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A catalyst-free method for the synthesis of 1,4,2-dithiazoles from isothiocyanates and hydroxylamine triflic acid salts†

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A catalyst-free method for the preparation of 1,4,2-dithiazoles is developed by reactions of isothiocyanates with hydroxylamine triflic acid salts. This reaction achieves C–S, C–N, and S–N bond formation, and a range of products are obtained in moderate to good yields. The obvious feature is using shelf-stable hydroxylamine triflic acid salts as a N source to synthesize heterocycles under mild conditions.

Dithiazoles, as five-membered heterocycles with nitrogen and two sulfur atoms, have attracted considerable attention because of their frequent appearance in a large number of natural products and biologically active molecules.[1] Furthermore, these molecules (1,2,3-, 1,2,4-, and 1,4,2-dithiazoles) often exhibit a broad spectrum of biological activities, such as antitubercular,[2] antifungal,[3] and anticancer activities (Fig. 1).[4] Particularly, 1,4,2-dithiazole analogues have also been proved to be useful for the treatment of cancer[5a] and identified as novel inhibitors of West Nile virus (WNV) replication.[5b]

Despite the promising applications, 1,4,2-dithiazoles still are rare skeletons with limited reports on their synthesis methods.[6] In 1998, Mloston[7] described a fast [3 + 2] cycloaddition of the fluorinated thione *S*-imide with aromatic thioketones for the synthesis of 1,4,2-dithiazolidines. In 2007, Yadav[8] reported an approach to produce 1,4,2-dithiazole-fused heterocycles through cyclization reaction of (methylsulfinyl) methyl carbamimidothioates. Recently, Shao[9] disclosed a novel synthetic methodology to generate 1,4,2-dithiazoles by reactions of phenylthioureas with 1,1-dichloro-2-nitroethene. Although some methods toward 1,4,2-dithiazoles were successfully developed, almost all strategies for producing these products required unavailable starting materials, multiple steps, and harsh reaction conditions. Therefore, the synthesis of 1,4,2-dithiazoles with simple substrates is still challenging and attractive.

Hydroxylamine triflic acid salts have recently emerged as an NH_2 or NH source to achieve C–H amination of arenes, difunctionalization of alkenes, thiol amino-oxidation, and sulfur imidation (Scheme 1). In recent years, Morandi,[10] Jiao,[11] Ritter,[12] and Falck[13] successively described direct radical aromatic amination reactions using hydroxylamine triflic acid salts as aminating reagents. Morandi[14] also reported some general strategies to access amines through iron-catalyzed difunctionalization of alkenes. In 2021, Morandi[15] designed an iron-catalyzed reaction for the selective amino-oxidation of thiols to unprotected sulfinamides. Bolm[16] discovered an iron-catalyzed synthesis of NH sulfoximines from sulfoxides and arylhydroxylamine triflic acid. However, using hydroxylamine triflic acid salts as a N source to construct heterocyclic compounds is less studied. Herein, we report a novel and facile procedure to build *N*-phenyl-5-(phenylimino)-1,4,2-dithiazol-3-amines from isothiocyanates and $[MsONH_3]OTf$ under catalyst- and additive-free conditions.

In recent years, hexafluoroisopropanol (HFIP) has received increasing attention as a catalyst, solvent, or co-solvent in

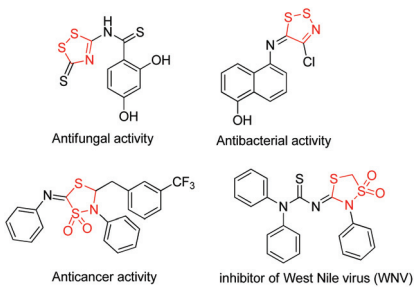

Fig. 1 Bioactive compounds containing dithiazoles.

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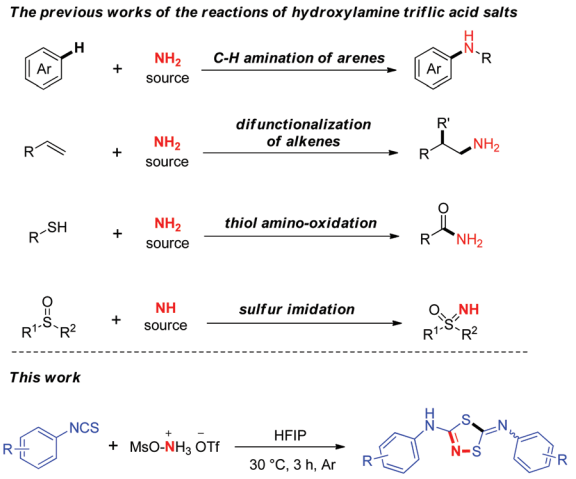
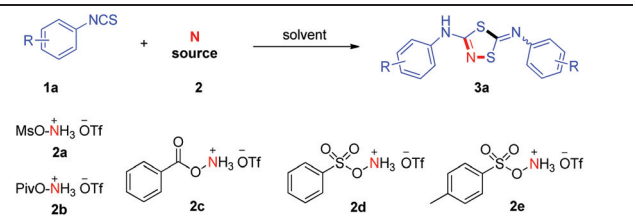


Scheme 1 Reactions of hydroxylamine triflic acid salts.

organic synthesis owing to its unique features.[17] So, our initial efforts were focused on the reaction of isothiocyanatobenzene **1a** with [MsONH$_3$]OTf **2a** using HFIP as a solvent under argon. The desired product **3a** was obtained in 56% yield (Table 1, entry 1). Subsequently, several analogous hydroxylamine triflic acid salts were examined and [MsONH$_3$]OTf **2a** was proved to be the most effective hydroxylamine triflic acid salt (Table 1, entries 2–5). Further optimization of solvents showed that

Table 1 Optimization of the reaction conditions[a]



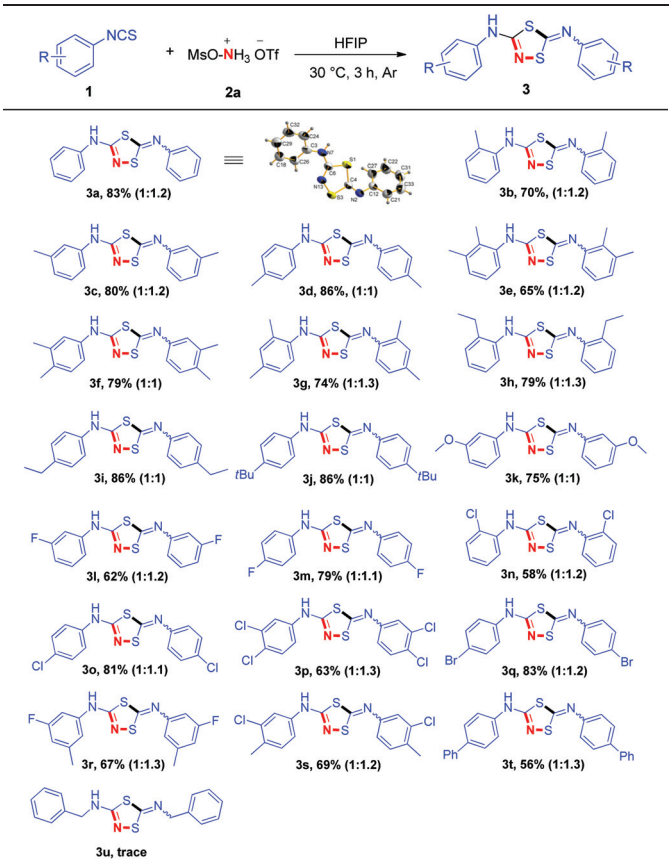
Entry	**N** source	Solvent	Temp. (°C)	Yield[b] (%)
1	**2a** (0.7)	HFIP	60	56
2	**2b** (0.7)	HFIP	60	35
3	**2c** (0.7)	HFIP	60	42
4	**2d** (0.7)	HFIP	60	38
5	**2e** (0.7)	HFIP	60	n.d.[c]
6	**2a** (0.7)	TFE	60	n.d.
7	**2a** (0.7)	MeCN	60	n.d.
8	**2a** (0.7)	EtOH	60	n.d.
9	**2a** (0.7)	DCM	60	n.d.
10	**2a** (0.7)	THF	60	n.d.
11	**2a** (0.7)	HFIP	20	69
12	**2a (0.7)**	**HFIP**	**30**	**83**
13	**2a** (0.7)	HFIP	100	Trace
14	**2a** (0.5)	HFIP	30	71
15	**2a** (1.5)	HFIP	30	38
16[d]	**2a** (0.7)	HFIP	30	76

[a] Reaction conditions: **1a** (0.2 mmol), N source, and solvent (2 mL) under argon for 3 h. [b] Isolated yield. [c] n.d. = not detected. [d] Under air. TFE = 2,2,2-trifluoroethanol. The entry in bold highlights the optimized reaction conditions, and the reaction time was monitored by TLC.

when TFE, MeCN, EtOH, DCM, and THF were used as solvents, no desired product was detected (Table 1, entries 6–10). The results indicated that HFIP was crucial for this process because HFIP might form radical species.[18] A screen of temperature indicated that 30 °C was superior to others, giving product **3a** in 83% yield (Table 1, entries 11–13). It was found that an adjustment of the amount of **2a** led to lower yields (Table 1, entries 14 and 15). Moreover, air conditions generated **3a** in a slightly lower yield (Table 1, entry 16). So, the optimized reaction system was established as shown in Table 1, entry 12.

With the optimized reaction conditions in hand, we first examined the scope of isothiocyanatobenzenes. As shown in Table 2, a variety of electron-donating and electron-withdrawing group-substituted isothiocyanatobenzenes were efficiently engaged in this reaction to provide various 1,4,2-dithiazoles in moderate to good yields. This reaction had no obvious steric effect of the substituents, and the *ortho*-, *meta*-, and *para*-methylphenyl-substituted 1,4,2-dithiazoles (**3b**, **3c**, and **3d**) were afforded in 70%, 80%, and 86% yields, respectively. Dimethyl-substituted isothiocyanatobenzenes **1e–1g** produced the corresponding products **3e–3g** in 65%–79% yields under

Table 2 Scope of substituted isothiocyanatobenzenes[a]

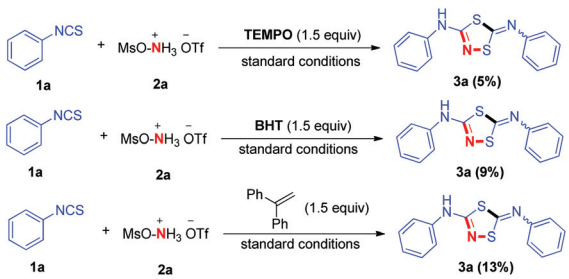


[a] Reaction conditions: **1** (0.20 mmol) and **2a** (0.14 mmol) in HFIP (2 mL) at 30 °C under argon for 3 h. The ratio was determined by ^{1}H NMR analysis.

the standard conditions. On the other hand, halogen substituents (F, Cl, and Br) on the aromatic ring were well tolerated, furnishing **3l–3q** in moderate yields. In addition, substrates **1r** and **1s** bearing 3-fluoro-5-methyl and 3-chloro-4-methyl groups gave products **3r** and **3s** in 67% and 69% yields, respectively. Substrate **1t** could successfully be converted into the desired product **3t**, albeit with a diminished yield. Unfortunately, the use of (isothiocyanatomethyl)benzene **1u** led to a trace amount of the desired product.

To gain insight into the mechanism, several control experiments were carried out, as shown in Scheme 2. Radical scavengers TEMPO (2,2,6,6,-tetramethylpiperidinooxy) and BHT (2,6-di-*tert*-butyl-4-methyl-phenol) were tested for this transformation, and the product **3a** was obtained in 5% and 9% yields, respectively. In addition, when 1,1-diphenylethylene was added under the standard conditions, the product **3a** was obtained in 13% yield. Moreover, an electron paramagnetic resonance (EPR) experiment was performed using 5,5-dimethy-1-pyrroline-*N*-oxide (DMPO) as a radical probe. As shown in Fig. 2, some radical signals were detected after a reaction mixture of **1a** and **2a** in HFIP was stirred at ambient temperature for 5 min in the presence of DMPO. These results indicated that the reactions involved radical-mediated pathways.

On the basis of the above results and literature reports, a possible mechanism is proposed, as shown in Scheme 3.[10–12,19] Initially, HFIP promotes the decomposition of [MsONH$_3$]OTf to generate MsOH and ammoniumyl radical **A**. The reaction of ammoniumyl radical **A** with isothiocyanatobenzene **1a** leads to intermediate **B**, which undergoes isomerization to give intermediate **C**. Subsequently, intermediate **C** reacts with another isothiocyanatobenzene to form intermediate **D**. Intermediate **E**, which is generated from intermediate **D** *via* a resonated procedure, can be transformed into intermediate **F** through intramolecular radical cyclization addition. Finally, intermediate **G**, which is formed by the oxidation of MsO· to intermediate **F**, produces the product **3a** by the elimination of a proton.



Scheme 2 Control experiments.

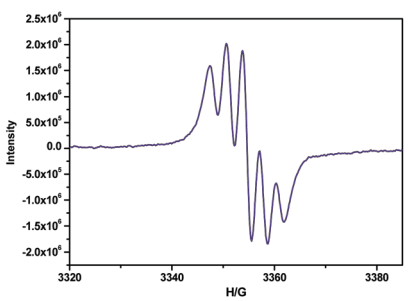
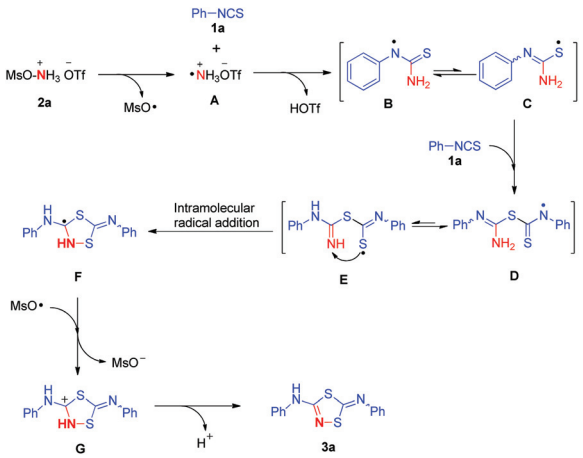


Fig. 2 EPR experiment using **1a** (1.0 equiv.) and **2a** (0.7 equiv.) in HFIP (2 mL) in the presence of DMPO (2.0 equiv.).



Scheme 3 Proposed mechanism.

In conclusion, we have developed a method for the synthesis of 1,4,2-dithiazole derivatives *via* the cyclization reaction of isothiocyanates with hydroxylamine triflic acid salts. The features of our presented methodology are mild reaction conditions and catalyst-free, additive-free, and simple operation. This transformation presents good functional group tolerance, and a series of *N*-phenyl-5-(phenylimino)-1,4,2-dithiazol-3-amines are obtained in moderate to good yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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