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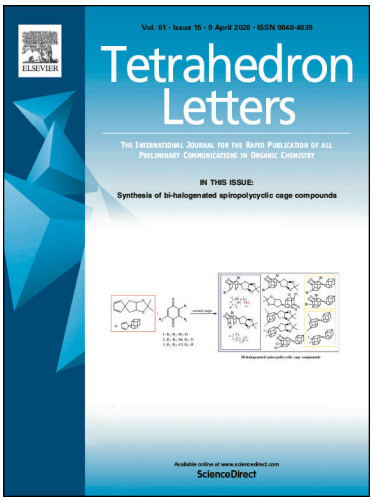

Trifluoromethylthiolation and Trifluoromethanesulfonylation of β,γ-Unsaturated Hydrazones

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Graphical Abstract

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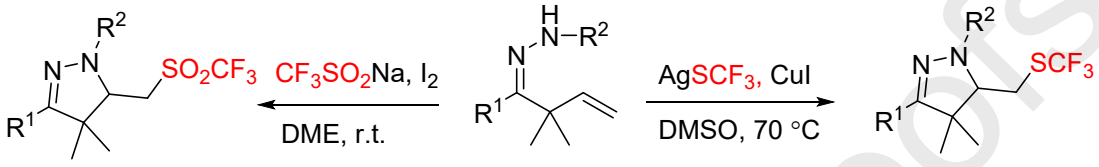

4

8 examples
43-63% yield

1

R^1 = Aryl, Alkyl
R^2 = Aryl

3

24 examples
32-81% yield

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Trifluoromethylthiolation and Trifluoromethanesulfonylation of β,γ-Unsaturated Hydrazones

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ABSTRACT

The trifluoromethylthiolation and trifluoromethanesulfonylation of β,γ-unsaturated hydrazones was accomplished with silver(I) trifluoromethanethiolate ($AgSCF_3$) as a CF_3S source and sodium trifluoromethylsulfinate (CF_3SO_2Na) as a CF_3SO_2 source, respectively. These general methods for the preparation of dihydropyrazoles containing CF_3S or CF_3SO_2 groups were characterized by mild reaction conditions and good functional group tolerance.

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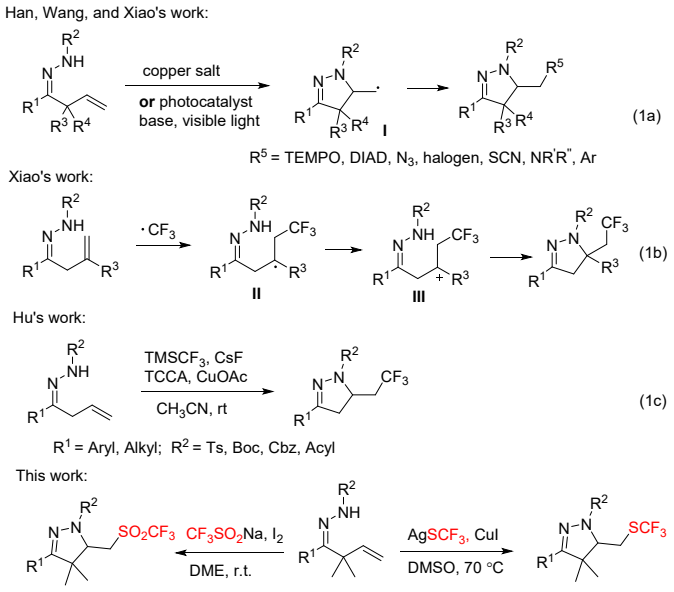
Fluorine-containing compounds are useful in applications as agrochemicals, pharmaceuticals and materials due to their significantly enhanced properties such as high thermal and oxidative stability, lipophilicity, metabolic stability, and improved bioactivities comparing to their non-fluorinated analogues.[1] Therefore, compounds containing trifluoromethylthio (CF_3S)[2] or trifluoromethanesulfonyl (CF_3SO_2)[3] groups have attracted significant attention due to their extremely high lipophilicity and electron-withdrawing properties. During the past decades, significant progress has been achieved in the formation of these compounds through direct trifluoromethylthiolation or trifluoromethanesulfonylation, and the trifluoromethylation of sulfur-containing compounds. Dihydropyrazole derivatives have been widely recognized for their remarkable biological activities and are widely found in Nature. They are also important intermediates in organic synthesis.[4] The direct cyclization/difunctionalization of β,γ-unsaturated hydrazones represents an attractive method for the synthesis of diversely functionalized dihydropyrazole compounds. Representative studies have been reported by Han, Wang and Xiao (Scheme 1a).[5] In the presence of copper salts, β,γ-unsaturated hydrazones can undergo rapid 5-exo-trig cyclization to give the corresponding C-centered radical **I**, which could be trapped by radical acceptors such as azides, halogens, thiocyanates and amines.[6] Xiao and co-workers have developed an efficient and mild strategy for generating free radical intermediates **I** using photocatalysts and bases under visible light (Scheme 1a).[7] They also discovered that under photocatalysis, Umemoto's reagent can act as a CF_3 source to react with β,γ-unsaturated hydrazones to produce the radical intermediate **II**, which was then further oxidized to carbocation intermediate **III**. The final cyclization afforded trifluoromethylated dihydropyrazoles (Scheme 1b).[8] Hu and co-workers also implemented the construction of trifluoromethylated dihydropyrazoles using the Ruppert-Prakash reagent as the CF_3 source and TCCA as a promoter (Scheme 1c).[9]



Scheme 1. Synthesis of functionalized dihydropyrazole compounds *via* β,γ-unsaturated hydrazones.

Considering the unique characteristics of CF_3S/CF_3SO_2 groups, herein, we report the cascade cyclization and trifluoromethylthiolation/trifluoromethanesulfonylation of β,γ-

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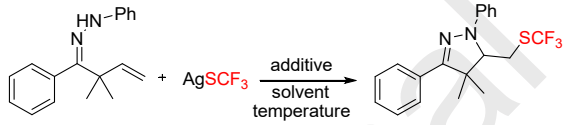
substituted dihydropyrazole derivatives.

Firstly, the trifluoromethylthiolation of β,γ-unsaturated hydrazones was investigated with $AgSCF_3$ as a CF_3S source. When a mixture of *N*-phenyl-β,γ-unsaturated hydrazone **1a** (0.1 mmol), $AgSCF_3$ (2.0 equiv.) and $Cu(OAc)_2$ (0.2 equiv.) in DMSO (1.0 mL) was stirred at 80 °C for 12 h, the expected cascade trifluoromethylthiolation/cyclization afforded the desired product **3a** in 33% yield (Table 1, entry 1). The reaction conditions were then further optimized. To explore the capacity of copper catalysts in this reaction, several copper salts including $Cu(BF_4)_2$, $CuCl_2$, $CuSO_4$, CuBr, CuCN, CuSCN, CuCl and CuI (Entries 2-9) were tested. The copper salts with different valences were all effective, and CuI gave the best yield (38%, entry 9). The yield could be slightly improved to 53% by decreasing the reaction time from 12 h to 4 h (Entries 10-12). DMSO was proved to be the only suitable solvent for the reaction; none of the desired product **3a** was detected when the reaction was carried out with other solvents, such as CH_2Cl_2, DMF, THF, and NMP (Entries 13-16). Further investigation of the reaction temperature revealed that 70 °C was optimal giving **3a** in 75% yield (Entries 17-18).

With the optimal reaction conditions (Table 1, entry 18) in hand, the scope of the substrates was then explored (Table 2). A series of β,γ-unsaturated hydrazones were reacted with $AgSCF_3$ to give the corresponding CF_3S-containing dihydropyrazole products. Aryl-substituted substrates with electron-donating (MeO, Me, phenyl and isopropyl) or electron-withdrawing (F, Cl, Br, I and CF_3) groups at the *para*- and *meta*- positions of the benzene ring gave the desired CF_3S-containing dihydropyrazoles **3b-j** and **3k-o**, respectively, in good yields. Moreover, naphthyl and heterocycle substituted unsaturated hydrazones were applicable in this transformation, giving the corresponding products **3p, 3q** and **3r** in 58%, 65% and 52% yield, respectively.

Table 1. Optimization of the reaction conditions for the trifluoromethylthiolation of **1a** with $AgSCF_3$.[a]

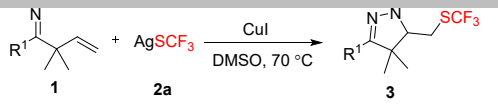


1a **2a** **3a**

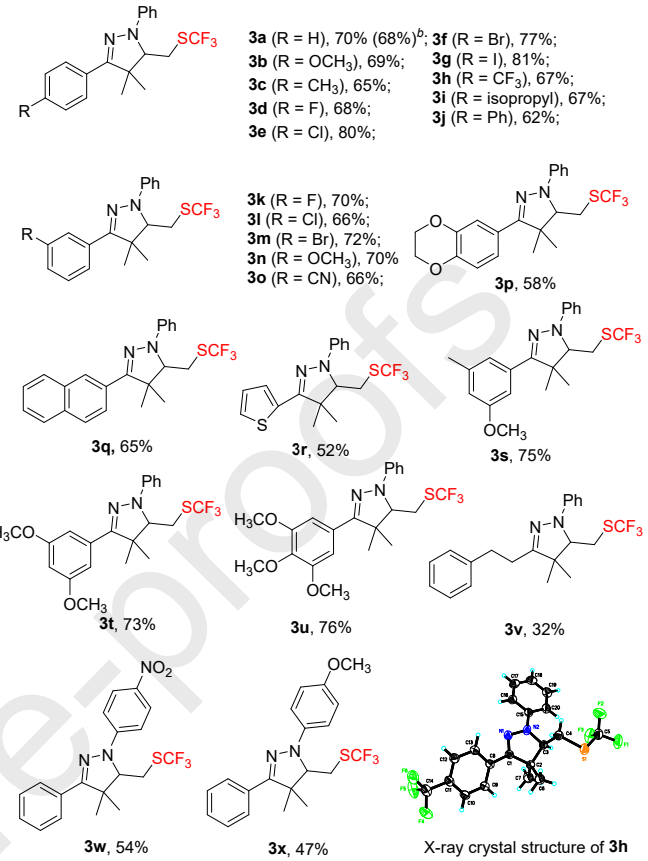
Entry	Additive	Solvent	Temp (°C)	Time (h)	Yield **3a** (%)[b]
1	$Cu(OAc)_2$	DMSO	80	12	33
2	$Cu(BF_4)_2$	DMSO	80	12	0
3	$CuCl_2$	DMSO	80	12	14
4	$CuSO_4$	DMSO	80	12	15
5	CuBr	DMSO	80	12	3
6	CuCN	DMSO	80	12	15
7	CuSCN	DMSO	80	12	16
8	CuCl	DMSO	80	12	17
9	CuI	DMSO	80	12	38
10	CuI	DMSO	80	2	45
11	CuI	DMSO	80	4	53
12	CuI	DMSO	80	6	42
13	CuI	CH_2Cl_2	80	4	0
14	CuI	DMF	80	4	0
15	CuI	THF	80	4	0
16	CuI	NMP	80	4	0
17	CuI	DMSO	60	4	69
18	CuI	DMSO	70	4	75

[a] Reagents and conditions: **1a** (0.1 mmol), $AgSCF_3$ (0.2 mmol), additive (0.02 mmol), solvent (1.0 mL), time, temperature, under N_2. [b] Yield determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard.

Table 2. Substrate scope for the trifluoromethylthiolation of β,γ-unsaturated hydrazones.[a]



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



[a] Reagents and conditions: **1** (0.2 mmol), $AgSCF_3$ (0.4 mmol), CuI (0.04 mmol), dry DMSO (2.0 mL), 70 °C, under N_2, 4 h, isolated yield. [b] 2.0 mmol scale.

β,γ-Unsaturated hydrazones with multiple substitutions on the benzene ring also afforded the corresponding products **3s-u** in good yields. However, aliphatic substituted β,γ-unsaturated hydrazone **1v** was not suitable and gave the desired product **3v** in low yield (32%). Substituents such as *p*-NO_2 and *p*-MeO on the aromatic hydrazines gave the corresponding products **3w** and **3x** in moderate yields of 54% and 47%, respectively. Unfortunately, *N*-acetyl hydrazones without two methyl groups in the allylic position[10] were incompatible with this transformation. Encouraged by the above results, we increased the scale of the reaction from 0.2 mmol to 2.0 mmol, and the isolated yield of dihydropyrazole **3a** remained high (68%). The structure of CF_3S-containing dihydropyrazole **3h** was unambiguously established by X-ray diffraction studies.[11]

Because of CF_3SO_2-containing compounds are highly interesting, oxidation of the CF_3S group to the CF_3SO_2 group was then tested. However, none of the desired product was isolated with CF_3S-containing dihydropyrazole **3a** as a substrate under different oxidation conditions including H_2O_2, H_5IO_6 and *m*-CPBA, which may due to the low stability of **3a** under oxidative conditions. In 2016, an iodine-mediated trifluoromethanesulfonylation of styrenes with sodium trifluoromethylsulfinate (CF_3SO_2Na) was developed in our group.[12] Under these conditions the CF_3SO_2-containing dihydropyrazole **4a** was detected in 30% yield (Table 3). Then the reaction conditions including iodine source, solvent, reaction temperature and time were further optimized, and the highest yield (65%) was achieved using 3.0 equiv. of CF_3SO_2Na, 4.0 equiv. of I_2 and glycol dimethyl ether (DME) as the solvent at 25 °C for 15 min (Table 3, entry 16). The generality of this trifluoromethanesulfonylation reaction was subsequently

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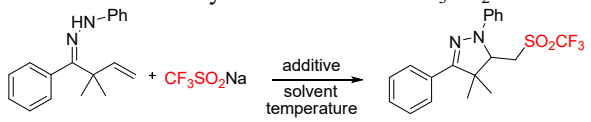
substituents on the benzene ring including electron-donating groups (Me, MeO) and electron-withdrawing groups (Cl, CN) gave products **4a-h** in moderate yields. A disadvantage of the direct introduction of CF_3SO_2 is that the substrate scope is not as broad as for trifluoromethylthiolation, which may due to the relatively lower stability of CF_3SO_2-containing dihydropyrazoles.

Table 3. Optimization of the reaction conditions for the trifluoromethanesulfonylation of **1a** with CF_3SO_2Na.[a]

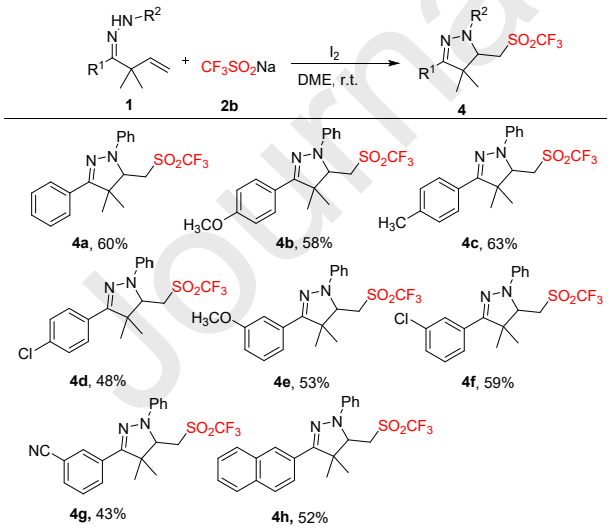


1a **2b** **4a**

Entry	Additive	Solvent	Temp (°C)	Time	Yield **4a** (%)[b]
1	I_2	CH_3CN	25	2 h	30
2	-	CH_3CN	25	2 h	0
3	NIS	CH_3CN	25	2 h	0
4	TBAI	CH_3CN	25	2 h	20
5	I_2	DMSO	25	2 h	8
6	I_2	THF	25	2 h	12
7	I_2	CH_2Cl_2	25	2 h	6
8	I_2	*t*-BuOH	25	2 h	3
9	I_2	DMF	25	2 h	10
10	I_2	DME	25	2 h	46
11	I_2	DME	40	2 h	36
12	I_2	DME	10	2 h	28
13	I_2	DME	25	1 h	50
14	I_2	DME	25	30	50
15	I_2	DME	25	10	48
16[c]	I_2	DME	25	15	65

[a] Reagents and conditions: **1** (0.1 mmol), CF_3SO_2Na (0.3 mmol), additive (0.3 mmol), solvent (1.0 mL), time, temperature. [b] Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard. [c] After 10 min, 0.1 mmol of I_2 was added and reacted for 5 min.

Table 4. Substrate scope for the trifluoromethanesulfonylation of β,γ-unsaturated hydrazones.[a]

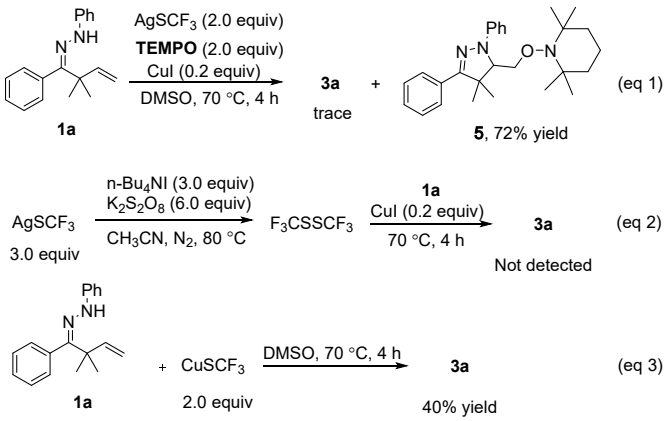


Reagents and conditions: **1** (0.2 mmol), CF_3SO_2Na (0.6 mmol), I_2 (0.6 mmol), DME (2.0 mL), 25 °C, 10 min, after 10 min, 0.1 mmol of I_2 was added and reacted for 5 min, isolated yield.

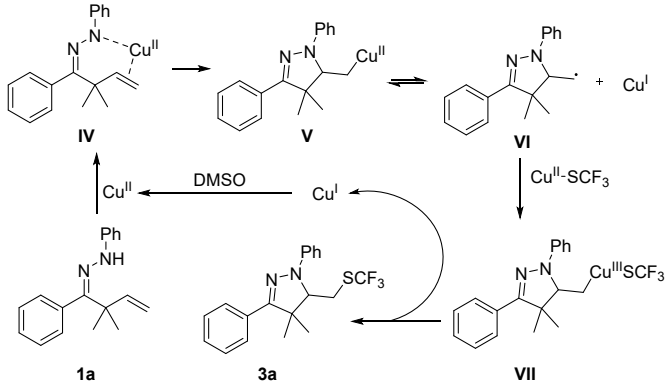
In order to further understand the reaction mechanism of trifluoromethylthiolation, three control experiments were carried out as shown in Scheme 2. First, the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl, 2 equiv.) was added to the reaction system, and only trace amounts of the desired product **3a** was detected by ^{19}F NMR spectroscopy analysis. The dihydropyrazole **5** was formed in 72% yield, due to trapping of the C-centered radical derived from the 5-exo-trig cyclization of radical was involved in this reaction, F_3CSSCF_3, which is known to produce SCF_3 radicals with Cu(I), was prepared in the presence of $K_2S_2O_8$ and introduced to the reaction (Scheme 2, eq 2). However, product **3a** was not observed, which indicated that the SCF_3 radical may not be involved in the trifluoromethylthiolation process. When the copper salt was removed and $CuSCF_3$ was used instead of $AgSCF_3$, the desired product **3a** was obtained in 40% yield, indicating that $CuSCF_3$ may be an intermediate during the reaction process (Scheme 2, eq 3).

On the basis of these observations and previous reports,[5b, 13] a plausible mechanism for the cascade cyclization trifluoromethylthiolation was proposed as shown in Scheme 3. First, Cu(I) is oxidized to Cu(II) by DMSO.[5b, 14] Next, an intramolecular amination of **1a** likely occurs to activate the olefin ultimately resulting in **V**. Intermediate **IV** undergoes cleavage to form the radical intermediate **VI**. The reaction of **VI** with $CuSCF_3$, which is derived from ligand exchange between the Cu(II) species and $AgSCF_3$, produces intermediate **VII**. Finally, product **3a** is formed through reductive elimination and regenerates the Cu(I) species.

Next, based on previous reports of the cyclization reaction of unsaturated hydrazones,[15] the reaction mechanism of the cascade cyclization/trifluoromethanesulfonylation was studied. Three control experiments were carried out as shown in Scheme 4. Under standard conditions, the reaction of iodide **6** with CF_3SO_2Na did not occur, indicating that it was not formed as an intermediate from the olefin and I_2 (Scheme 4, eq 4). Upon addition of TEMPO to this reaction system, the desired product **4a** could only be observed in 5% yield based on ^{19}F NMR analysis and the starting material **1a** was recovered in 87% yield (Scheme 4, eq 5). However, the reaction gave the desired product **4a** in 62% yield in the presence of the free radical scavenger BHT (2,6-di-*tert*-butyl-4-methylphenol, 3 equiv.) (Scheme 4, eq 6). These results indicated that the reaction might not proceed through a free radical pathway. The reaction was dramatically suppressed by TEMPO mainly due to its oxidizing capacity instead of its free radical scavenging ability.[14a]



Scheme 2. Control experiments for the trifluoromethylthiolation of **1a** with $AgSCF_3$.



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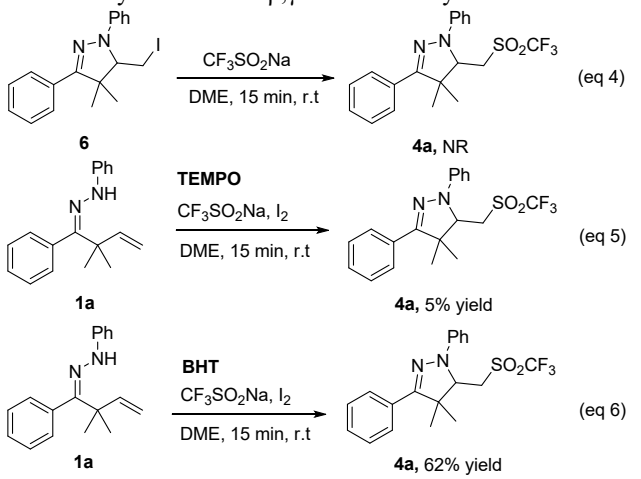
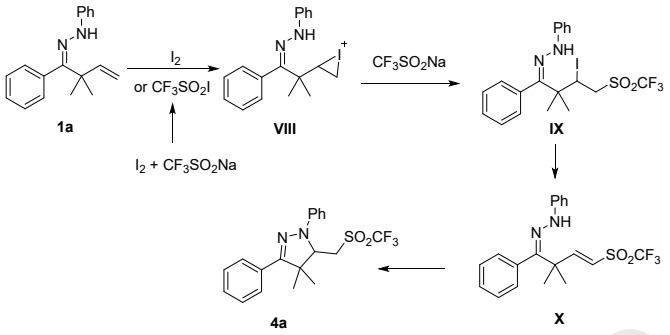


Scheme 4. Control experiments for the trifluoromethanesulfonylation of **1a** with CF_3SO_2Na.



Scheme 5. Proposed reaction mechanism for the trifluoromethanesulfonylation of β,γ-unsaturated hydrazones.

Although the precise mechanism of the reaction is unclear at present, a plausible reaction mechanism is depicted in Scheme 5 based on these observations and previous reports of the iodine-mediated trifluoromethanesulfonylation of styrenes.[12] First, CF_3SO_2Na reacts with I_2 to form CF_3SO_2I or I_2 which electrophilically adds to the double bond of **1a** to give the three-membered iodonium ion intermediate **VIII**. Subsequently, CF_3SO_2Na attacks **VIII** in an anti-Markovnikov manner to give intermediate **IX**. Finally, the elimination of HI takes place to afford CF_3SO_2-substituted intermediate **X**, which undergoes intramolecular ring closure and proton transfer to obtain the final product **4a**.

In summary, straightforward methods for preparing various CF_3S/CF_3SO_2-functionalized dihydropyrazole derivatives *via* the reaction of $AgSCF_3/CF_3SO_2Na$ with β,γ-unsaturated hydrazones were developed. Mechanistic studies showed that different reaction pathways were involved for the trifluoromethylthiolation and trifluoromethanesulfonylation. Further studies on the application of $AgSCF_3/CF_3SO_2Na$ as CF_3S/CF_3SO_2 sources are ongoing in our laboratory.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures and full characterization for all compounds) associated with this article can be found, in the online version, at xxx.

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11. The supplementary crystallographic data can be obtained free of charge from The Cambridge Cryatallographic Data Center via www.ccdc.cam.uk/data_request/cif (CCDC No. 1921839).

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Graphical Abstract

Trifluoromethylthiolation and Trifluoromethanesulfonylation of β,γ-Unsaturated Hydrazones

Hongqing Xiao, Weidong Meng, Xiu-Hua Xu and Yangen Huang

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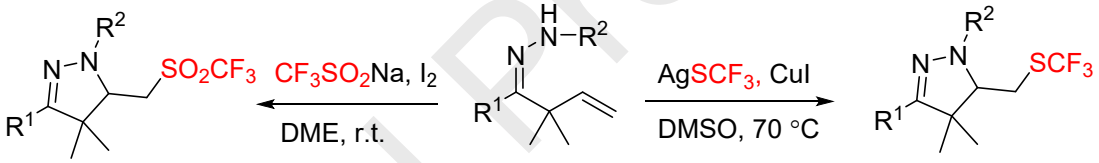

4
8 examples
43-63% yields

1
R^1 = Aryl, Alkyl
R^2 = Aryl

3
24 examples
32-81% yield

Highlights

- A rapid access to heterocyclic compounds with fluorinated substituents.
- Cascade cyclization and trifluoromethylthiolation/trifluoromethanesulfonylation.
- Under a mild condition with a good functional group tolerance.

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