Redox-Neutral Synthesis of Sulfilimines through the S-Alkylation of Sulfenamides

Xunbo Lu,* Guoling Huang, Kaiyuan Yang, and Xinyu Xu

KEYWORDS: Sulfenamides • S-Alkylation • Redox-Neutral • Metal-free

ABSTRACT: Sulfilimines are a class of bioisosteres with immense potential in medicinal chemistry, characterized by the presence of a tetravalent sulfur atom bearing one nitrogen and two distinct carbon substitutes. The conventional methods for synthesizing sulfilimines, relying on metal-catalyzed oxidative thioesters, suffer from a poor atomic economy and wastage of resources. To this end, we present a metal-free and redox-neutral approach for the first selective S-alkylation of sulfenamides under basic conditions to obtain sulfilimines. Our sustainable and efficient strategy involves sulfur-selective alkylation of easily accessible sulfenamides and commercially available halogenated hydrocarbons, leading to the successful synthesis of 60 sulfimides with high yields (36–99%) in a short reaction time. This novel approach not only offers a promising alternative to traditional methods but also expands the synthetic toolbox for the preparation of sulfilimines in medicinal chemistry.

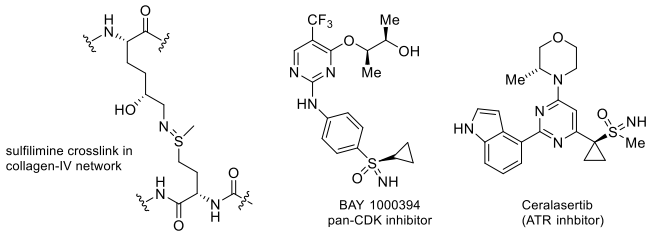
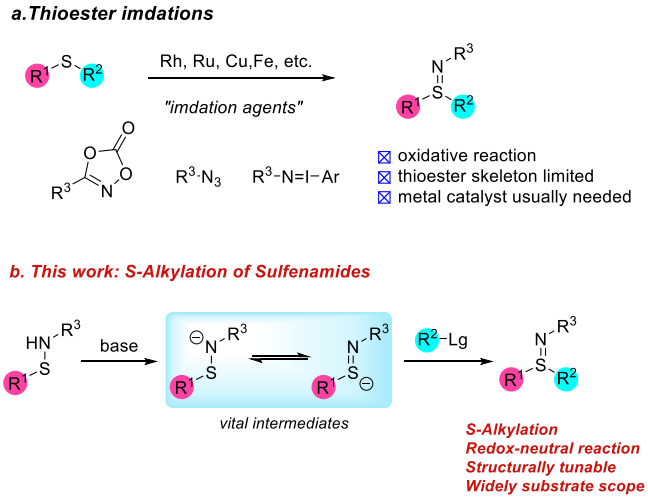


Figure 1. Bioactive compounds contain of sulfilimines

Exploring neglected chemical reagents can lead to the synthesis of exciting, diverse molecules.[1] Sulfilimines, aza-analogues of sulfoxides, are a class of sulfur(IV)-derived scaffolds that are valuable building blocks in organic synthesis. They have been utilized as important directing groups and chiral auxiliaries. [2] Additionally, sulfilimines have garnered attention as privileged functional groups in medicinal chemistry, serving as functional groups in biologically active agents due to their structural similarity to sulfoxides while possessing an additional site for derivatization. [3] In 2009, Hudson and colleagues identified the biologically relevant role of sulfilimine bonds in collagen IV networks, a highly conserved major component of basement membranes across the animal kingdom. [4] Furthermore, the sulfoximine skeleton, which can be easily prepared by oxidation of the sulfilimine group, is considered a valuable group that widely exists in medicinal molecules. [5] Consequently, the development of efficient and reliable methods for their synthesis is in high demand.

Traditional strategies for constructing sulfilimines rely heavily on the imidation of thioethers using structurally and skeletally diverse imidation reagents. These reagents, including azides, oxaziridines, 1,4,2-dioxazol-5-one, N-haloamides, and iminoiodinanes derived from amination agents and hypervalent iodine, have facilitated the expansion of the flexibility and potential bioactivity of sulfilimines (Scheme 1a). [6] While exceptional contributions in this area have been made by Lebel, [7] Bolm, [8] and Uemura, [9] most of these methodologies suffer from the use of an equivalent of oxidants, hazardous reagents, expensive transition-metal catalysts, and cumbersome operation steps, limiting their practical applications. [7-10] Therefore, chemists have been seeking better methods for constructing sulfilimines. Recent advances, such as the metal-free coupling method developed by Zhao and colleagues [11] and the S-alkylation of sulfenamides reported by Ellman and coworkers, [12] offer promising alternatives to traditional approaches. However, these methods still have limitations in terms of substrate scope and practicality, highlighting the continued need for further research in this area.

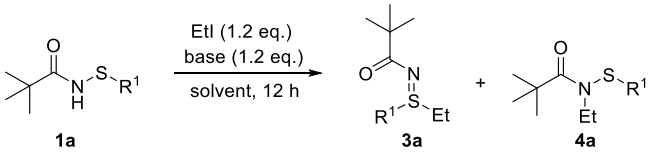


Scheme 1. Traditional methods of construct sulfilimines and our design

Sulfenate anions are recognized as important reagents in organic chemistry due to their high S-nucleophilicity. [13] From a mechanistic standpoint, the formation of tetravalent sulfenate anions can occur through tautomerization, which involves the

deprotonation of divalent sulfenic acids or the deprotection of sulfenate RSOLg. However, no related instances have been documented. [14] The principal reason for this could be the intrinsic instability and considerable challenges associated with synthesizing both sulfenic acids and sulfenate RSOLg. [15] Inspired by the properties of sulfenate anions, we hypothesized that divalent sulfenamides could be used to achieve S(IV)=N bond formation under metal- and oxidant-free conditions. Achieving S-alkylation of sulfenamides under basic and oxidant-free conditions is highly challenging due to the inflexibility of the sulfenamide skeleton. This task is further complicated by Billard's previous demonstration that N-alkylation of trifluoromethanesulfenamide dominates under basic conditions. [16] To our knowledge, no metal-free S-alkylation of sulfenamides under an alkali-atmosphere has been reported. [17] Our research group has taken on the formidable challenge of effecting S-alkylation of sulfenamides under basic and oxidant-free conditions, through the systematic optimization of reaction conditions, by synthesizing sulfenamides bearing a range of tunable and steric groups in order to achieve precise control over regioselectivity, in keeping with our dedication to developing highly efficient and environmentally sustainable reactions. [18]

Table 1. optimization of reaction conditions [a]

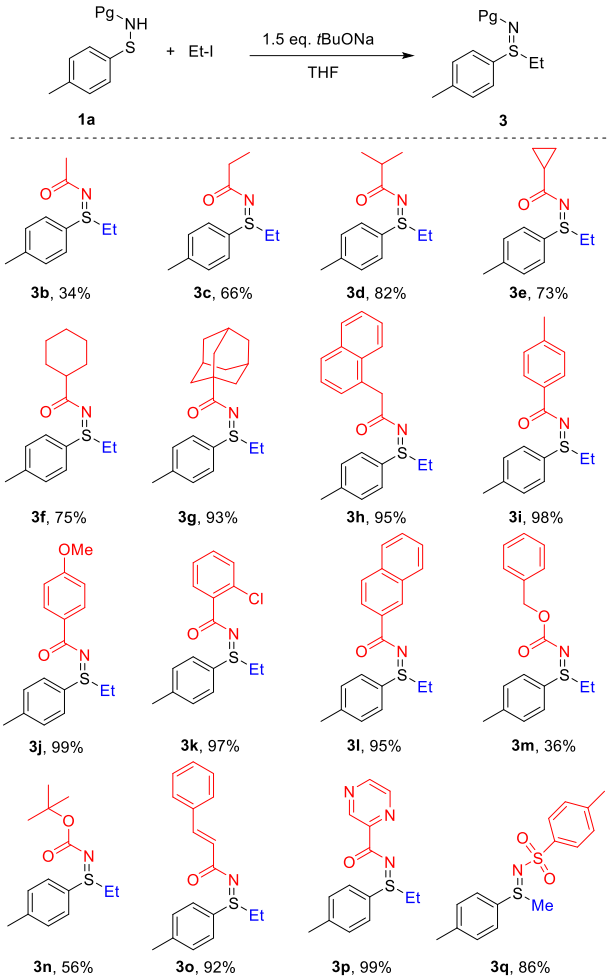


Entry	Base	Solvent	T[°C]	3a[%] [b]	4a[%] [b]
1 [c]	NaH	THF	40	88	trace
2 [c]	NaH	THF	r.t.	86	trace
3 [c]	NaH	DMF	r.t.	82	trace
4 [c]	*t*BuONa	THF	r.t.	87	trace
5 [c,d]	Na_2CO_3	THF	r.t.	n.d.	n.d.
6 [c,d]	Cs_2CO_3	THF	r.t.	20	trace
7 [d]	Cs_2CO_3	THF	r.t.	21	trace
8 [d,e,f]	*t*BuONa	THF	r.t.	95	trace

[a] Reactions were performed at a 0.1 mmol scale in 1.5 mL of solvent for 8h. [b] Isolated yields. [c] 15-Crown-5 (1.5 eq.) was added. [d] 1.5 eq. base was used. [e] Performed for 2 h. [f] 1.5 eq. EtI was added. n.d. = not detected.

Initially, we endeavored to perform alkylation on readily available reagents, namely N-cyclohexyl-2-benzothiazolesulfenamide, N-tert-butyl-2-benzothiazolesulfenamide, and 1,2-benzothiazol-3-one, using various bases and solvents. Regrettably, the sulfur alkylation could not be accomplished since the alkylation of 1,2-benzothiazol-3-one occurred predominantly at the more nucleophilic nitrogen and oxygen atoms (see Supporting Information for more details). Therefore, we turned to N-(p-tolylthio)pivalamide **1a**, featuring a sterically hindered moiety (tert-butyl) on the nitrogen atom to prevent preferential O-alkylation, as our model substrate. Our investigation revealed that sulfenamide **1a** could be successfully transformed into the desired product by treating it with Et-I in various solvents and in the presence of NaH (1.2 equiv.) and 15-crown-5. The results, depicted in table 1, indicated that THF was the optimal solvent in terms of yield, and the temperature had a negligible effect on yield (entries 1-3). Substituting NaH with *t*BuONa did not affect S-productivity (entry 4). Even though the equivalent of the base was increased, the use of weaker bases such as Cs_2CO_3 and Na_2CO_3 resulted in lower or no yields (entries 5 and 6). We observed that the absence of ligands did not impact yield or selectivity. Finally, due to the reaction's operational simplicity, we conducted the reaction with an increased amount of *t*BuONa (1.5 equiv.), which resulted in the desired product with a yield of 95% (entry 8).

Scheme 2. substrate scope of *N*-protecting groups of sulfenamides [a]

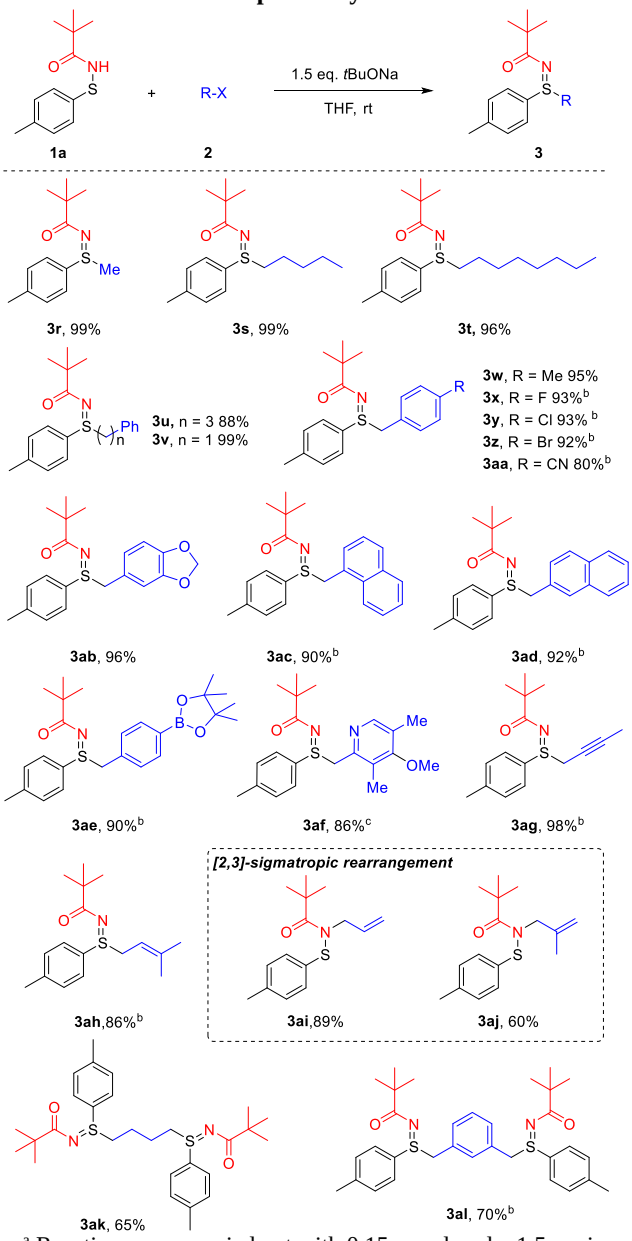


[a] Reactions were performed at a 0.15 mmol scale in 2.5 mL of THF for 2 h. Base on isolated yields.

Remarkably, trace amounts of competing O-selectivity byproduct were observed in the aforementioned reaction system, indicating that steric hindrance undoubtedly plays a crucial role in determining the selectivity. Nevertheless, the inherent electronic differences between nitrogen and sulfur atoms may be the decisive factor for such reactions. To confirm this theory, sulfenamides with diverse steric and electronic substituents on the nitrogen were synthesized and tested under the given conditions, as shown in Scheme 2. It was found that steric hindrance does have an effect on the regioselectivity of the reaction. When N-methyl substituted sulfenamides were used under standard reaction conditions, only a 34% yield of the *S*-ethyl product was

obtained (**3b**), while a 40% yield of the *N*-ethyl byproduct was isolated.

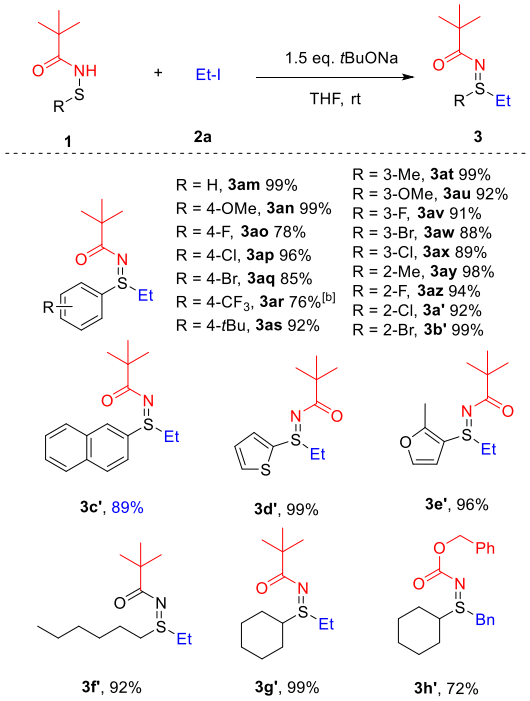
Scheme 3. Substrate scope of alkyl halides [a]



[a] Reactions were carried out with 0.15 mmol scale, 1.5 equiv. of iodoalkanes in 2.5 mL of THF for 2 hours, and the yields were determined based on isolation. [b] Bromoalkanes (1.5 eq.) were used. [c] 1.5 eq. chloroalkanes were used, and the reaction was performed for 5 hours.

Encouragingly, increasing the steric hindrance of the *N*-substituent significantly improved site selectivity (**3c**, **3d**). Sulfenamides bearing naphthenic groups, such as cyclopropyl (**3e**) and cyclohexyl (**3f**), were compatible partners under the optimal alkaline conditions, affording **3e** and **3f** in 73% and 75% yields, respectively. The neutral and oxidant-free conditions allowed for the successful transformation of a range of functionalized sulfenamides, including steric hindered adamantine (**3g**), naphthalen-1-ylmethyl (**3h**), and aryl (**3i-3l**). Furthermore, benzyl carbamate ($CbzNH_2$) and *tert*-butyl carbamate ($BocNH_2$) derived sulfenamides were compatible with the reaction, albeit with lower yields (**3m** and **3n**). The tested amides were well-tolerated despite the presence of a C=C double bond and an easily modifiable heterocycle, yielding **3o** and **3p** in excellent yields. Notably, the novel protocol exhibited excellent regioselectivity, favoring *S*-methylation of sulfonamide derived sulfenamides over methylation of the sulfonamide N-H bond (**3q**).

Scheme 4. Substrate scope of sulfenamides [a]



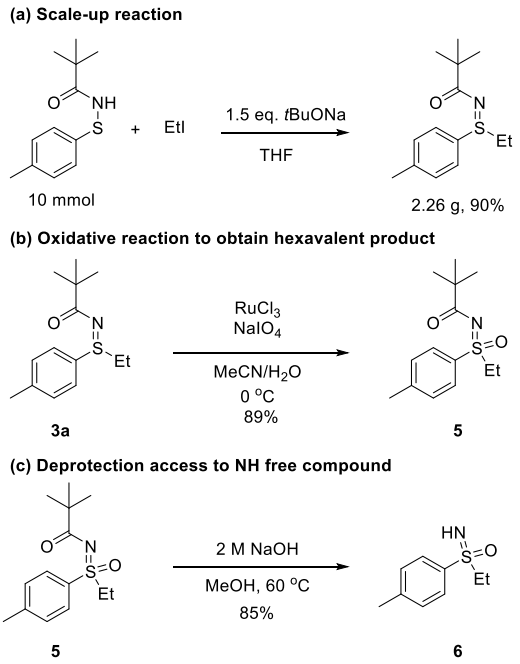
[a] The reactions were conducted in 2.5 mL of THF at a 0.15 mmol scale for 2 hours, and the yields were determined based on isolation. [b] The reaction was performed for 10 hours.

After the successful S-alkylation of sulfenamides with iodoethane, we decided to expand this reaction to other alkyl halides. The results, shown in Scheme 3, indicate that short and long straight chain iodoalkanes react well with *N*-(*p*-tolylthio)pivalamide, producing the desired products in yields ranging from 84% to 99% (**3r**-**3v**). Additionally, we found that a variety of benzylic halides with *para* substituents react smoothly with sulfenamides, resulting in good to excellent yields of sulfilimines, with electronic effects not significantly affecting reactivity (**3w**-**3aa**). Piperonyl iodine, 1-(bromomethyl)naphthalene, and 2-(bromomethyl)naphthalene were also suitable for S-alkylation (**3ab**-**3ad**). The pinacolatoboryl group at the phenyl ring was well-tolerated as well (**3ae**), providing a synthetic handle for further synthetic elaboration through classic cross-coupling strategies. Heteroatomfunctionalized pyridine was found to be a good substrate, although chlorinated hydrocarbon was used (**3af**). Interestingly, both the acetyl propyl and allyl groups were suitable, delivering sulfilimines **3ag** and **3ah** in moderate to excellent yields, with no [2.3]-sigmatropic rearrangement products observed. The latter case is likely due to the sterically disfavored di-methyl substituted allyl bromide. Terminal-unsubstituted allyl bromides were also found to be suitable, as seen in the smooth tandem substitution and [2.3]-sigmatropic rearrangement reaction to yield products **3ai** and **3aj** in good yields. This novel protocol is also suitable for the synthesis of di-sulfilimines, with diiodoalkane and dibenzyl substrates producing **3ak** and **3al**, respectively. This appealing skeleton can be further modified to investigate the influence of a nitrogen atom as a potential coordination site.

Following the successful S-alkylation of sulfenamide **1a** with iodoethane, the investigators explored the reaction using a range of sulfenamides and Et-I under identical conditions (Scheme 4). Substrates containing aryl sulfenamides with various electron-donating and electron-withdrawing groups at different positions around the aromatic ring were deemed suitable, producing an array of functionalized sulfilimines in good to excellent yields (**3am**-**3c'**). However, substrates with electronically deficient phenyl rings containing fluoro and trifluoromethyl groups resulted in reduced yields of 78% and 76%, respectively. Interestingly, the reaction also proceeded smoothly at room temperature with favorable yields, although substrates with electron-withdrawing groups in the *para* and *meta* positions of the benzene ring required a longer reaction time. The reaction was also compatible with diverse heteroaromatic sulfenamides, producing sulfilimines **3d'** and **3e'** with yields near equivalence. Linear or branched alkyl derived sulfenamides enabled access to sulfilimines **3f'** and **3g'** with excellent yields. Furthermore, $CbzNH_2$ and branched alkyl derived sulfenamides were suitable, with the *S*-alkylation product **3h'** generated in 72% yield. This product may provide a platform for further functionalization with a free-NH group.

To provide evidence of the scalability of our synthetic method, a gram-scale synthesis was conducted under standard conditions, and no significant yield degradation was observed compared to the low stoichiometric model reaction performed under optimal conditions (as shown in Scheme 5a). The resulting product **3a** was found to be readily oxidizable in the presence of an Ru(II) catalyst, yielding hexavalent product **5** with an 89% yield (Scheme 5b). Furthermore, removal of the *N*-pivaloyl group using basic hydrolytic conditions produced an NH-free product **6** in a yield of 90% (Scheme 5c), providing an easily modifiable group for the development of novel sulfilimines for drug discovery purposes.

Scheme 5. Gram scale synthesis and applications



Our proposed mechanism suggests that during the S-alkylation reaction, the sulfur atom develops a partial positive charge in the transition state. To confirm this prediction, we conducted a Hammett analysis to investigate the stereoelectronic situation at the sulfur atom (Figure 2). We examined five para-substituted phenylsulfenamides and observed that electron-donating substituents increased the reaction rate while electron-withdrawing groups decreased it. The decadic logarithm of the relative rates k_X/k_H correlates well with the tabulated σ_p values of the substituents X.[19] The linear function's slope was determined as ρ = -1.10, in agreement with the predicted positive charge at the reactive center. Further details can be found in the Supporting Information.

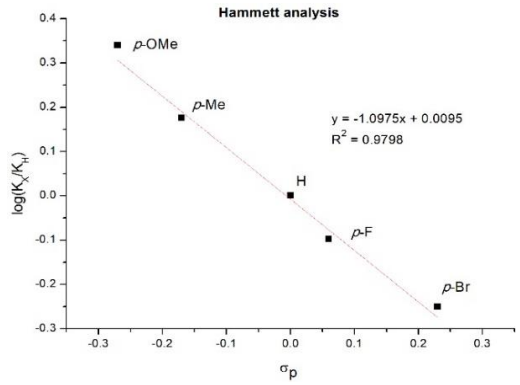


Figure 2. Hammett analysis performed for substrates 1a, 1am, 1an, 1ao, 1aq.

In summary, we have established a groundbreaking approach to S-alkylating easily available sulfenamides using widely accessible reagents, such as alkyl halides and tBuONa. Notably, this method represents a pioneering example of a redox-neutral, metal-free, and facile synthesis of sulfilimines in high yields and with a broad substrate scope. We anticipate that the present method will serve as a fundamental basis for future explorations and advancements in the synthesis of sulfenamide-containing molecules, with potential applications in the fields of medicine and ligand design.

ASSOCIATED CONTENT

Supporting Information.
General information, experimental section, compound characterization, and NMR spectra (PDF).

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A pioneering method for sulfur-alkylating sulfenamides has been developed, utilizing easily accessible reagents without the requirement of catalysts or oxidants. The technique has resulted in the successful synthesis of 60 sulfimides with high yields in a short reaction time, by employing commercially available halogenated hydrocarbons and readily accessible sulfenamides. This breakthrough approach represents a fundamental step in the advancement of the synthesis of sulfenamide-containing molecules, and has the potential for broad applications in the fields of medicinal chemistry and ligand design. The unprecedented simplicity and efficiency of this method make it an attractive option for future investigations in this area.