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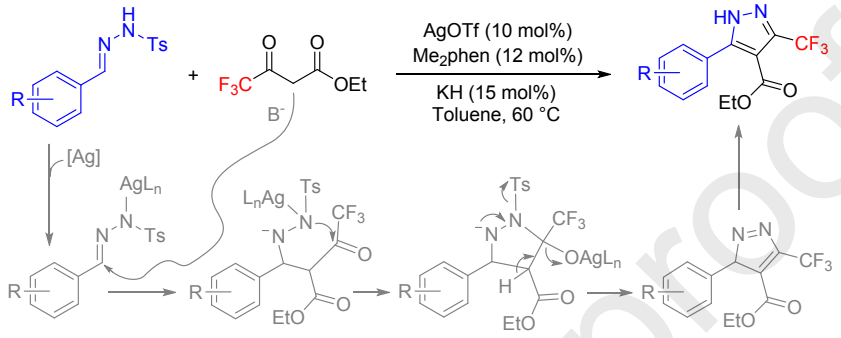

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Silver-catalyzed synthesis of 5-aryl-3-trifluoromethyl pyrazoles

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ABSTRACT

A silver-catalyzed synthesis of 5-aryl-3-trifluoromethyl pyrazoles from reaction of various *N*'-benzylidene tolylsulfonohydrazides with ethyl 4,4,4-trifluoro-3-oxobutanoate is described. The reaction proceeds via sequential nucleophilic addition, intramolecular cyclization, elimination, and [1,5]-*H* shift steps to afford the trifluoromethylated pyrazole products in moderate to excellent yields. The reaction is compatible with a variety of functional groups.

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The pyrazoles are ubiquitous structural motifs present in a number of natural products and drugs that exhibit a wide range of biological activities.[1] Particularly, the trifluoromethylated pyrazoles have been gaining much attention in recent years as potential pharmaceuticals and agrochemicals.[2] Representative examples of bioactive molecules containing trifluoromethylated pyrazole motifs with various pharmacological properties are enlisted below in Figure 1: Celecoxib is a nonsteroidal anti-inflammatory drug used in the treatment of pain or inflammation;[3] SC-560 exhibits significant anticancer activities;[4] Razaxaban is a factor Xa inhibitor for the treatment of thrombosis;[5] Fluazolate is a broad spectrum preemergent herbicide used on winter wheat.[6]

The development of efficient methodologies for the synthesis of trifluoromethyl pyrazole derivatives is of great importance for academic research, as well as for chemical industries.[7] The most common route to access this class of heterocycles is the condensation of 1,1,1-trifluoromethyl-1,3-diketones, or their synthetic equivalents, with hydrazines.[8] Several new synthetic methods have also been developed in recent years, including the cycloaddition of alkynes with 2,2,2-trifluorodiazoethane,[9] the cyclocondensation of trifluoromethyl-α,β-ynones with hydrazines,[10] trifluoromethylation/cyclization of α,β-alkynic hydrazones,[11] intramolecular cyclization of *N*-propargylhydrazones,[12] the cyclization of trifluoromethyl alkenone with tosylhydrazone,[13] the cycloaddition of trifluoroacetonitrile imines with enol ethers.[14] These transformations provide efficient and flexible methods for the synthesis of 3-trifluoromethylpyrazoles. However, some of them suffered from serious limitations, such as the formation of regioisomeric mixtures, narrow substrate scopes, the requirement of using expensive reagents. As a result, there remains a need for further development for the efficient construction of such molecules.

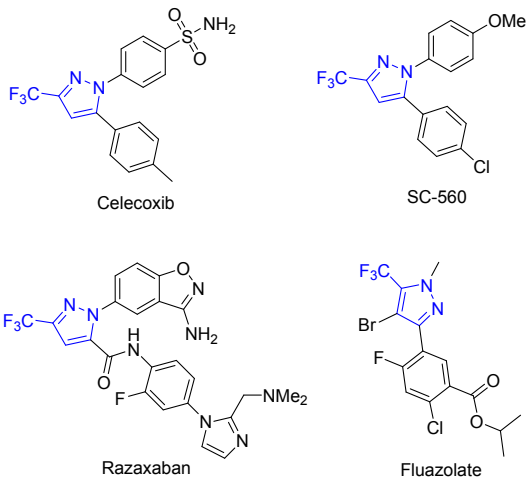

Figure 1. Biologically important trifluoromethylated pyrazoles.

We have been interested for several years in the utility of readily available and inexpensive fluorinating reagents for the construction of trifluoromethylated heterocyclic compounds.[15] Recently, we reported a copper-catalyzed chemoselective synthesis of 4-trifluoromethyl pyrazoles from the reaction of *N*-arylsydnone derivatives with 2-bromo-3,3,3-trifluoropropene under mild conditions.[16] As part of this initial investigation, we extended this condensation strategy to the reaction between *N*'-benzylidene tolylsulfonohydrazides and ethyl 4,4,4-trifluoro-3-

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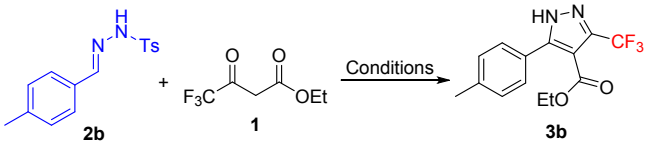
5-aryl-3-trifluoromethyl pyrazoles in good yields.

Table 1 Optimization of the reaction [a]



Entry	[*Cat.*]	Ligand	Base	Solvent	Temp. (°C)	Yield (%)[b]
1	AgOTf	-	KH	Toluene	40	62
2	AgOTf	-	KH	Toluene	60	69
3	AgOTf	-	KH	Toluene	70	59
4	$Cu(OTf)_2$	-	KH	Toluene	60	60
5	$Fe(OTf)_3$	-	KH	Toluene	60	33
6	AgOTf	-	KH	THF	60	12
7	AgOTf	-	KH	Dioxane	60	9
8	AgOTf	-	NaH	Toluene	60	8
9	AgOTf	-	K_2CO_3	Toluene	60	63
10	AgOTf	-	KO*t*-Bu	Toluene	60	52
11	AgOTf	-	NaO*t*-Bu	Toluene	60	14
12	-	-	KH	Toluene	60	51
13	AgOTf	-	-	Toluene	60	30
14	AgOTf	bpy	KH	Toluene	60	57
15	AgOTf	phen	KH	Toluene	60	92
16	AgOTf	Me_2phen	KH	Toluene	60	>99
17	$Cu(OTf)_2$	bpy	KH	Toluene	60	86
18	$Cu(OTf)_2$	phen	KH	Toluene	60	63

[a] Reaction conditions: **1** (0.25 mmol, 2.5 equiv), **2b** (0.10 mmol, 1.0 equiv), [*cat.*] (10 mol%), ligand (12 mol%), base (0.15 equiv), solvent (1.0 mL), 20 h, under N_2 atmosphere; bpy = 2,2′-bipyridine, phen = 1,10-phenanthroline, Me_2phen = neocuproine.
[b] The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard.

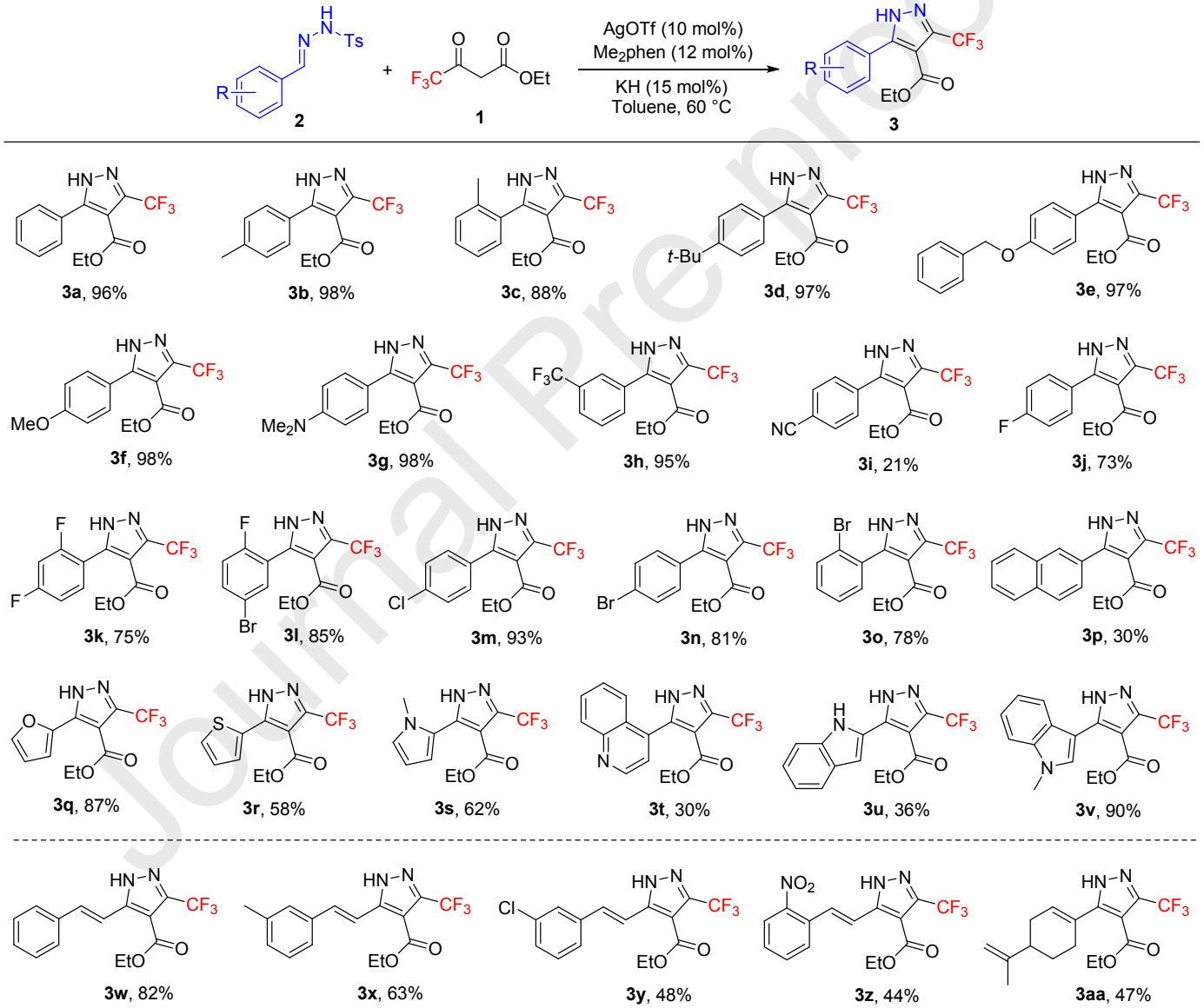
We initiated our investigation by utilizing tosyl-protected benzylidene hydrazine **2b**, easily prepared from commercially available *p*-tolualdehyde, as a substrate to react with **1** for the optimization of the reaction conditions (Table 1). A mixture of **2b** (0.10 mmol) and **1** (0.25 mmol) in toluene (1.0 mL) in the presence of AgOTf (10 mol%) and KH (0.15 equiv) was stirred at 40 °C. The desired trifluoromethylated pyrazole product **3b** was formed in 62% NMR yield (Entry 1). The yield of the **3b** was further improved to 69% by raising the reaction temperature to 60 °C (Entry 2). However, further increasing the reaction temperature to 70 °C only resulted in lower yield (59%; Entry 3). Other transition-metal catalysts were also examined, and it was found that the reaction using $Cu(OTf)_2$ afforded product **3b** in comparable yield (60%; Entry 4), while $Fe(OTf)_3$ was ineffective for this reaction (Entry 5). The choice of solvent proved crucial for this transformation. The use of THF or dioxane gave poor yield of the product (Entries 6 and 7). Other bases were tested, and K_2CO_3 also proved to be an effective base for the reaction (Entry 9), while NaH, KO*t*-Bu, and NaO*t*-Bu were less efficient (Entries 8, 10, and 11). In the absence of either the silver species or KH, the reaction efficiency was significantly decreased (Entries 12 and 13). To further improve the product yield, the cyclization was examined in the presence of some bidentate dinitrogen ligands. The use of Me_2phen as the ligand gave the best yield (>99%; Entry 16), while a 57% or 92% yield was achieved by using bpy or phen as the ligand, respectively (Entries 14 and 15). However, in the presence of bpy or phen ligand, $Cu(OTf)_2$ provided relatively low yields of the desired product (Entries 17 and 18).

With the optimized conditions in hand, we investigated the substrate scope using various *N*′-benzylidene tolylsulfonohydrazides **2** and ethyl 4,4,4-trifluoro-3-oxobutanoate **1**. As showed in Table 2, the cyclization reaction worked efficiently to afford the corresponding 5-aryl-3-trifluoromethyl pyrazole products in good to high yields. For instance, excellent yield was obtained when a simple hydrazine substrate **2a** was reacted with **1** to give **3a** (96% yield). *N*′-benzylidene tolylsulfonohydrazides **2b**–**2d** containing alkyl groups such as

metl…yl catalysis, furnishing the expected 5-aryl-3-trifluoromethyl pyrazoles **3b**–**3d** in 88%–98% yields. Similarly, *N*'-benzylidene tolylsulfonohydrazides **2e**–**2h** having electron-donating and -withdrawing groups, such as 4-benzyloxy, 4-methoxy, 4-dimethylamine, and 3-trifluoromethyl on the aromatic rings, exhibited good reactivity, generating **3e**–**3h** in excellent yields. As an exception, *N*'-(4-cyanobenzylidene)-4-methylbenzenesulfonohydrazide **2i** afforded the trifluoromethylated pyrazole product **3i** in only 21% yield. It is worthy of note that the sulfonohydrazide substrates bearing halogen substituents such as F (**2j**–**2l**), Cl (**2m**), and Br (**2l**, **2n**, and **2o**) on the phenyl rings were also tolerated and furnished the desired products **3j**–**3o** in moderate to excellent yields (73%–93%), thereby providing possibilities for further elaboration. The cyclization of 4-methyl-*N*'-(naphthalen-2-ylmethylene)benzenesulfonohydrazide **2p** with **1** also took place to give the corresponding product **3p**, albeit in somewhat lower moieties, such as furyl, thienyl, pyrrolyl, quinolyl, and indolyl were also efficiently converted to the desired products **3q**–**3v** in 30%–90% yields. The structure of product **3r** was unambiguously determined by single-crystal X-ray crystallography demonstrating the successful synthesis of the trifluoromethylated pyrazole compound (Figure 2).

The scope of the cyclization reaction was then further explored with a range of 4-methyl-*N*'-(3-phenylallylidene)benzenesulfonohydrazides (Table 2). The cyclization reaction of these substrates with **1** provided the desired trifluoromethylated pyrazole products **3w**–**3z** in 44%-82% yields. Various functional groups including methyl, chloro, and nitro substituents on the aromatic rings were well tolerated. In addition, a menthadiene-containing substrate reacted smoothly with **1** to furnish the corresponding pyrazole product **3aa** in 47% yield.

Table 2. Scope of reaction [a, b]



[a] Reaction conditions: **1** (1.25 mmol), **2** (0.50 mmol), AgOTf (0.050 mmol, 10 mol%), Me_2phen (0.060 mmol, 12 mol%), KH (0.075 mmol, 15 mol%), toluene (3.0 mL), 60 °C, 20 h, under N_2 atmosphere.

[b] Isolated yields.

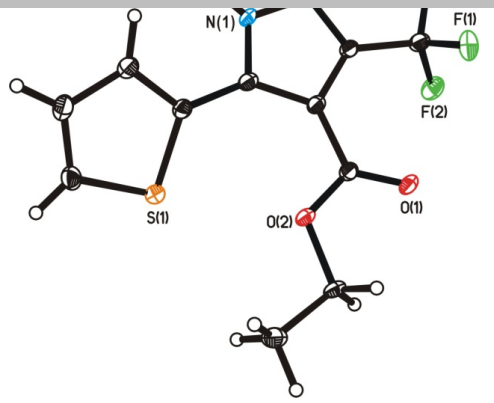
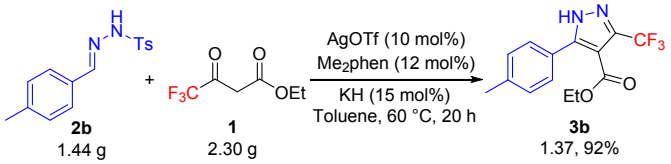
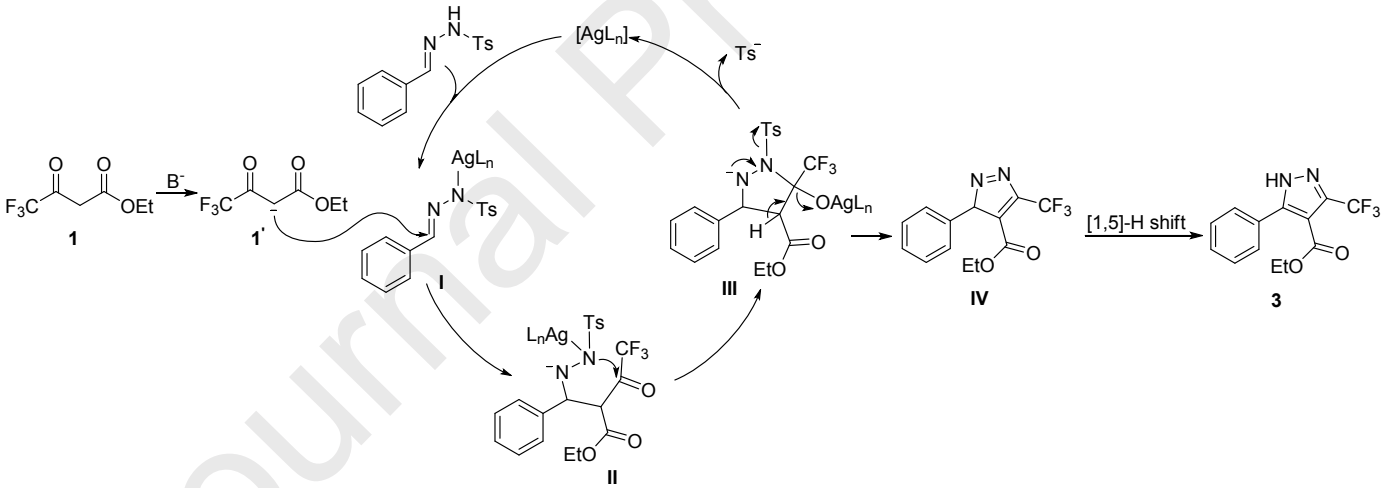


Figure 2. ORTEP drawing of **3r**. Thermal ellipsoids are drawn at 40% probability.



Scheme 1. Gram scale experiment.



Scheme 2. Plausible reaction mechanism.

ting 4-methyl-*N*'-(4-methylbenzylidene)benzenesulfonohydrazide **2b** with ethyl 4,4,4-trifluoro-3-oxobutanoate **1** on a 5.0 mmol scale (Scheme 1). As anticipated, the reaction proceeded smoothly to give the desired product **3b** in 92% yield (1.37 g).

A plausible reaction mechanism for the formation of the trifluoromethylated pyrazoles is depicted in Scheme 2. Initially, the complexation of silver species with hydrazine would form the silver complex **I**. Subsequently, complex **I** underwent an nucleophilic addition with an anion of **1** to generate the intermediate **II**. Finally, intramolecular cyclization of the amine moiety with the ketone C=O bond in **II** could furnish **III**, which underwent elimination and subsequent [1,5]-*H* shift to afford the trifluoromethylated pyrazole product **3**.

In conclusion, we have developed a silver-catalyzed synthesis of 5-aryl-3-trifluoromethyl pyrazoles starting from easily accessible *N*'-benzylidene tolylsulfonohydrazides and ethyl 4,4,4-trifluoro-3-oxobutanoate under basic conditions. The sequential nucleophilic addition, intramolecular cyclization, elimination, and [1,5]-*H* shift afforded the trifluoromethylated pyrazole products in moderate to excellent yields in a single operation. This work provides a complementary method to access 3-trifluoromethyl pyrazoles.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in t

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Highlights:

- A silver-catalyzed synthesis of 5-aryl-3-trifluoromethyl pyrazoles was developed.
- Various 5-aryl-3-trifluoromethyl pyrazoles were obtained in moderate to excellent yields.
- A variety of functional groups were tolerated.