Ring-closing Disulfenylation of Alkenoic Thioester

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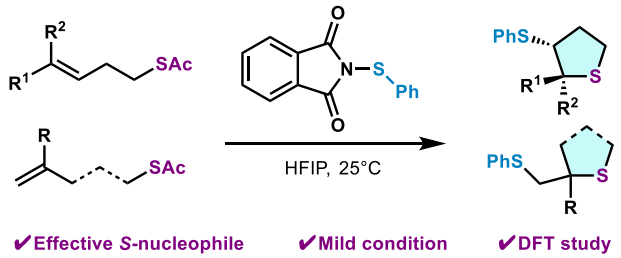


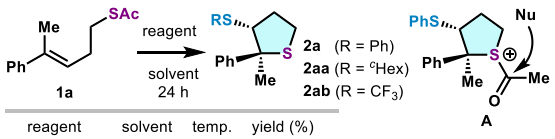
ABSTRACT: This study demonstrated for the first time that alkenoic thioesters can be effectively used as nucleophiles in ring-closing disulfenylation reactions. Our investigation revealed that the reaction in hexafluoroisopropanol with an electrophilic sulfur reagent significantly enhances the product yield. We gathered experimental and theoretical evidence to support the superiority of thioesters over traditionally used benzyl sulfide. Additionally, we explored the substrate scope and identified various factors affecting reaction selectivity and yield.

The field of organic synthesis has long been fascinated with the development of efficient methodologies for the formation of carbon–chalcogen bonds, given their widespread applications in natural products, pharmaceuticals, agrochemicals, and materials science.[1] Among these bonds, dichalcogenation (chalcogen = S, Se, Te) of unsaturated compounds has emerged as a powerful tool in synthetic chemistry, enabling the construction of complex molecules with high precision and functional diversity.[2] Recent advancements in dichalcogenation reactions have significantly broadened the scope of available synthetic routes. These transformations allow for the introduction of sulfur, selenium, and tellurium atoms into organic molecules, which can profoundly influence their chemical reactivity and biological properties. Ring-closing dichalcogenation reactions have proven to be particularly valuable, providing efficient pathways to construct sulfur- or selenium-containing heterocycles. These heterocycles are of substantial interest owing to their unique chemical properties and potential applications in drug discovery and materials science.[3] However, despite extensive exploration of these reactions, there remains a significant gap in the literature regarding the ring-closing disulfenylation of unsaturated compounds. Although there are numerous examples of the ring-closing disulfenylation of alkynoic sulfides[4] and intermolecular disulfenylation of alkenes,[5] the scope of ring-closing disulfenylation of alkenoic compounds remains to be explored. For example, *N*-allylthioamide has been utilized in disulfenylation; however, the products are limited, yielding only thiazoline and thiazine.[6]

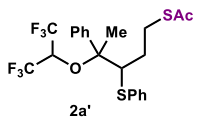
We recently investigated various cyclization reactions of unsaturated thioesters and reported metal hydride hydrogen atom transfer (MHAT)/radical-polar crossover (RPC) promoted hydrothiolation of alkenoic thioesters,[7] bromocyclization of alkenoic thioesters,[8] and halocyclization–oxidative aromatization of alkynoic thioesters.[9] In these studies, we demonstrated the nucleophilicity of the sulfur atom in thioesters, which had not been previously examined as extensively as that of sulfide.[10] Ever since a selenosulfenylation reaction was reported in 1981,[11] the disulfenylation of alkenoic thioesters has not been explored. Building on these foundational studies, herein, we investigated ring-closing disulfenylation by combining alkenoic thioesters and a commercially available electrophilic sulfur reagent,

further demonstrating the value of thioester as a nucleophile.

First, we investigated the disulfenylation reaction using alkenoic thioester **1a** (Figure 1). The reaction was initially carried out in dichloromethane, used in our previously reported bromocyclization reaction,[8a] with 1.2 equivalents of the commercially available electrophilic sulfur reagent **S1**. However, the starting material **1a** remained unchanged. The reaction was performed in hexafluoroisopropanol (HFIP) to activate **S1**, which dramatically improved the yield, successfully providing **2a** in 85% yield. Upon optimizing the reagent amount, we found that using an equimolar amount of **S1** slightly decreased the yield of **2a**, whereas using a large excess resulted in the formation of a side product, **2a'**. When other commercial electrophilic sulfur reagents were used, **S2** produced **2aa** in low yield, but **S3** did not yield **2ab** at all. Based on these results, subsequent studies were conducted using 1.2 equivalents of **S1**. We confirmed the scalability of this reaction using 1.0 mmol of **1a** and obtained **2a** in almost the same yield. Considering the previous literature reports,[12] we believe that **S1** was activated by multiple HFIP molecules through hydrogen bonding, which allows the molecules to interact with the alkene to enable C–S bond formation. We confirmed that **S1** preferentially interacts with the alkene moiety over thioester because benzyl thioester remained unchanged by **S1** treatment in HFIP. The C–S bond formation likely produces *S*-acetylsulfonium intermediate **A**, followed by deacetylation to yield the desired product. Potential nucleophiles that facilitate deacetylation include phthalimide and HFIP.



reagent	solvent	temp.	yield (%)
S1 (1.2 equiv)	DCM	25°C	**2a**, 0
S1 (1.2 equiv)	HFIP	25°C	**2a**, 85 (65)
S1 (1.0 equiv)	HFIP	25°C	**2a**, 80
S1 (2.0 equiv)	HFIP	25°C	**2a**, 63, 15%[a]
S2 (1.2 equiv)	HFIP	60°C	**2aa**, 39 (30)
S3 (1.2 equiv)	HFIP	60°C	**2ab**, 0



2a'

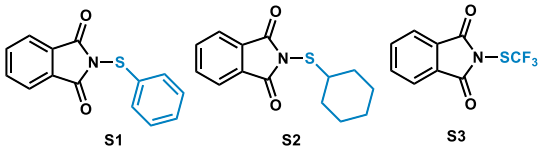


Figure 1: Reaction conditions: **1a** (0.1 mmol), reagent in solvent (1.0 mL), 24 h; NMR yields (dibromomethane as an internal standard) are given. Isolation yields are given in parentheses. [a]yield of **2a´**

To confirm the effectiveness of thioesters as *S*-nucleophiles, we investigated disulfenylation using benzyl sulfide **1b** for comparison (Figure 2). Benzyl sulfide is known to be an effective *S*-nucleophile, as demonstrated in bromocyclization. However, neither the desired product **2a** nor any cyclized molecule was obtained; instead, the HFIP-addition product **2b** was obtained in 51% yield. This result indicated that debenzylation from *S*-benzylsulfonium intermediate **B** did not proceed, and the nucleophilic attack of HFIP affording **2b** occurred instead. Conversely, in the case of **1a**, we assume that deacetylation of *S*-acetylsulfonium intermediate **A** is more rapidly facilitated, leading to the formation of **2a**, which clearly supports the advantage of thioester as a nucleophile over sulfide.

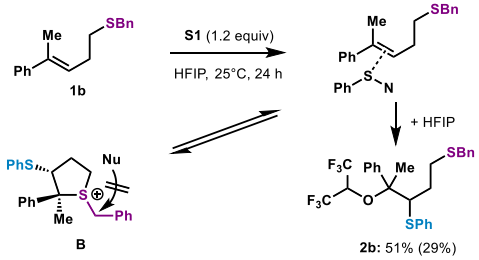


Figure 2. Reaction of benzylsulfide **1b** with an *S*-nucleophile.

To gain further insights into the mechanism of disulfenylation in HFIP, we performed density functional theory (DFT) studies using a mixed explicit–implicit solvation model (Figure 3). In our calculations, two explicit HFIP molecules were included due to the calculation cost. The inclusion of this specific number of HFIPs can be justified given the previous bromocyclization, in which similar outcomes were observed among one, two, and three HFIPs.[12c] Our DFT calculations for alkenoic thioester **1a** indicate that the favorable pathway of disulfenylation in HFIP is the traditional stepwise Ad_E2-type mechanism, rather than the concerted Ad_E3-type mechanism.[13] The activation barrier to form episulfonium intermediate **I** was calculated to be 19.4 kcal/mol. **I** was observed to be consistent with the HFIP-promoted bromocyclization reported by Mai and Nguyen.[12c] Furthermore, the interaction

between the phenyl group in **1a** and the phenylthiol group in **S1** assisted in the formation of the episulfonium intermediate. Indeed, the free energy of the transition state (**TS$_{1a}$´**) without this interaction was 5.9 kcal/mol higher than with the interaction (**TS$_{1a}$**). The lack of this interaction likely explains why **S2** yields less product than **S1** does. The activation barrier of forming the *S*-acetylsulfonium intermediate was calculated to be 9.7 kcal/mol. The final deacetylation step was found to be a more rapid process given the low activation energy, which was calculated to be 5.1 kcal/mol. This deacetylation step proceeded via concerted nucleophilic substitution rather than a stepwise mechanism.[14] However, in the case of alkenoic benzylsulfide **1b**, the barrier heights for debenzylation were much higher (23.9 kcal/mol) than that of alkenoic thioester **1a**. The results of our DFT calculations are clearly in agreement with the experimental result that **1a** was a superior substrate for disulfenylation over **1b**. Taken together, our experimental and theoretical results strongly support the advantage of thioester as a nucleophile in HFIP-promoted disulfenylation.

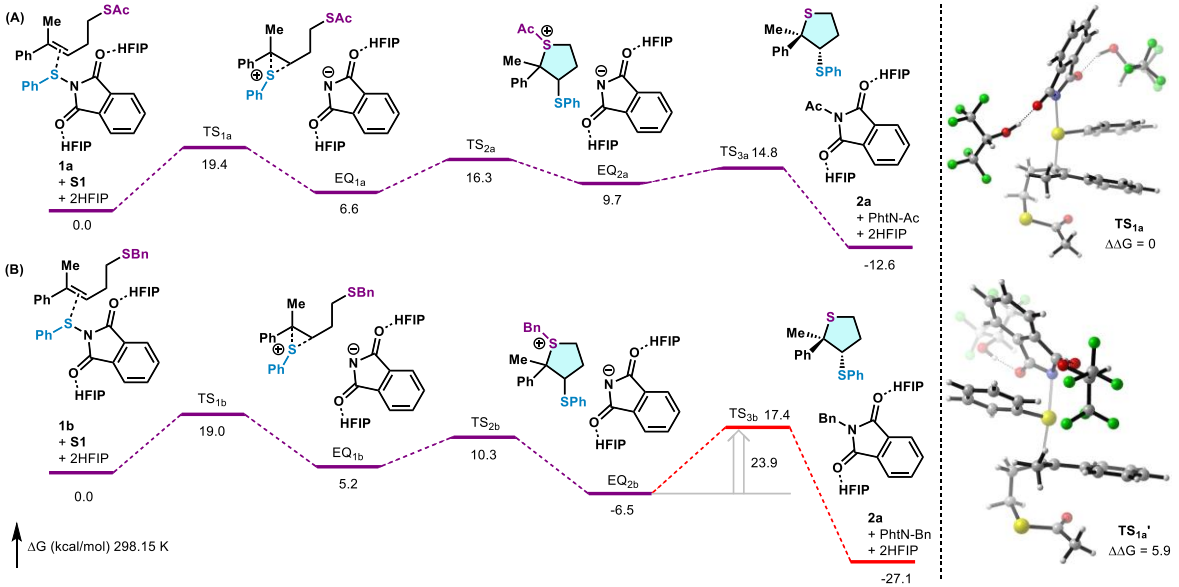


Figure 3. DFT study of the reaction path (A) derived from **1a** and (B) derived from **1b**, M06-2X/6-311+G(2d,2p)/SMD(HFIP)//M06-2X/6-31G(d,p)/SMD(HFIP) at 298.15 K (kcal/mol).

We next investigated the substrate scope of disulfenylation (Figure 4). Stereospecificity was examined using the *Z*-isomer of **1a**, which produced **2c** in 60% yield along with diastereomer **2a** in 25% yield. Although stereospecific bromocyclization of alkenoic thioesters using *N*-bromoacetamide was confirmed, this disulfenylation yielded some isomers, likely due to the ring opening of the episulfonium intermediate generating the planar carbocation, thus reducing selectivity. Similar results were obtained with **1e**, which lacked the methyl group. The selectivity for the disulfenylation of the *Z*-isomer **1e** was improved over that of **1c**, likely due to a destabilization of the corresponding carbocation. Subsequently, we examined the electronic effects of the aromatic ring of the substrates. Introducing an electron-donating methoxy group to **1a** resulted in a complex mixture, making it difficult to purify **2f**. When the reaction was carried out using **1g**, which lacked a methyl group to restrict the carbocation pathway, **2g** was obtained in 83% yield, along with HFIP-added product **2g'** in 13% yield (Supporting Information). The electron-withdrawing chlorine atom in **1h** and the trifluoromethyl group in **1i** led to the formation of **2h** and **2i**, respectively.

Next, 5-exocyclization was examined; the substrate scope and mechanism are presented in Figure 5. For example, monosubstituted alkene **1j** produced **2j** in 85% yield, whereas the disubstituted alkene **1k** resulted in **2k** in 44% yield, along with a complex mixture. Even in the case of alkenoic thioester **1l**, which is not unbiased for cyclization, **2l** was produced in 65% yield. Attempts at 6-exocyclization

of disubstituted alkene **1m** and monosubstituted alkene **1n** yielded **2m** and **2n,** respectively. Interestingly, a non-ring-closing 1,2-disulfenylation byproduct **2n'** was observed, but its detailed reaction mechanism remains unclear. The disulfenylation of **1o**, an isomer of **1a,** resulted in the formation of the desired **2o** in 44% yield, along with **2o'** in 30% yield. When reacted in HFIP, **2o'** has a 6-membered ring skeleton instead of a phenylthio group.

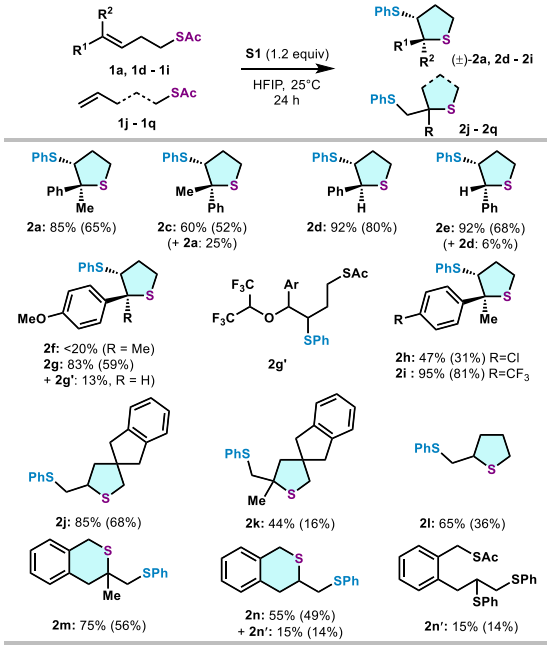


Figure 4. Substrate scope. Reaction conditions: starting material (0.1 mmol), **S1** (1.2 equiv) in HFIP (1.0 mL), 24 hours; NMR yields (dibromomethane as an internal standard) are given. Isolation yields are given in parentheses.

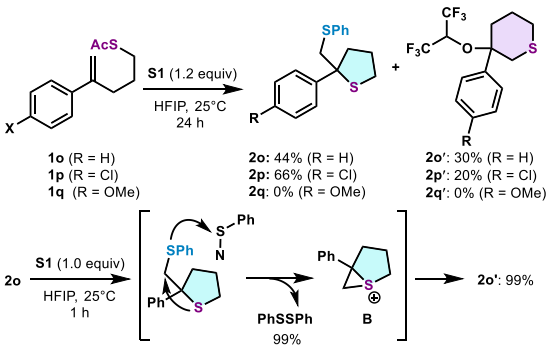


Figure 5. Further substrate scope and mechanistic experiments.

Introducing an electron-withdrawing chlorine atom on the aromatic ring of **1o** produced a similar result, affording **2p** and **2p'**, whereas the presence of the electron-donating methoxy group resulted in a complex mixture without **2q** and **2q'**.

To explore the subsequent skeletal rearrangement, we next conducted an additional experiment using product **2o**. We found that treatment of product **2o** with **S1** resulted in the quantitative formation of **2o'** and diphenyldisulfide. This result indicates that six-membered **2o'** and **2p'** were not formed directly from **1o** and **1p** but through a five-membered ring construction followed by skeletal rearrangement. The sulfur atom of the phenylthiol group in **2o** was likely to react with **S1** to form episulfonium intermediate **B** and diphenyldisulfide. Finally, the ring opening of the episulfonium intermediate by HFIP occurred via a skeletal rearrangement, affording six-membered product **2o'**. In contrast, the treatment of **2a** with **S1** resulted in the recovery of **2a** along with a complex product mixture.

In summary, we have successfully developed a novel methodology for the ring-closing disulfenylation of alkenoic thioesters, addressing a significant gap in the literature. By utilizing hexafluoroisopropanol (HFIP) as a solvent and the electrophilic sulfur reagent **S1**, we achieved efficient disulfenylation with high yields. Our study highlights the effectiveness of alkenoic thioesters as nucleophiles compared to other sulfur sources, such as benzyl sulfide, which exhibit lower reactivity. Theoretical studies using DFT support our experimental results, demonstrating a favorable pathway for disulfenylation in HFIP and the preference for thioesters as nucleophiles over benzyl sulfides owing to the energetic result of the deprotection step. We also explored the substrate scope, revealing insights into the stereospecificity, electronic effects, and cyclization preferences of alkenoic thioesters. This work not only advances the methodology of disulfenylation reactions but also opens new avenues for the synthesis of sulfur-containing heterocycles. Future research will focus on developing new reactions using thioesters as nucleophiles and exploring asymmetric variants of these reactions to expand their applicability and efficiency in organic synthesis.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the

published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at

http://pubs.acs.org.

Experimental procedures, characterization data, NMR spectra, computational details, and crystal data (PDF)

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Notes

The authors declare no competing financial interest.

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