

Divergent S- and C-Difluoromethylation of 2-Substituted Benzothiazoles

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Cite This: *Org. Lett.* 2021, 23, 8554–8558



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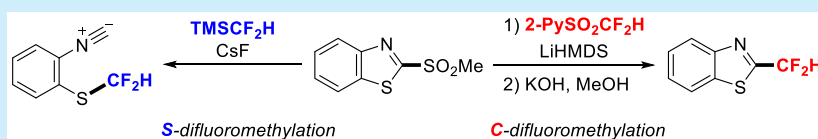
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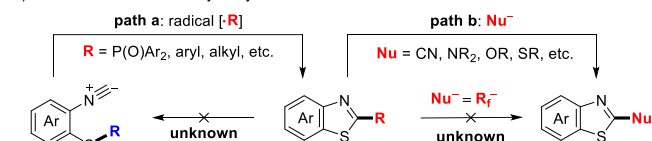


ABSTRACT: Two unprecedented and complementary synthetic strategies for S- and C-difluoromethylation of 2-substituted benzothiazoles have been developed by taking advantage of the remarkably different reactivity of CF_2H^- and $2\text{-PySO}_2\text{CF}_2^-$ nucleophiles. A variety of structurally diverse difluoromethyl 2-isocyanophenyl sulfides and 2-difluoromethylated benzothiazoles were synthesized with these two new synthetic protocols.

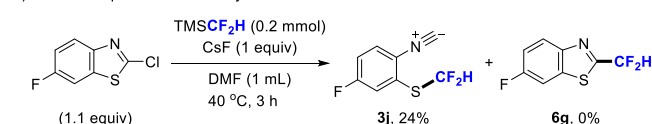
Isocyanides are versatile synthetic building blocks for the synthesis of nitrogen-containing molecules.¹ Their wide applications in multicomponent reactions,² transition-metal-catalyzed isocyanide insertions,³ and radical cascade reactions^{4,5} provide efficient access to an array of pharmaceutically relevant molecules. In particular, 2-isocyanophenyl thioethers could be used as radical acceptors in radical cyclization reactions to construct 2-substituted benzothiazoles (Scheme 1a, path a),⁶ which are prevalently existing in various naturally occurring compounds and drugs.⁷ However, despite the remarkable progress in the cyclization of 2-isocyanophenyl thioethers to 2-substituted benzothiazoles,⁶ its reverse process, namely, the ring-opening reaction of 2-substituted benzothiazoles to give 2-isocyanophenyl thioethers, still remains unknown.

Scheme 1. Transformations of 2-Isocyanophenyl Thioethers and 2-Substituted Benzothiazoles

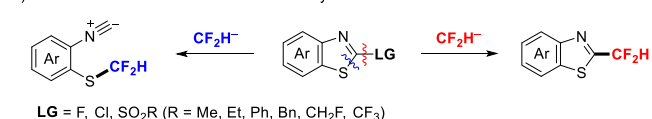
a) Reaction modes of 2-isocyanophenyl thioethers and 2-substituted benzothiazoles



b) Initial attempt on difluoromethylation of 2-substituted benzothiazoles



c) **This work:** selective S- and C-difluoromethylation of 2-substituted benzothiazoles



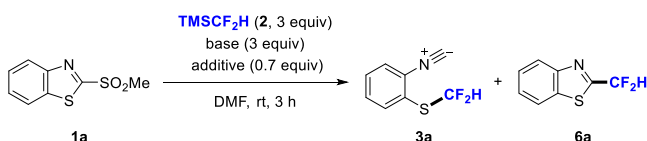
To date, the known reaction mode of 2-substituted benzothiazoles is the nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) at the C-2 position with a series of C-, N-, O- and S-nucleophiles (Scheme 1a, path b).⁸ However, to the best of our knowledge, the $\text{S}_{\text{N}}\text{Ar}$ reaction between a fluoroalkyl nucleophile and a 2-substituted benzothiazole has never been reported. Difluoromethyl group (CF_2H) can serve as a lipophilic hydrogen bond donor, and a bioisostere of OH or SH functionality.⁹ In this context, we initially attempted the $\text{S}_{\text{N}}\text{Ar}$ -type nucleophilic difluoromethylation of 2-substituted benzothiazoles with (difluoromethyl)trimethylsilane¹⁰ (TMSCF_2H , **2**). To our surprise, the expected product 2-difluoromethyl benzothiazole (**6g**) was not observed, and instead, difluoromethyl 2-isocyanophenyl sulfide (**3j**) was obtained in 24% yield (Scheme 1b). It is likely that an unprecedented S-difluoromethylation-ring-opening elimination tandem occurred.¹¹ This unexpected result intrigued us to investigate the nucleophilic difluoromethylation of 2-substituted benzothiazoles, especially the selectivity between $\text{S}_{\text{N}}\text{Ar}$ and aromatic ring opening reactions (Scheme 1c).

At the onset of our investigation, we chose 2-methanesulfonyl benzothiazole **1a** as a model substrate and TMSCF_2H (**2**) as the difluoromethyl anion precursor, and the reaction conditions were screened (Table 1). When a mixture of **1a** (0.2 mmol), **2** (3 equiv), CsF (3 equiv) in DMF were stirred at room temperature, neither ring-opening product **3a** nor $\text{S}_{\text{N}}\text{Ar}$ product **6a** was observed (entry 1). It is interesting that when

Received: September 24, 2021

Published: October 20, 2021



Table 1. Optimization of the Reaction Conditions of Ring-Opening S-Difluoromethylation of Benzothiazole 1a


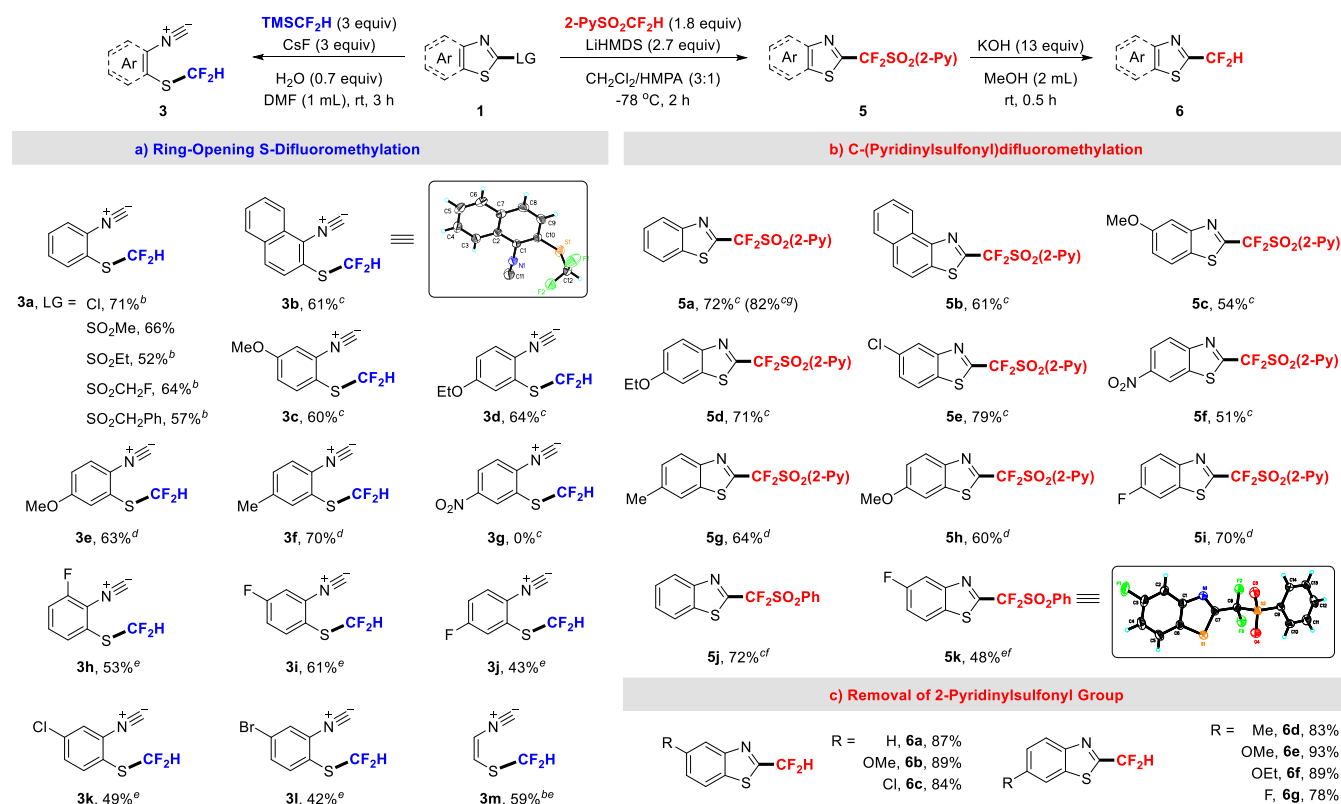
entry ^a	base	additive	3a yield (%) ^b	6a yield (%) ^b
1	CsF	none	0	0
2	CsF	H ₂ O	70 (66)	0
3	CsF	MeOH	53	0
4	TBAT	H ₂ O	33	0
5	KF	H ₂ O	6	0
6	K ₂ CO ₃	H ₂ O	14	0
7	CsOH	H ₂ O	9	0

^aReaction conditions: **1a** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), base (3 equiv), additive (0.7 equiv), DMF (1 mL), rt, 3 h. ^bYields were determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard, and the isolated yield was shown in parentheses.

0.7 equiv of water was added, 70% yield of the ring-opening product **3a** was formed (entry 2). To figure out the role of water, we replaced water with another proton source methanol, and found that **3a** was formed in slightly lower yield (53%; entry 3). Furthermore, when a mixture of **3a** (0.2 mmol), TMSCF₂H (3 equiv), CsF (3 equiv) and DMF (1 mL) was stirred at room temperature for 3 h in the absence of water,

compound **3a** completely decomposed (Scheme S1 in Supporting Information). These results indicate that water serves as a proton source and quenches the unreacted difluoromethyl anion (forming CH₂F₂), which diminishes the decomposition of **3a**. The amount of water was carefully screened, and 0.7 equiv of water was identified as optimal for the reaction (Table S2 in Supporting Information). In addition to CsF, other Lewis base activators such as TBAT, KF, K₂CO₃, and CsOH were tested, but all showed lower efficiency than CsF in activating the Si–CF₂H bond cleavage in DMF at room temperature (entries 4–7). Notably, in all cases, no formation of S_NAr-type C-difluoromethylation product **6a** was observed during the current ring-opening S-difluoromethylation reaction (Table 1).

With the standard reaction conditions in hand (Table 1, entry 2), the substrate scope of the ring-opening S-difluoromethylation reaction with TMSCF₂H was investigated (Scheme 2a). First, the leaving group ability of different groups at C-2 position of **1** was examined (LG = Cl, SO₂Me, SO₂Et, SO₂CH₂F, and SO₂CH₂Ph), and in all cases the reaction proceeded smoothly, affording product **3a** in moderate to good yields. Second, we chose 2-(methanesulfonyl)naphthothiazole as a substrate in the reaction, and product **3b** was obtained in 61% yield. The structure of **3b** was confirmed by its single crystal X-ray analysis. Third, benzothiazoles bearing electron-donating groups (such as methyl, methoxyl and ethoxyl) are amenable to the present ring-opening S-difluoromethylation reaction, with the corresponding products **3c–3f** being formed in 60–70% yields. However, no desired product **3g** was

Scheme 2. Divergent S- and C-Difluoromethylation of 2-Substituted Benzothiazoles^a

^aIsolated yields. ^bYields were determined by ¹⁹F NMR spectroscopy using trifluorotoluene as an internal standard. ^cLG = SO₂Me. ^dLG = SO₂Ph. ^eLG = Cl; 2.0 equiv of H₂O were used in S-difluoromethylation. ^fPhSO₂CF₂H was used instead of 2-PySO₂CF₂H, THF (1.2 mL) was used instead of CH₂Cl₂. ^g6 mmol scale reaction.

detected when a nitrated benzothiazole was subjected to the standard reaction conditions. Fourth, in cases of 2-chlorobenzothiazoles, the halogen substituents (such as F, Cl and Br) on the aromatic ring were compatible with the reaction conditions (see **3h–3l**). Finally, 2-chlorobenzothiazole was also able to participate in the reaction, and target product **3m** was formed in 59% yield (determined by NMR).

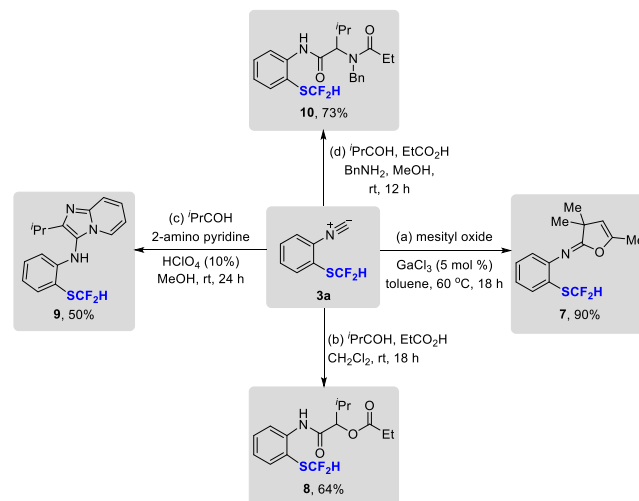
Encouraged by the aforementioned ring-opening S-difluoromethylation of 2-substituted benzothiazoles with TMSCF_2H , we further applied other fluorinated nucleophiles in the reaction with 2-substituted benzothiazoles. Difluoromethyl 2-pyridyl sulfone (2-PySO₂CF₂H), a reagent developed by us, is now commercially available and widely used for fluoroalkylation and fluoroolefination reactions.¹² We were surprised to find, when 2-(methanesulfonyl)benzothiazole **1a** reacted with 2-PySO₂CF₂[−] (derived from 2-PySO₂CF₂H and LiHMDS) in CH₂Cl₂/HMPA at −78 °C for 2 h, no ring-opening S-(2-pyridinesulfonyl)difluoromethylation product was formed, but S_NAr-type C-(2-pyridinesulfonyl)difluoromethylation product **5a** was obtained in 72% isolated yield (see Table S3 in Supporting Information and Scheme 2b). This result suggests that different α -fluoro carbanions show remarkably different reactivity (chemoselectivity) in their reactions with 2-substituted benzothiazoles.

Next, we examined the generality of the current S_NAr-type C-(2-pyridinesulfonyl)difluoromethylation of **1** (Scheme 2b). First, the reaction was not sensitive to leaving groups at C-2 position of benzothiazoles **1**. When chloro, methanesulfonyl, and benzenesulfonyl groups were used as the leaving groups, the S_NAr-type C-fluoroalkylation reactions proceeded smoothly to yield the corresponding products in 48–79% yields (**5a–5k**). The current C-fluoroalkylation reaction was applied in gram-scale synthesis, and product **5a** was obtained in 82% isolated yield (1.6 g). Second, the reaction was able to tolerate different substituents on **1**, including methyl, methoxyl, ethoxyl, chloro, and nitro groups (**5c–5i**). Third, when we replaced 2-PySO₂CF₂H with PhSO₂CF₂H, the S_NAr-type C-benzenesulfonyl difluoromethylation products **5j** and **5k** were also successfully formed in 72% and 48% yields, respectively. With products **5** in hand, we performed the base-promoted selective desulfonylation to transform **5** to difluoromethylated compounds **6** (Scheme 2c, also see details in Table S4 in Supporting Information). In the presence of KOH (13 equiv) in methanol at room temperature, **5** were readily converted into **6** within 30 min in 78–93% yields (Scheme 2c). Given the results shown in Scheme 2, it is intriguing that the remarkably different reactivity of CF₂H[−] and 2-PySO₂CF₂[−] have enabled two complementary synthetic strategies for highly chemoselective S- and C-difluoromethylation of 2-substituted benzothiazoles **1**.

To demonstrate the synthetic utility of the current synthetic protocol, we applied **3a** as a valuable building block in multicomponent reactions. First, **3a** was used in a GaCl₃-catalyzed [4 + 1] cycloaddition with mesityl oxide, which afforded SCF₂H-substituted unsaturated lactone derivative **7** in 90% yield (Scheme 3a).¹³ Furthermore, **3a** was also applied in Passerini, Gröbcke–Blackburn–Bienaymé, and Ugi reactions, giving products **8–10** in moderate to good yields (Scheme 3b–d).

In summary, we have successfully developed two unprecedented and complementary synthetic strategies for divergent S- and C-difluoromethylation of 2-substituted benzothiazoles by taking advantage of the remarkably different reactivity of

Scheme 3. Synthetic Applications of **3a**



CF₂H[−] and 2-PySO₂CF₂[−] nucleophiles. A variety of structurally diverse difluoromethyl 2-isocyanophenyl sulfides **3** and 2-difluoromethylated benzothiazoles **6** were synthesized with these two new synthetic protocols. Our study uncovers the unique reactivity of CF₂H[−], which promises to stimulate further development of new difluoromethylation reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c03267>.

Full characterization, copies of all spectral data, crystallographic data of CCDC 2031759 (**3b**) and CCDC 2031760 (**5k**), and experimental procedures (PDF)

■ Accession Codes

CCDC 2031759–2031760 contain 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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Author Contributions

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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), 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 fellowship of China Postdoctoral Science Foundation (2020M671273).

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