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Difluorocarbene-Triggered Cyclization: Synthesis of (Hetero)arene-Fused 2,2-Difluoro-2,3-dihydrothiophenes

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Cite This: *Org. Lett.* 2020, 22, 7047–7051 Read Online

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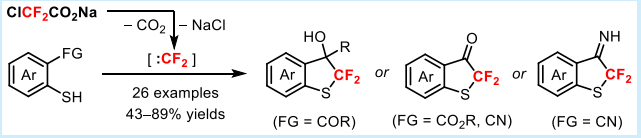
ABSTRACT: An efficient method for the synthesis of (hetero)-arene-fused 2,2-difluoro-2,3-dihydrothiophene derivatives using readily available sodium chlorodifluoroacetate ($ClCF_2CO_2Na$) has been developed. This transformation is achieved through a combination of a thiolate with difluorocarbene, followed by intramolecular nucleophilic addition to a ketone, cyano, or ester functional group.



Organofluorine compounds make up a fascinating class of molecules, which have shown wide applications in the fields of pharmaceuticals, agrochemicals, and material sciences.[1] Selective introduction of fluorine atoms or fluorinated moieties has become a routine strategy for imparting significant properties on organic molecules, particularly in terms of reactivity and biological activity.[2] Among various fluorinated moieties, the sp^3-hybridized difluoromethylene ($-CF_2-$) can be regarded as the bioisostere of the oxygen atom and has been applied to mimic the metabolically labile oxygen atom in ether, phosphonate, and sulfate.[3] Moreover, substitution of a methylene group with CF_2 can alter the conformation and reactivity of an organic molecule, thus bringing about a dramatic improvement in biological activity.[3a,f,4] For instance (Figure 1),[5] compared to non-

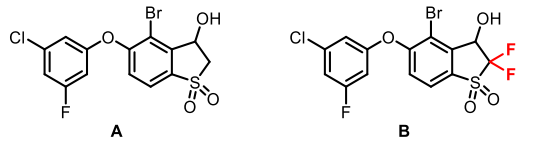


Figure 1. Dramatic effect of fluorine substituents on the HIF-2α activity of benzo-cyclic sulfone compounds.

fluorinated benzo-cyclic sulfone **A**, *gem*-difluorinated benzo-cyclic sulfone **B** showed an at least 100-fold higher HIF-2α activity due to the enhancement of the electron-withdrawing ability of the sulfonyl group, as well as the change of the environment of the hydroxyl group by the two geminal fluorine substituents.

Among various methods for the construction of *gem*-difluorinated compounds, difluorocarbene-involved reactions have attracted a great deal of attenton.[6] Since 2013, difluorocarbene has been exploited as a versatile C1 building block for the synthesis of *gem*-difluorinated compounds through its sequential reaction with a nucleophile and an electrophile (rather than a proton).[6] However, this approach has witnessed limited success in bridging a heteroatom nucleophile and a ketone[7] (Scheme 1a) because of the poor stability of the newly generated *gem*-difluorinated carbanion species, with only two examples being reported (Scheme 1b).[8] One is the three-component reaction of triphenylphosphine, difluorocarbene, and a ketone, which requires the action of a silyl cation to trap the *in situ*-formed *gem*-difluorinated alcoholate intermediate;[8a] the other is the cyclization of *o*-hydroxyaryl ketones with difluorocarbene, which was demonstrated with only chalcones.[8b]

Previously, we reported the nucleophilic difluoro(phenylthio)methylation of a series of electrophiles with $PhSCF_2H$ using *t*-BuOK or KOH as the base and found that $PhSCF_2^-$ can readily react with ketones.[9] In view of this, we envisioned that the combination of an aromatic thiolate anion (ArS^-) and difluorocarbene (to *in situ* generate $ArSCF_2^-$) would provide a novel method for nucleophilic difluoro(arylthio)methylations. However, our initial attempt to difluoromethylate ketones using 2-$PySCF_2^-$ generated *in situ* from 2-PyS^- and a difluorocarbene source such as sodium chlorodifluoroacetate (SCDA) failed to afford the desired product (Scheme 1c). Instead, the protonation of the 2-$PySCF_2^-$ anion proceeded much faster than the ketone addition reaction. In this context, we speculated that the combination of the thiolate nucleophile and the ketone electrophile within the same molecule might facilitate the addition step. Herein, we report the cyclization of *o*-

Received: August 11, 2020
Published: August 20, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02688
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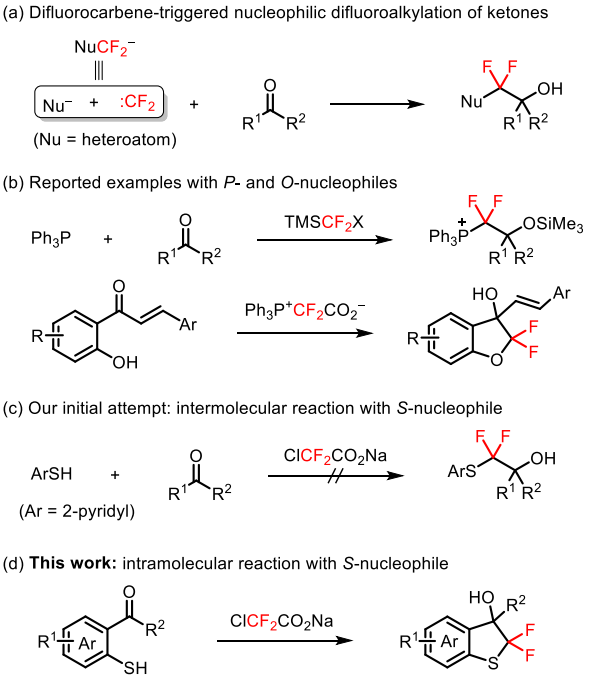
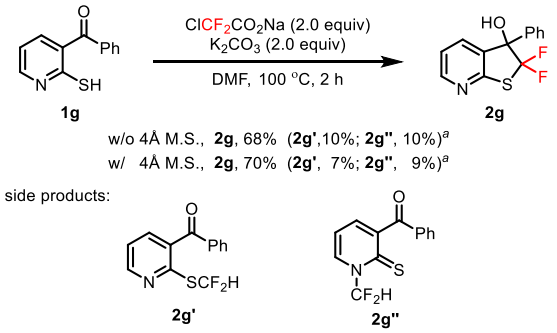
Scheme 1. Nucleophilic Difluoroalkylation of Ketones with Difluorocarbene



mercapto(hetero)aryl ketones with difluorocarbene derived from sodium chlorodifluoroacetate (Scheme 1d), which provides a concise method for the construction of novel (hetero)arene-fused 2,2-difluoro-2,3-dihydrothiophene derivatives.[10]

Our study began with the reaction of *o*-mercaptoheteroaryl ketone **1g** with sodium chlorodifluoroacetate (SCDA) (Scheme 2). We chose SCDA as the difluorocarbene reagent

Scheme 2. Cyclization Reaction of 2-Mercaptopyridin-3-yl Ketone 1g with Difluorocarbene

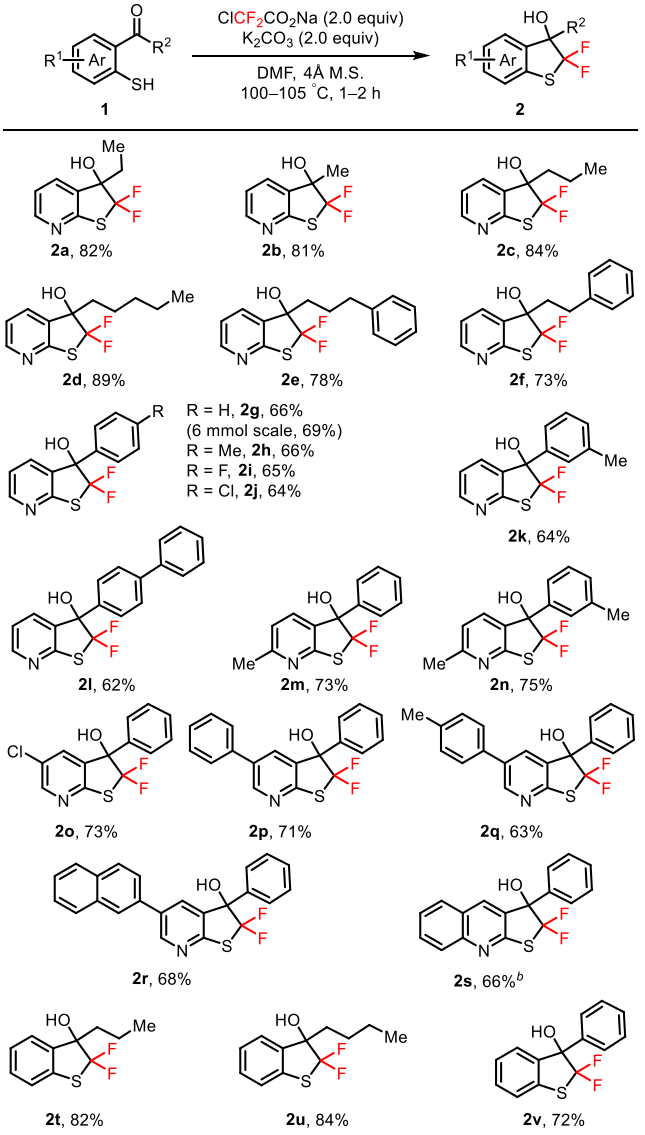


[a]The yield and product ratio were determined by ^{19}F NMR spectroscopy with benzotrifluoride as the internal standard.

for two reasons. (1) It is readily available, and (2) it can generate difluorocarbene and react with aromatic thiols under non-aqueous conditions,[11] thus minimizing the competitive protonation of the arylthiodifluoromethyl anion intermediate. To our delight, when **1g** was treated with 2.0 equiv of SCDA in the presence of 2.0 equiv of K_2CO_3 as the base in DMF at 100 °C, the reaction proceeded smoothly to provide the desired product **2g** in 68% ^{19}F NMR yield. Meanwhile, difluoromethyl compounds **2g′** and **2g″** were formed as side products. When 4 Å molecular sieves (MS) were used as an additive, the yield of the desired cyclization product **2g** was slightly increased, with inhibition of S- and N-difluoromethylation to some extent.

We next explored the substrate scope of *o*-mercapto(hetero)aryl ketones by using SCDA as the difluorocarbene precursor, K_2CO_3 as the base, and 4 Å MS as the additive (Scheme 3). The reaction tolerated 2-mercaptopyridin-3-yl

Scheme 3. Scope of *o*-Mercapto(hetero)aryl Ketones 1[a]



[a]The reactions were conducted on a 0.35−1.0 mmol scale; for experimental details, see the Supporting Information. Unless otherwise noted, isolated yields are given. [b]The yield was calculated according to the ^{19}F NMR spectroscopy analysis of the isolated crude product. An analytically pure sample was obtained through HPLC separation.

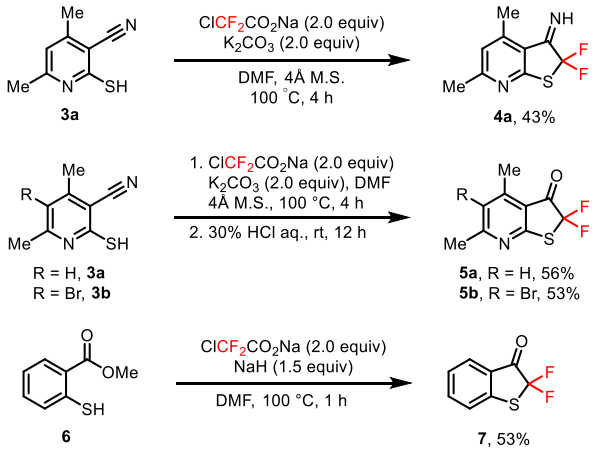
ketones with various substitution patterns. Both alkyl and aryl substituents led to the formation of the expected cyclization products **2a**−**2l** in 62−89% yields. It is noteworthy that the alkyl-substituted ketones took part in the reaction to afford the products (**2a**−**2f**) in yields that were significantly higher than those of the aryl-substituted ketones (products **2g**−**2l**) due to the decreased steric hindrance. In the cases of aryl-substituted ketones, the electronic nature of the aryl substituents had little influence on the yields of the desired products **2g**−**2l**. The

https://dx.doi.org/10.1021/acs.orglett.0c02688
Org. Lett. 2020, 22, 7047−7051

electron-rich and electron-deficient aryl-substituted ketones underwent the reaction to afford the products in similar yields. A variety of substituents on the pyridyl ring of the substrates, such as methyl, chloro, phenyl, and naphthyl, were also tolerated and produced the corresponding cyclization products **2m**−**2r** in similar yields (63−75%). In addition to the pyridyl ring, the reaction is also amenable to other heteroaromatic rings such as the quinolinyl ring. For example, the reaction of (2-mercaptoquinolin-3-yl)(phenyl)methanone (**1s**) gave the desired product **2s** in 66% yield. The cyclization reaction was also examined using aryl- and alkyl-substituted 2-mercaptophenyl ketones, which proceeded smoothly to furnish benzo-fused 2,2-difluoro-2,3-dihydrothiophen-3-ols **2t**−**2v** in 72−84% yields.

Furthermore, other functional groups such as cyano and ester functionalities could also serve as acceptors of the *in situ*-formed $ArSCF_2^-$ (Scheme 4). Thus, treatment of 2-

Scheme 4. Cyclization Reaction of 2-Mercaptonicotinonitrile and 2-Mercaptobenzoate with Difluorocarbene

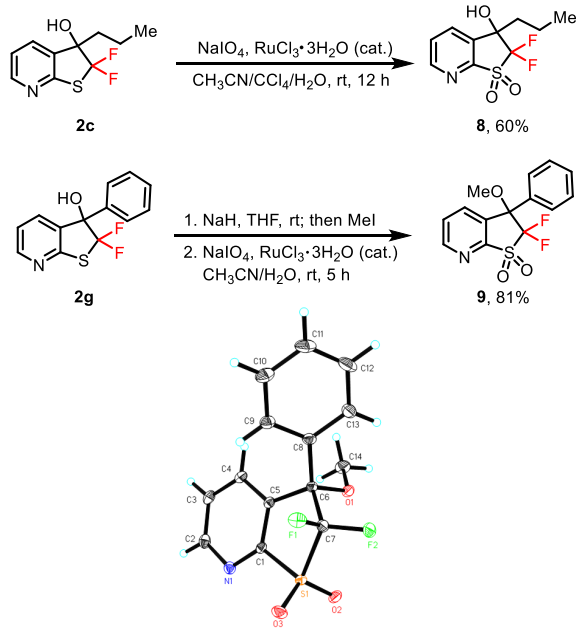


mercaptonicotinonitrile **3a** with SCDA and K_2CO_3 at 100 °C delivered the pyridine-fused 2,2-difluorothiophen-3(2*H*)-imine **4a** in 43% isolated yield. The difluorinated cyclic imines could be transformed into the corresponding cyclic ketones under acidic hydrolysis. The one-pot reaction of 2-mercaptonicotinonitrile **3a** and **3b** with SCDA followed by hydrolysis with concentrated hydrochloric acid gave **5a** and **5b** in 56% and 53% yields, respectively. When 2-mercaptobenzoate **6** was subjected to the reaction with SCDA, the employment of NaH instead of K_2CO_3 was required to promote the cyclization reaction, providing benzo-fused difluorinated cyclic ketone **7** in 53% yield.

Finally, to demonstrate the synthetic utility of the obtained cyclization products, we explored the transformation of products **2** (Scheme 5). Oxidation of cyclic sulfide **2c** with $NaIO_4$ at room temperature generated the desired cyclic sulfone **8** in 60% yield. It is worth mentioning that the difluorinated five-membered cyclic sulfone scaffold in **8** has found application in the design of specific HIF-2α inhibitors.[5] In addition, selective O-methylation of **2g** with CH_3I followed by oxidation produced the corresponding sulfone product **9** in 81% yield. The structure of **9** has been unambiguously confirmed by single-crystal X-ray analysis.

On the basis of our experimental results and in combination with a previous report on S-difluoromethylation with SCDA,[11]

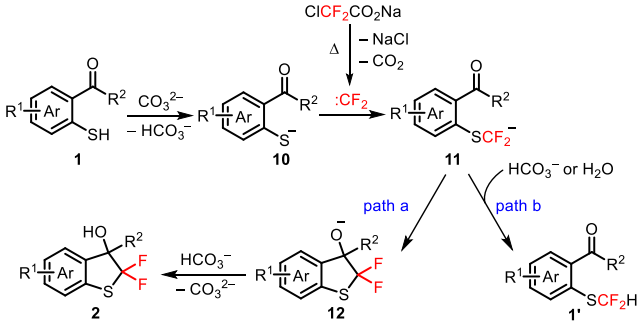
Scheme 5. Further Transformation of 2



Molecular structure of **9**
(with thermal ellipsoids at the 30% probability level)

a plausible reaction mechanism for a reaction in which sulfur participates was proposed (Scheme 6). Deprotonation of **1**

Scheme 6. Proposed Reaction Mechanism



with K_2CO_3 would generate thiolate nucleophile **10**, and the latter would react with difluorocarbene to generate difluorinated carbanion **11**. The fate of **11** is determined by the type of proton source. When K_2CO_3 is used as the base under anhydrous conditions, $KHCO_3$ would serve as a proton source, and the intramolecular cyclization of carbanion **11** followed by protonation by $KHCO_3$ (path a) would proceed much faster than the direct protonation of carbanion **11** by $KHCO_3$ (path b). Thus, the formation of the desired cyclization product would predominate. When K_2CO_3 was used in the presence of water, water quenched carbanion **11** preferentially to give the S-CF_2H product (path b).

In conclusion, we report a new entry of tandem cyclization reactions of *o*-acyl-, aroyl-, alkoxycarbonyl-, and cyano-substituted (hetero)aromatic thiols with difluorocarbene derived from sodium chlorodifluoroacetate.[12] The reaction proceeds via the trapping of difluorocarbene by the thiolate anion followed by intramolecular addition. This method allows the synthesis of a series of novel (hetero)arene-fused 2,2-difluoro-2,3-dihydrothiophene derivatives, which promises to

https://dx.doi.org/10.1021/acs.orglett.0c02688
Org. Lett. 2020, 22, 7047−7051

find applications in drug design and agrochemical development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02688.

Detailed experimental procedures, characterization data, and copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra of new compounds (PDF)

Accession Codes

CCDC 1896932 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.

■ ACKNOWLEDGMENTS

This work was supported by the National Key Research and Development Program of China (2016YFB0101200), the National Natural Science Foundation of China (21632009 and 21421002), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049), and the Shanghai Science and Technology Program (18JC1410601). H.L. thanks Jie Sun (SIOC) for assistance with the X-ray crystallographic analysis.

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(12) The reaction of a five-membered heterocycle-containing substrate, 1-(2-mercapto-1-methyl-1*H*-indol-3-yl)ethan-1-one, afforded the desired cyclization product in low yields (for details, see the Supporting Information).

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Org. Lett. 2020, 22, 7047−7051