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Anionic Triflyldiazomethane: Generation and Its Application for Synthesis of Pyrazole-3-triflones via [3 + 2] Cycloaddition Reaction

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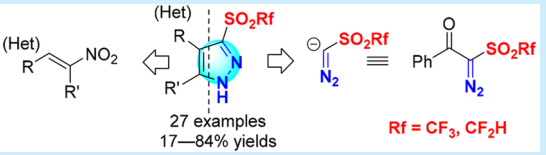
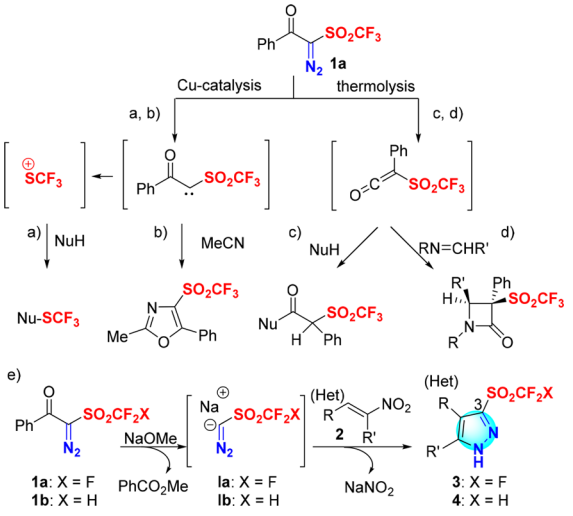
Supporting Information

ABSTRACT: The synthesis of pyrazole triflones containing a triflyl group at the 3-position is disclosed. Treatment of 2-diazo-1-phenyl-2-((trifluoromethyl)sulfonyl)ethan-1-one with nitroalkenes under basic conditions gave pharmaceutically attractive pyrazole 3-triflones in good to high yields. The generation of anionic triflyldiazomethane species followed by the [3 + 2] cycloaddition reaction with nitroalkenes is proposed for this transformation. 3-(Difluoromethanesulfonyl)pyrazoles were also synthesized by using a previously unknown anionic (difluoromethanesulfonyl)diazomethane species under a similar strategy.



The expedited synthesis of organofluorine compounds via novel and efficient methods is of prime importance in the fields of pharmaceuticals and agrochemicals.[1] Trifluoromethyl (CF_3) compounds are one of the most attractive targets in these areas of study owing to their unique properties induced by the high lipophilicity and strong electron-withdrawing effect of the CF_3 group (σ_m = 0.43, σ_p = 0.54; π = 0.88).[2] Recently, heteroatom-linked CF_3 variants, i.e., XCF_3, including trifluoromethoxy (OCF_3),[3] trifluoromethylthio (SCF_3),[4] and trifluoromethanesulfonyl (triflyl, SO_2CF_3),[5,6] have gained attention. In particular, we are interested in the SO_2CF_3 compounds (triflones)[5−7] because of their high electron-withdrawing ability and mild lipophilicity of SO_2CF_3 (σ_m = 0.79, σ_p = 0.93; π = 0.55)[6a] compared to CF_3. Numerous triflones have been reported, even though compounds with an SO_2CF_3 on the heterocyclic ring, i.e., heterocyclic triflones, are rather limited.[7] Our group has been engaged for decades in the development of shelf-stable reagents for fluoro-functionalization reactions such as fluorination, trifluoromethylation, and trifluoromethylthiolation reactions.[8] One of the reagents, 2-diazo-1-phenyl-2-((trifluoromethyl)-sulfonyl)ethan-1-one (**1a**), is unique.[9] Reagent **1a** was originally developed for the electrophilic trifluoromethylthiolation reaction.[9a] In the presence of a copper catalyst, **1a** generates a reactive electrophilic trifluoromethylthio species of $^+SCF_3$ in situ from an SO_2CF_3−carbene intermediate resulting in the trifluoromethylthiolation of a wide range of substrates such as enamines, indoles, β-keto esters, pyrroles, and iodoarenes (Scheme 1a).[9a] In the presence of acetonitrile, the SO_2CF_3−carbene intermediate promptly reacts with acetonitrile before the generation of $^+SCF_3$ species to provide oxazole triflone (Scheme 1b).[9b] Interestingly, under thermal conditions without copper catalysis, **1a** is transformed into a ketene triflone via the Wolf rearrangement and reacts with nucleophiles to provide acyclic triflones (Scheme 1c).[9b] Multiply substituted β-lactam triflones are also accessed by the reaction of ketene triflone with imines via the Staudinger [2 + 2] cycloaddition reaction (Scheme 1d).[9c] As an extension of our research work on heterocyclic triflones,[7,9] we herein report the synthesis of pyrazole triflones **3** by the reaction of **1a** with nitroalkenes **2** under basic conditions (Scheme 1e). Nitroalkenes **2** bearing electron-withdrawing, electron-donating, or halogenyl substituents on the aryl ring gave the desired pyrazole triflones **3** in good to high yields almost independent of their substitution and positions.

Scheme 1. Four Different Reactive Species Generated from 1a and Their Diversity in Organic Synthesis



Heterocyclic variants of nitroalkenes **2** were also feasible in this transformation with **1a** under the same conditions to furnish the corresponding 4-heteroaryl-substituted pyrazole triflones **3**. The

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in situ generation of reactive anionic triflyldiazomethane species **Ia** should be a key for this transformation which undergoes a [3 + 2] cycloaddition reaction with **2**. Diazomethane derivatives having electron-withdrawing groups represented by N═N═CH-EWG (EWG: esters, sulfonates, phosphates, etc.) have gained attention in recent years as versatile building blocks in organic chemistry;[10] however, to our knowledge, triflyldiazomethane **Ia** including its protonated form (N═N═$CHSO_2CF_3$) has never been reported. This is the first example for the generation of **Ia** and its application to organic synthesis. The reaction was extended to the synthesis of 3-difluoromethanesulfonyl (SO_2CF_2H) pyrazoles **4** by using a previously unknown 2-diazo-1-phenyl-2-((difluoromethyl)sulfonyl)ethan-1-one (**1b**) under the same basic conditions via the generation of anionic (difluoromethanesulfonyl)diazomethane species **Ib**.

Pyrazoles are often an integral part of drugs and are biologically active molecules;[11] thus, pyrazole-3-triflones are also likely to be attractive drug candidates (Figure 1a).[12,13]

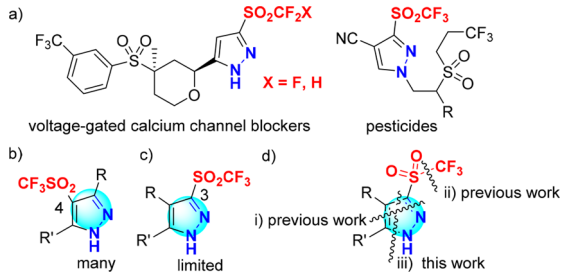


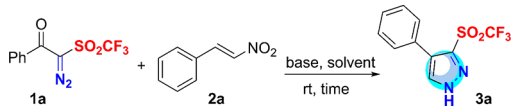
Figure 1. (a) Biologically active 3-SO_2CF_2X-pyrazoles; (b, c) structures of 4- and 3-SO_2CF_3-pyrazoles; (d) disconnection approaches i, ii, and iii for 3-SO_2CF_3-pyrazoles.

Although there are many papers for the preparation of 4-SO_2CF_3-pyrazoles (Figure 1b),[14] reports on synthetic pyrazole-3-triflones are extremely limited (Figure 1c), and only a single publication (disconnection i, in Figure 1d)[12] and several patents (disconnection ii, in Figure 1d)[13] are available. The product diversity in these reported methods is highly dependent on the starting materials used, while the scope of substrates used in these methods is narrow.[12,13] We thus were interested in a novel synthetic method for pyrazole-3-triflones based on a disconnection approach iii (Figure 1d).

We began our investigation by treating **1a** with nitrostyrene **2a** in the presence of KOEt in EtOH or KO^{t}Bu in ^{t}BuOH, and a trace amount of product was formed (entries 1 and 2, Table 1). Desired pyrazole-3-triflone **3a** was detected in 22% yield by the reaction of **1a** with **2a** in the presence of NaOMe in MeOH at room temperature (rt) (entry 3). Solvent screening did not improve the yield (entries 4—6). Next, we optimized the amount of base. In the presence of 2.0 equiv of NaOMe, 39% of pyrazole triflone **3a** was formed in 12 h (entry 7). A dramatic improvement of both yield and reaction time were observed when an excess amount of base was used (entries 9 and 10). The highest NMR yield of **3a** (80%) was observed in 10 min when 10 equiv of NaOMe was used (entry 10).

With the optimized reaction conditions in hand, the scope of the cyclization reaction was investigated with **1a** and nitrostyrene derivatives **2a—o** containing electron-donating, electron-withdrawing, and halogenyl substituents at different positions on the benzene ring. Fortunately, all of these reactions proceeded very smoothly to furnish the corresponding pyrazole triflones **3** in good to high yields irrespective of the electronic character and

Table 1. Optimization of the Reaction Conditions[a]

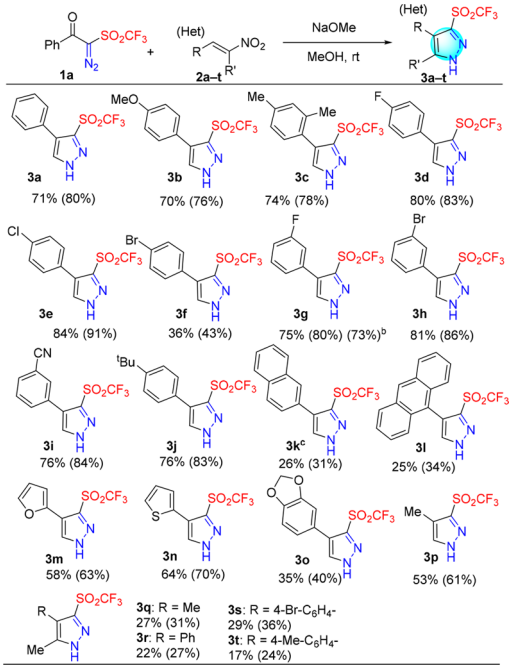


entry	base (equiv)	solvent	time	yield[b] (%)
1	KOEt (1.5 equiv)	EtOH	36 h	trace
2	KO^{t}Bu (1.5 equiv)	^{t}BuOH	36 h	trace
3	NaOMe (1.5 equiv)	MeOH	12 h	22
4	NaOMe (1.5 equiv)	EtOH	12 h	13
5	NaOMe (1.5 equiv)	acetone	12 h	–
6	NaOMe (1.5 equiv)	MeCN	12 h	–
7	NaOMe (2.0 equiv)	MeOH	12 h	39 (33)
8	NaOMe (4.0 equiv)	MeOH	10 min	64 (61)
9	NaOMe (5.0 equiv)	MeOH	10 min	76 (68)
10	NaOMe (10.0 equiv)	MeOH	10 min	80 (71)

[a]Reaction conditions: diazotriflone **1a** (0.18 mmol), nitrostyrene **2a** (0.15 mmol), base, solvent (1.0 mL), at rt. [b]^{19}F NMR yields are shown (the internal standard is $PhCF_3$). Yields are also shown in parentheses.

the steric effect of arenes, with a couple of exceptions (Scheme 2). The pyrazole triflones with electron-donating substituents

Scheme 2. Scope of the Reaction of Diazotriflone 1a with Nitroalkenes 2a—t[a]



[a]Experiments were performed with **1a** (0.18 mmol), **2a—t** (0.15 mmol), and NaOMe (1.5 mmol) in 1.0 mL of dry MeOH with stirring at rt for 10—15 min. [b]1.2 mmol of **1a** and 1.0 mmol of **2g** were used (see the SI for details). [c]0.30 mmol of **1a** was used. ^{19}F NMR yields with internal standard ($PhCF_3$) also shown in parentheses.

(OMe and ^{t}Bu) at the *p*-position (**3b**: 70%; **3j**: 76%), an electron-withdrawing CN substituent at the *m*-position (**3i**: 76%) and halogens (**3d**: 80%; **3e**: 84%, **3g**: 75%) were obtained in good to high yields. On the other hand, a Br substituent at the *p*-position of nitrostyrene furnished low yield (**3f**: 36%), whereas *m*-substituted nitrostyrene afforded the desired product in good yield (**3h**: 81%), although the reason for the low yield of **3f** is not clear. Electron-rich nitrostyrene **2c** with two Me substituents on

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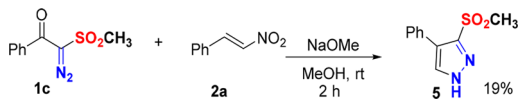
the benzene ring also afforded good yield (**3c**: 74%). Subsequently, heterocyclic variants of nitrostyrene (**2m**: 2-furyl; **2n**: 2-thienyl) that were treated with **1a** furnished moderate to good yields (**3m**: 58%; **3n**: 64%). In contrast, nitrostyrene-containing benzo[*d*][1,3]dioxole **2o** and sterically demanding naphthyl **2k** and anthracene **2l** substituents afforded the corresponding products in low yields (**3o**: 35%; **3k**: 26%; **3l**: 25%). The reaction of aliphatic nitroalkene **2p** with **1a** also delivered the desired product **3p** in 61% yield. Multiply-substituted pyrazoles **3q,r** and **3s,t** were also accessed by the reaction of nitroalkenes **2q,r** and **2s,t** with **1a** independent of the aromatic and aliphatic substitutions at the 4-positions of **3** (Scheme 2). All compounds **3** were confirmed on the basis of spectroscopic data (^{1}H and ^{13}C NMR, HRMS). To unambiguously confirm the structure, 2D-NMRs (COSY, HMQC, NOESY, HMBC) of **3g** and *N*-4-bromobenzylated **3g** were carried out (see the Supporting Information).

To ensure the incorporation of the CF_3 group of **1a**, next we examined the reaction of a nonfluorinated counterpart, 2-diazo-1-phenyl-2-(methanesulfonyl) ethenone (**1c**)[14] with nitrostyrene **2a** under the optimized reaction conditions (Scheme 3).

Scheme 3. Reaction of Methanesulfonyl Diazo Compound 1c with Nitrostyrene 2a[a]

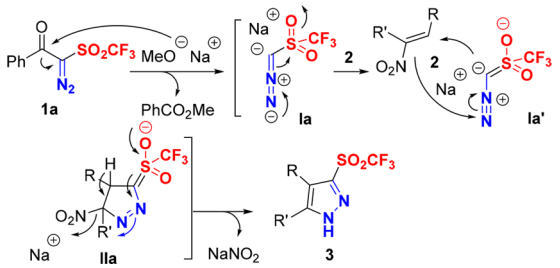


[a]Experiment was performed with **1c** (0.18 mmol), **2a** (0.15 mmol), and NaOMe (1.5 mmol) in MeOH (1.0 mL) at rt.

While the starting material **1c** was consumed, the reaction was disorganized and desired product **5** was obtained in very low yield (19%) in 2 h. This observation clearly indicates the advantage of the SO_2CF_3 moiety for this cyclization reaction.

A plausible reaction mechanism of the base-initiated cyclization reaction of **1a** with **2** to form **3** is depicted in Scheme 4.[15] First, sodium methoxide attacks the carbonyl carbon of **1a** to

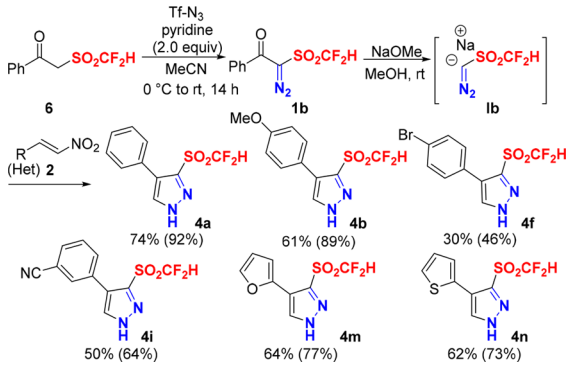
Scheme 4. Plausible Reaction Mechanism



generate an anionic triflyl diazomethane **Ia** with the release of methyl benzoate ($PhCO_2Me$). The generated anionic triflyl diazomethane **Ia** then reacts with **2** through **Ia′** via a [3 + 2] cycloaddition mode to furnish cyclized intermediates **IIa**. Finally, the elimination of $NaNO_2$ from **IIa** followed by tautomerization gave the desired pyrazole triflones **3** (Scheme 3). As we failed to isolate the protonated form of **Ia** (N_2=CHSO$_2$CF$_3$), the **Ia** should be reactive and unstable.[16]

Finally, we extended the method for the synthesis of 3-difluoromethanesulfonyl (SO_2CF_2H) pyrazoles **4**. The heteroatom-linked difluoromethanes represented by XCF_2H, such as OCF_2H,[17] SCF_2H,[18] and SO_2CF_2H,[13,19,20] would be the next targets of fluorinated functional groups in medicinal chemistry. The H in XCF_2H has the potential to be a hydrogen-bonding donor and would play an important role in binding to enzymes if they were to be used as a part of drug structure. We thus synthesized 2-diazo-2-((difluoromethyl)sulfonyl)-1-phenylethan-1-one (**1b**) in 56% yield from ((difluoromethyl)sulfonyl)-acetophenone **6** with triflyl azide (Tf-N$_3$) in MeCN. The [3 + 2] cycloaddition reaction of **1b** with nitroalkenes **2** with aromatic groups and heteroaromatics of different electronic density was examined under the same conditions. The reaction proceeded smoothly to provide the desired 3-SO$_2$CF$_2$H-pyrazoles **4** in good to high yields almost independent of the substitution of the arene moiety, such as nonsubstituent (**4a**: 74%), OMe (**4b**: 61%), Br (**4f**: 30%), CN (**4i**: 50%), 2-furyl (**4m**: 64%), and 2-thienyl (**4n**: 62%) (Scheme 5).

Scheme 5. Synthesis of Diazodifluoromethylsulfonyl Acetophenone 1b and its Reaction with Nitroalkenes 2[a]



[a]Reaction of **1**−**4** was performed with **1b** (0.18 mmol), **2** (0.15 mmol), and NaOMe (1.5 mmol) in 1.0 mL of MeOH with stirring at rt for 10−15 min. ^{19}F NMR yields with internal standard (Ph−F) also shown in parentheses.

In conclusion, we disclosed the synthesis of pyrazole-3-triflones **3** by the reaction of diazotriflone **1a** with nitroalkenes **2**. The key for this transformation is the base-induced generation of anionic triflyldiazomethane **Ia** followed by the [3 + 2] cycloaddition reaction. While diazomethane derivatives having electron-withdrawing groups are well-known versatile building blocks,[10] the generation of triflyldiazomethane represented by **Ia** is the first example. Tolerance of the functional group when using this method is very high, and a variety of pyrazole triflones can be synthesized depending on the use of nitroalkenes. (Difluoromethanesulfonyl)pyrazoles **4** are also accessible by this method using difluoromethanesulfonyl diazo compound **1b**. These results not only indicate the efficient synthesis of pyrazole triflones **3** but also expand the diversity of diazotriflone **1a** for the synthesis of fluoro-functionalized compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03664.

Syntheses, NMR spectra, and 2D NMR of **3g** and *N*-4-Br-benzylated **3g** (PDF)

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Notes

The authors declare no competing financial interest.

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