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# Direct Regioselective [3 + 2] Cycloaddition Reactions of Masked Difluorodiazoethane with Electron-Deficient Alkynes and Alkenes: Synthesis of Difluoromethyl-Substituted Pyrazoles

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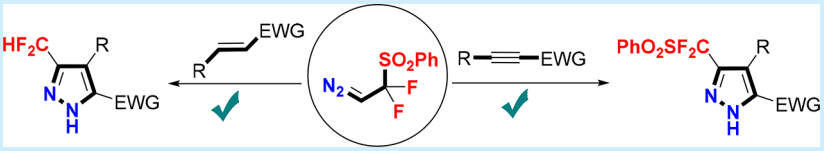
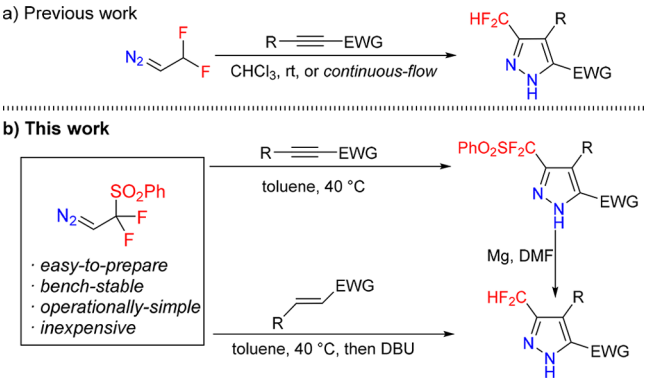
Supporting Information




**ABSTRACT:** Phenylsulfone difluorodiazoethane ($PhSO_2CF_2CHN_2$), an easy-to-prepare and bench-stable masked $CF_2$-building block, has been developed. The synthetic utility of this reagent is demonstrated by a direct regioselective [3 + 2] cycloaddition with electron-deficient alkynes and alkenes. This protocol enables facile construction of an array of difluoromethyl-substituted pyrazoles in good to high yields under mild reaction conditions.

Over the past decade, remarkably increasing efforts have been devoted to the construction of difluoromethyl ($CF_2H$)-containing molecules in synthetic chemistry.[1] It has been demonstrated that introducing a $CF_2H$ moiety into biologically active compounds could bring dramatic effects, such as improvement of lipophilicity, metabolic stability, or bioavailability relative to their nonfluorinated counterparts.[2] Besides, the difluoromethyl group can also act as a bioisostere for carbinols, thiols, hydroxamic acids, and amides.[3] Among plenty of $CF_2H$-functionalized entities, the difluoromethylated pyrazoles represent an important class of core-structure in agrochemicals.[4] As a consequence, the efficient and divergent synthesis of difluoromethyl-substituted pyrazoles are in high demand.[5] In this context, conventional synthetic methods to access $CF_2H$-pyrazolic skeletons mainly employ condensation of difluoromethyl-substituted ketones with hydrazines under acidic conditions.[6] Despite considerable effort, these protocols often encounter formation of regioisomeric mixtures with respect to substituents incorporated at the 3- and 5-positions of the pyrazole ring. To overcome these limitations, Mykhailiuk reported the in situ generation of difluorodiazoethane ($CF_2HCHN_2$) and its [3 + 2] cycloaddition with alkynes to provide 3-$CF_2H$ pyrazoles (Scheme 1a).[7] Subsequently, both the groups of Koenigs and Jamison have developed elegant methods to prepare $CF_2H$-pyrazoles with $CF_2HCHN_2$ by the utilization of continuous-flow technology (Scheme 1a).[8] Nevertheless, as an unstable and hazardous gas, the wide applicability of $CF_2HCHN_2$ still suffers from difficult handling along with its generation, storage, and reaction operation. In this regard, we speculated that a suitable masked difluorodiazoethane might serve as promising difluoromethyl building block to provide target fluorinated entities.[9] To our delight, phenylsulfone difluorodiazoethane ($PhSO_2CF_2CHN_2$), prepared from thiophenol within five steps in 62% yield, is found to be a stable liquid compound. More importantly, the [3 + 2] cycloaddition with electron-deficient alkynes and alkenes proceed smoothly, thus providing facile access to difluoromethyl-substituted pyrazoles in good to high yield (Scheme 1b). Moreover, it has been disclosed that DBU can be employed as an efficient desulfonation reagent to produce pyrazoles from pyrazolines.[10] Herein, we would like to report our investigations on the development and utility of this masked difluorodiazoethane.

**Scheme 1. Strategies for Synthesis of $CF_2H$-Containing Pyrazoles with Diazo Compounds**




A classic tactic to develop fluoroalkylation reagents is the combination of sulfur and fluorine, as exemplified by a long list of fluorinated sulfones, sulfoxides, sulfides, and sulfoximines in organic synthesis.[11] With this concept in mind and inspired by the elegant work from Hu's group,[12] we set out to investigate the

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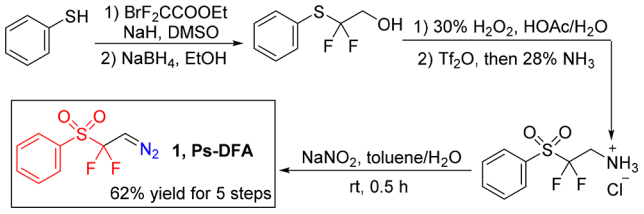
feasibility of employing a sulfone moiety for the development of masked difluorodiazoethane. Pleasingly, phenylsulfone difluorodiazoethane **1** ($PhSO_2CF_2CHN_2$ or Ps-DFA) has been synthesized smoothly within five steps in 62% yield (Scheme 2). The synthetic route starts with ethyl bromodifluoroacetate,

**Scheme 2. Synthesis of $PhSO_2CF_2CHN_2$**

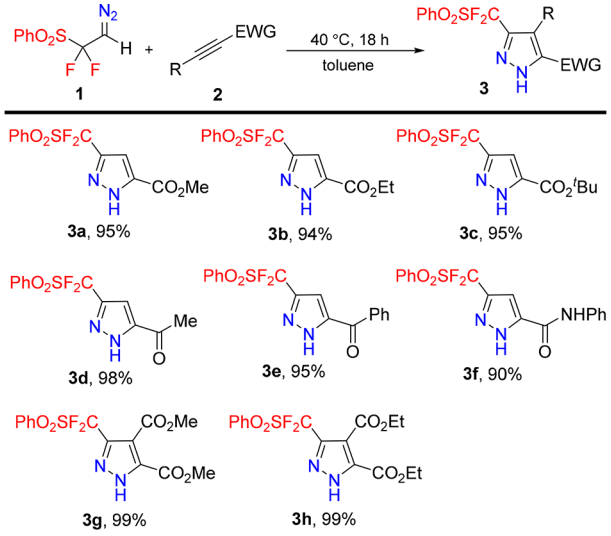



through sulfidation, reduction of ester, oxidation of sulfide, amination, and diazotization, and finally provides target reagent **1** as a liquid compound. It should be noted that previous studies from Mykhailiuk reveal that the in situ generation of fluorinated diazoalkanes only worked for difluoro compounds, $RCF_2CH_2NH_2$, where R was a fluorine atom or a fluoroalkyl substituent.[13] In this context, our result provides solid proof for the feasibility of generating masked difluorinated diazoalkanes. Typical features of this procedure include inexpensive reagents, simple operations, and easiness to scale-up (see the Supporting Information (SI)). More importantly, owing to the strong electron-withdrawing property of the sulfone group, Ps-DFA **1** is a bench-stable diazo compound, thus rendering the easy handling as a great merit. Furthermore, as the sulfone group has the ability to be readily removed or transformed, this newly developed masked difluorodiazoethane offers great opportunities for the generation of difluoromethyl-functionalized molecules.

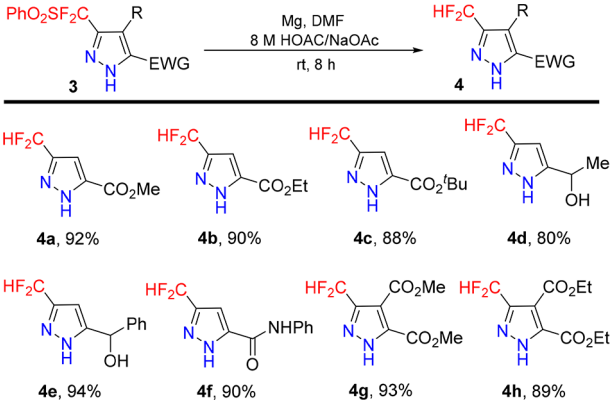
With masked difluorodiazoethane Ps-DFA in hand, we first engaged our efforts in the [3 + 2] cycloaddition with alkynes to highlight the synthetic utility of this reagent. Pleasingly, a screening of several reaction parameters (solvents, temperature, and reaction time) revealed that phenylsulfone difluoromethylpyrazole **3a** was obtained in 95% yield when the reaction with methyl propiolate was performed in toluene at 40 °C for 18 h. Having the optimal reaction conditions in hand, we then proceeded to investigate the scope of this cycloaddition reaction (Scheme 3). Alkynes substituted with an electron-withdrawing group including ester, amide, and ketone, are all found to be good substrates, thereby generating the corresponding phenylsulfone difluoromethylpyrazoles **3a–f** in excellent yields (90–95%). Disubstituted alkynes are also compatible with this [3 + 2] cycloaddition reaction, leading to the formation of 3-(difluoroalkyl)pyrazoles **3g–h** in nearly quantitative yield. Moreover, it is worth mentioning that only one equivalent of Ps-DFA was employed in these cycloaddition reactions. This is a distinct advantage compared with previously reported $CF_2HCHN_2$ chemistry in which the diazo compound was often requisite for more than two equivalents.[7,8]

Next, the desulfonylation process of compounds **3a–h** was conducted to provide the corresponding $CF_2H$-substituted pyrazoles. As depicted in Scheme 4, the phenylsulfone moiety was smoothly cleaved in the presence of magnesium at room temperature. This protocol enables the rapid preparation of $CF_2H$-substituted pyrazoles **4a–h** in high yields under mild conditions. It should be noted that ketone-containing compounds **3d** and **3e** underwent this transformation to give

**Scheme 3. Synthesis of Phenylsulfone Difluoromethylpyrazoles from Alkynes**




**Scheme 4. Synthesis of 3-$CF_2H$ Pyrazoles**




$CF_2H$-substituted pyrazoles **4d** and **4e** in good yields (80%, 94%), while the ketone functional group was also reduced to alcohol in the meantime.

These results demonstrate that the phenylsulfone moiety can act as a traceless group for the preparation of $CF_2H$-contaning pyrazoles. However, a two-step procedure is inevitable for the transformations with electron-deficient alkynes. To address this issue, we envisioned that a one-pot manner to synthesize $CF_2H$-contaning pyrazoles might be achieved by the transformations of Ps-DFA with electron-deficient alkenes. Moreover, the use of alkenes as cyclization partners is more appealing attributed to their abundance, lost cost, as well as wide synthetic accessibility. It has been reported that [3 + 2] cycloaddition of difluorodiazo compounds with alkenes would produce pyrazolines.[7b,8a,b] Thus, the key of this proposal relies on the subsequent desulfonylation process to give target $CF_2H$-pyrazoles. To test this hypothesis, Ps-DFA **1** was first treated with ethyl acrylate **5b** in THF at 40 °C for 36 h (Table 1, entry 1). Reaction detection indicated that Ps-DFA was consumed completely, then DBU was added to facilitate the desulfonylation step. To our delight, the $CF_2H$-pyrazole **4b** was obtained in 58% yield in one-pot operation. The yield of **4b** was further increased to 78% when ethyl acrylate was employed as the limiting reagent, while Ps-DFA was still only used in 1.1 equiv (entry 2). Next, various solvents and organic bases were evaluated for this one-pot



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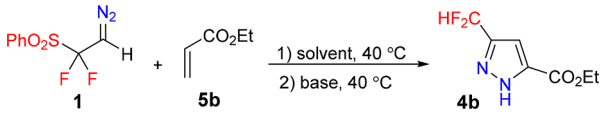
**Table 1. Optimization Studies**[a]



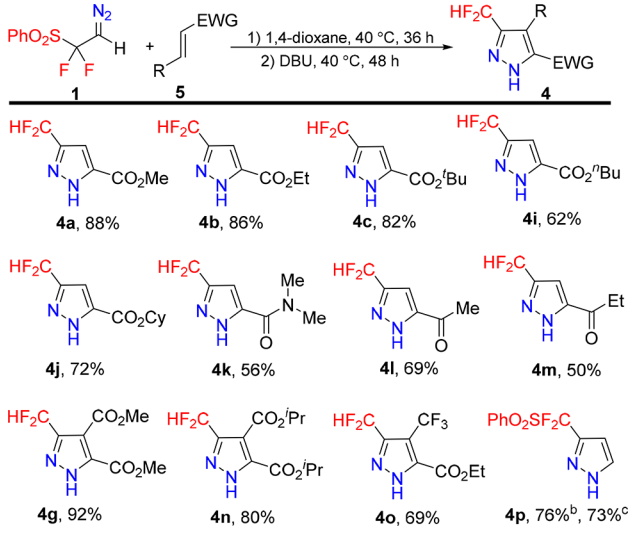

| entry | 1/5b (equiv) | solvent | base | yield (%)[b] |
|---|---|---|---|---|
| 1 | 1.0:1.2 | THF | DBU | 58 |
| 2 | 1.1:1.0 | THF | DBU | 78 |
| 3 | 1.1:1.0 | toluene | DBU | 83 |
| 4 | 1.1:1.0 | MeCN | DBU | 52 |
| 5 | 1.1:1.0 | $CHCl_3$ | DBU | 37 |
| 6 | 1.1:1.0 | DCM | DBU | 20 |
| 7 | 1.1:1.0 | 1,4-dioxane | DBU | 89 (86)[c] |
| 8 | 1.1:1.0 | 1,4-dioxane | DMAP | 3 |
| 9 | 1.1:1.0 | 1,4-dioxane | $Et_3N$ | 5 |
| 10 | 1.1:1.0 | 1,4-dioxane | $(^iPr)_2NEt$ | 0 |

[a]Reaction conditions: Ps-DFA **1** (0.22 mmol), **5b** (0.2 mmol), solvent (3 mL), 40 °C, 36 h; then base (0.4 mmol), 40 °C, 48 h. [b]Yields were determined by $^{19}F$ NMR. [c]Isolated yield.

reaction (entries 3−10), and the desired product **4b** was afforded in 86% yield when 1,4-dioxane was chosen as the reaction media (entry 7). It is worth noting that other bases such as DMAP, $Et_3N$, or DIPEA, could not lead to the generation of target pyrazole in practical amount (entries 7−10), highlighting the crucial role of DBU in the desulfonylation step.

With the optimized conditions in hand, the generality of this one-pot reaction was probed with a series of electron-deficient alkenes. As shown in Scheme 5, an array of $CF_2H$-pyrazoles were

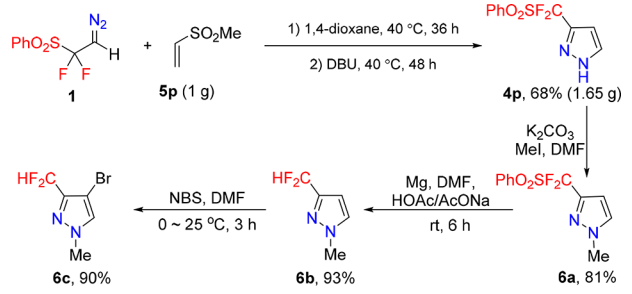
**Scheme 5. Synthesis of 3-$CF_2H$ Pyrazoles from Alkenes**[a]




[a]Reaction conditions: Ps-DFA **1** (0.22 mmol), **5** (0.2 mmol), solvent (3 mL), 40 °C, 36 h; then DBU (0.4 mmol), 40 °C, 48 h. [b]Methyl vinyl sulfone as starting material. [c]Phenyl vinyl sulfone as starting material.

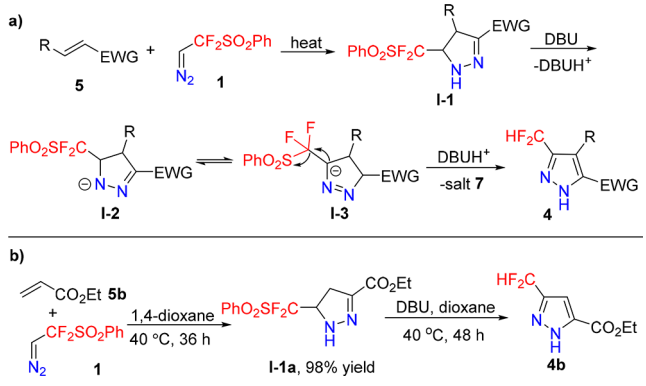
smoothly obtained in good to high yield under mild conditions. For instance, various acrylates with an ester or amide group underwent the [3 + 2] cycloaddition and subsequent desulfonylation to give the desired products **4a**−**k** in 56−88% yields. The ketone-containing alkenes are also compatible with this transformation to furnish the corresponding products **4l** and **4m** in 69% and 50% yields, respectively. Two fumarate compounds also worked well under the identical reaction conditions to give the products **4g** and **4n** in high yield. Ethyl (*E*)-4,4,4-trifluorobut-2-enoate also proved to be a viable substrate, thus delivering the cycloadduct **4o** equipped with both of $CF_2H$ and $CF_3$ groups. When vinyl sulfones were employed under the current reaction conditions, very interestingly, monosubstituted pyrazole **4p** was obtained in good yield. To highlight the synthetic value of our approach, this cycloaddition was scaled up to the gram-scale, and further transformation of the cycloadduct **4p** proceeded efficiently through methylation, desulfonylation, and bromination (Scheme 6). 4-Bromo-3-difluoromethyl-1-methylpyrazole **6c**, an important intermediate of agrochemicals,[14] was obtained in good yield.

**Scheme 6. Gram-Scale Cycloaddition Reaction and Further Synthetic Transformation of the Cycloadducts**




On the basis of our experimental results and previous studies,[15] a possible mechanism for the one-pot transformation of Ps-DFA **1** with electron-deficient alkene **5** is illustrated in Scheme 7a. First, [3 + 2] cycloaddition of alkene with a diazo

**Scheme 7. Plausible Mechanism of One-Pot Transformation**




compound would proceed to give pyrazoline **I-1**. This step is confirmed by the isolation and characterization of a pyrazoline intermediate **I-1a** in control experiment without DBU (Scheme 7b). Subsequently, DBU would abstract a proton from intermediate **I-1** to form the anionic intermediate **I-2**, followed by an isomerization process to generate intermediate **I-3**. Then the $PhSO_2^-$ would eliminate as a combination with $DBUH^+$ to give the desired $CF_2H$-substituted pyrazoles **4**. Specifically, a salt complex **7**, which is predicted to be generated from the reaction, was successfully isolated and subjected to X-ray analysis to support the proposed mechanism (see the SI).[16]

In summary, a bench-stable difluorodiazoethane reagent with a masked phenylsulfonyl group has been designed and successfully synthesized in good yield within five steps from



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thiophenol and ethyl bromodifluoroacetate. The potential application of this complementary and viable compound is demonstrated by direct regioselective [3 + 2] cycloaddition reactions with electron-deficient alkynes and alkenes. This protocol provides facile access to a variety of difluoromethyl-containing pyrazoles under mild reaction conditions. DBU is found to be an efficient desulfonation reagent to produce pyrazoles from pyrazolines. Further exploration of this masked difluorodiazoethane in other synthetic reactions is currently underway in our laboratory, the results of which will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01854.

Experimental details and spectral data of all the new compounds(PDF)

### Accession Codes

CCDC 1837133 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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(16) The obtained salt complex **7** after recrystallization was $PhSO_3H$·DBU due to oxidation under air.




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