the transformation proceeded well to lead to the desired 2-aryl substituted 1,2,4-triazoles **4d-h** in acceptable yields in the presence of 0.5 equiv $FeCl_3$. The inferior yields of arylhydrazides presumably resulted from the reduced reactivity of amino group and carbonyl group of the arylhydrazides due to the conjugation effect of aryl ring. When formohydrazide was used as substrate, 4-(*p*-tolyl)-3-(trifluoromethyl)-4*H*-1,2,4-triazole **4i** was successfully furnished as desired product in 86% yield. Noteworthy was that cinnamohydrazide was also compatible with the optimized conditions, providing the targeted 3-alkenyl-1,2,4-triazole **4j** in 52% yield as a mixture of E/Z isomers.

Table 3. Scope of Hydrazides.[a]



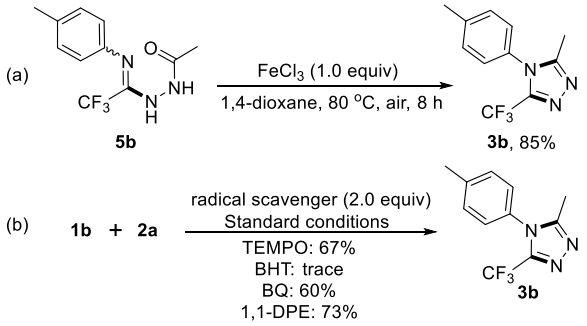
[a] Reaction conditions: **1b** (0.3 mmol), **2** (0.45 mmol), 4 Å MS (40 mg) and $NaHCO_3$ (1.0 equiv) in 1,4-dioxane (2.0 mL) under air at 40 °C for 12 h, and then adding $FeCl_3$ (0.3 mmol for **4a-c**, **4i-j**; 0.15 mmol for **4d-h**) at 80 °C for another 8 h, isolated yields.

The reaction could be operated in a consecutive one-pot manner as well (Scheme 2). At first, the reaction of acetylchloride and hydrazine hydrate was performed in 1,4-dioxane at 5 °C for 30 minutes. Then, trifluoroacetimidoyl chloride **1b** was added to the mixture in the presence of 1.0 equiv of $NaHCO_3$. The reaction was conducted at 40 °C for 12 hours and then the coupling product **5b** was formed and unnecessary to be isolated. Finally, 1.0 equiv of $FeCl_3$ was subjected into the mixture for another 8 hours at 80 °C and the desired 1,2,4-triazole product **3b** could be isolated in 70% overall yield.



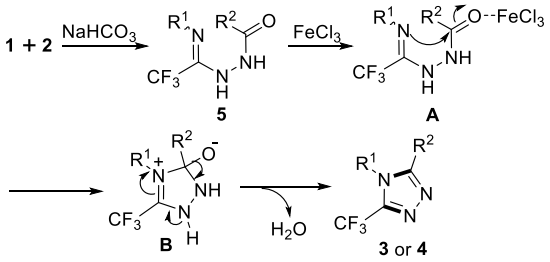
Scheme 2. One-pot Reaction.

Several control experiments were preformed to gain some understanding of the reaction mechanism (Scheme 3). We successfully synthesized the coupling product **5b** from trifluoroacetimidoyl chloride **1b** and acetohydrazide **2a** and subjected it into the reaction in the presence of 1.0 equiv of $FeCl_3$. Expectedly, the desired product **3b** could be obtained in 85% yield, which illustrated that compound **5b** possibly acted as the reaction intermediate (Scheme 3a). The radical trapping experiments were carried out by the addition of 2.0 equiv. of radical scavengers. The yield was reduced to 67% when TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) was added into the reaction and trace of product was detected with regard to BHT (2,4-di-*tert*-butyl-4-methylphenol). Other radical scavengers, such as BQ (benzoquinone) and 1,1-DPE (1,1-diphenylethylene), enabled the formation of product **3b** in 60 and 73% yield, respectively (Scheme 3b). It was speculated that the reaction did not proceed through a single electron transfer (SET) process.



Scheme 3. Mechanistic Investigations.

Based on the results from the mechanistic investigations and in previous literatures,[10,13] a plausible reaction mechanism was proposed as depicted in Scheme 4. Initially, the base-mediated C-N bond coupling of trifluoroacetimidoyl chloride **1** with hydrazide **2** generated amidine derivative **5**. Then, the coordination of Lewis acid $FeCl_3$ to **5** formed the complex **A** with the activation of carbonyl group. The intramolecular nucleophilic attack of nitrogen to the activated carbonyl group led to intermediate **B**, followed by the subsequent dehydration process to deliver the 5-trifluoromethyl-1,2,4-triazole product.



Scheme 4. Plausible Reaction Mechanism.

In conclusion, we have developed a facile approach for the synthesis of 5-trifluoromethyl-1,2,4-triazoles through $FeCl_3$-mediated cascade annulation of trifluoroacetimidoyl chlorides and hydrazides. Notable features of the protocol include relatively mild reaction conditions, low cost iron mediator, simple operation, broad substrate scope and scalability. The transformation offers a complementary route to the expeditious construction of 5-trifluoromethyl-1,2,4-triazole derivatives. Further investigations toward the broader application of trifluoroacetimidoyl halides are underway.

Experimental Section

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

$NaHCO_3$ (25.2 mg, 0.3 mmol) and 4 Å MS (40 mg) were added to a solution of substrate **1** (0.3 mmol) and **2** (0.45 mmol) in 1,4-dioxane (2 mL). The

mixture was stirred at 40 °C under air for 12 h. Then, $FeCl_3$ (48.7 mg, 0.3 mmol) was added into the reaction at 80 °C for another 8 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 x 15 mL). The extract was 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 5-trifluoromethyl-1,2,4-triazole products **3** or **4**.

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UPDATE

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