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Oxygen-to-Oxygen Silyl Migration of α-Siloxy Sulfoxides and Oxidation-Triggered Allicin Formation

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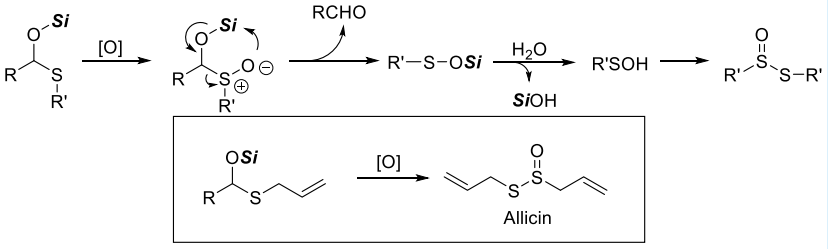
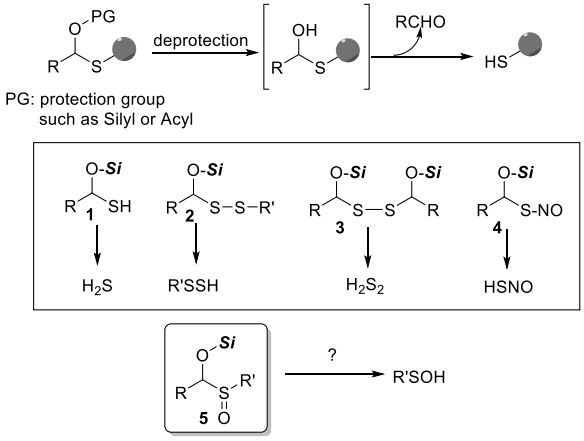


ABSTRACT: Oxidation of α-siloxy thioethers leads to the formation of the corresponding sulfoxides as unstable intermediates, which undergo an intramolecular oxygen-to-oxygen silyl migration to break the C−S linkage. This process produces silyl protected sulfenic acids and subsequently thiosulfinates. It was used to develop oxidation-triggered allicin donors.

Reactive sulfur species (RSS) are sulfur-containing molecules that exhibit regulatory functions in biological systems. These include small molecule species, such as hydrogen sulfide (H_2S), hydrogen polysulfide (H_2S_n), and cysteine- or glutathione-derived *S*-nitrosothiols and persulfides (RSNO and RSSH), as well as protein-bound sulfur adducts such as disulfides (PSSR), *S*-nitrosothiols (PSNO), sulfenic acids (PSOH), and persulfides (PSSH). Many of these species are highly reactive and short-lived, which makes their studies quite challenging. To precisely generate specific RSS and understand their associated biology, much effort has been expended exploring RSS releasing scaffolds (i.e., donors) and several donor molecules for H_2S, RSSH, and H_2S_n have been reported.[1]

Our laboratory recently developed a general scaffold for the design of RSS donors (Scheme 1).[2] These donors share a common α-hydroxyl protected sulfur structure. Upon deprotection, the resulting α-hydroxyl sulfur derivative degrades to produce the desired sulfur-containing molecule. This O-to-S relay deprotection strategy has been used to develop donors for H_2S, RSSH, H_2S_2, and HSNO (compounds **1**−**4**).[2] To further extend this strategy to other RSS we decided to explore sulfenic acid (RSOH) donors. RSOH are known to be critical in maintaining cellular redox homeostasis. However, the full extent of their biological significance remains unclear. This is due in part to the inherent challenges with studying RSOH whose average half-life is less than 1 min.[3] Their short life span stems from their high reactivity with both nucleophiles and electrophiles. The most successful attempts to stabilize them have employed a high degree of steric hindrance achieved through embedment within a macrobicyclic cyclophane or bowl-type cage, effectively preventing condensation.[4,5] In situ

Scheme 1. Design of RSS Donors



RSOH formation methods have also been explored. These include base hydrolysis of a sulfenic acid ester or disulfide, acid hydrolysis of oxidized mixed thioacetal, or thermolysis of sulfoxides.[6−9] These methods typically require harsh conditions that are not biologically compatible. We envisioned that compounds like **5** could serve as deprotection-triggered RSOH donors. Herein we would like to report our attempts to prepare

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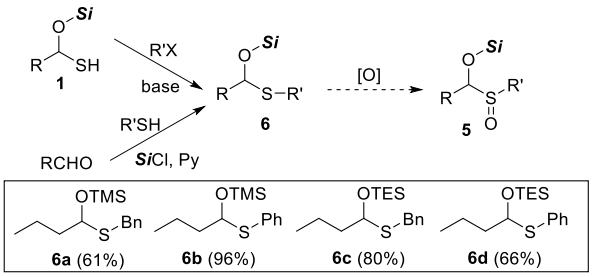
compounds **5** and the discovery of a unique O,O-silyl migration that could be used to design oxidation-triggered donors for thiosulfinates such as allicin.

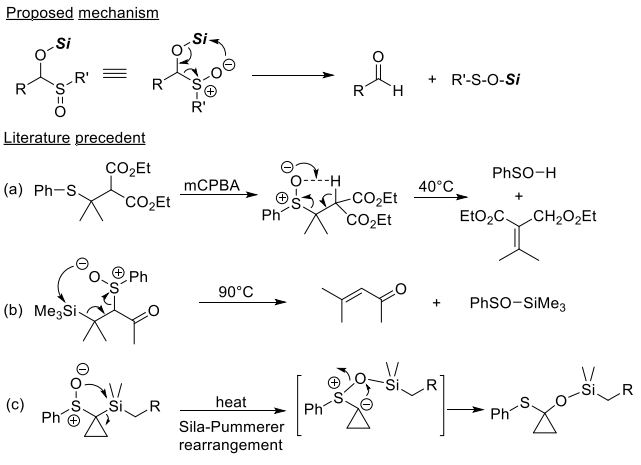
We expected the desired RSOH donors (**5**) could be obtained through oxidation of the corresponding α-siloxy thioethers **6** (Scheme 2). Two methods were employed to prepare **6**: (1) simple S-alkylation of our known α-siloxy thiol **1**; (2) condensation of aldehyde and thiol in the presence of silyl chloride and pyridine. With these methods, we quickly assembled a small library of thioethers **6a**–**d**. These compounds were found to be stable in both organic and aqueous (pH 5–9) solutions over 24 hours.

Scheme 2. Intended Synthesis of RSOH Donors



Next, we attempted to oxidize the thioether substrates. Several established oxidation conditions were tried, which included (1) Oxone in EtOH, (2) DMDO in acetone, (3) mCPBA with Et_3N or pyridine in DCM, and (4) mCPBA, aq. phosphate buffer (pH 7.5), DCM. Unfortunately, this oxidation was found to be more difficult than expected as we could not obtain the desired sulfoxides. While it was likely the oxidation on sulfur atom of these substrates should proceed as expected, the extreme difficulty in obtaining the sulfoxide products led us to speculate their inherent instability. A previous report by Clennan et al. also found that α-siloxy sulfoxides were very unstable.[10] They can only exist at very low temperature and rapidly decompose above −20 °C. It is known that the oxygen atom of a sulfoxide possesses nucleophilicity. Based on the unique structure of sulfoxide **5** we proposed an O-to-O silyl migration as shown in Scheme 3. This process should go through a favorable five-member ring transition state to provide an aldehyde and a silyl-protected RSOH. To the best of our knowledge, this reaction is unknown in literature.

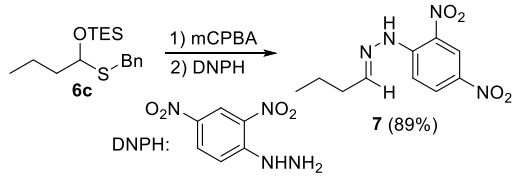
Scheme 3. Oxygen-to-Oxygen Silyl Migration



However, sulfoxide's strong nucleophilicity and oxygen's high affinity to silyl are well documented. For example, during dehydrosulfenylation of esters/ketones, the sulfoxide β to the carbonyl undergoes an intramolecular proton transfer and β-elimination to yield the unsaturated compound and RSOH (Scheme 3a).[9] Transfer of an alkylsilane to a sulfoxide oxygen has also been reported in β-elimination reactions (Scheme 3b).[11,12] Additionally, sulfoxides can attack a nearby silyl group under heat via sila-Pummerer rearrangement to form alkoxysilanes (Scheme 3c).[13] These silyl transfers are reminiscent of that observed presently in which a silyl moiety undergoes O-to-O transfer, concurrent with cyclo-elimination, producing a silyl protected sulfenic acid.

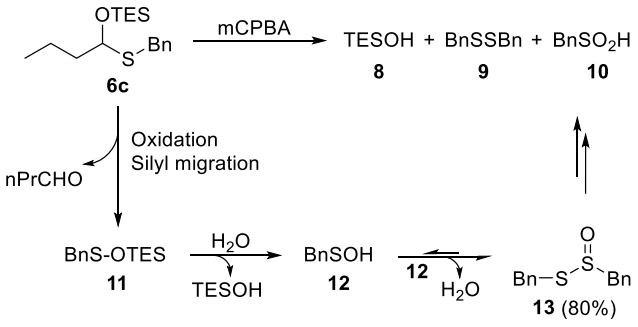
As shown in Scheme 3, the proposed silyl migration should produce the parent aldehyde and silyl protected sulfenic acid. The formation of the aldehyde product was demonstrated via Brady's test (Scheme 4). When **6c** was subjected to oxidation by mCPBA under an argon atmosphere, Brady's Reagent (DNPH or 2,4-dinitrophenylhydrazine) was used to detect the presence of aldehyde. As expected, the desired hydrazone product was obtained in high yield. This demonstrated the unmasking of the parent aldehyde.

Scheme 4. Brady's Test



Next, we attempted to identify other decomposition products and understand the reaction mechanism. When **6c** was subjected to oxidation and then decomposition under argon, subsequent MS analysis identified triethylsilanol **8**, benzyl disulfide **9**, and sulfinic acid **10** as final products (Scheme 5). The formation of **9** and **10** implicates dibenzyl thiosulfinate **13** as the intermediate. In fact, we were able to isolate thiosulfinate **13** in good yield (80%) if the reaction was purified immediately after the oxidation. With these products identified, we proposed the mechanism as the following: The oxidation of **6c** and silyl migration should lead to compound **11**. Silyl-protected sulfenic acids are known to be highly susceptible to hydrolysis and solvolysis by protic reagents.[14,15] Therefore, sulfenic acid **12** and silanol **8** should be readily formed from **11**. Sulfenic acids (**11**) are extremely unstable and rapidly condense to form thiosulfinates (**13**). There are

Scheme 5. Proposed Reaction Pathway of 6c under Oxidation



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many possible pathways for **13** to produce final products **9** and **10**. For example, thiosulfinate hydrolysis has been reported to ultimately produce a 1:1 molar ratio of disulfide and sulfinic acid (RSO_2H) at all pH values.[16] Thiosulfinates are also inherently unstable and can spontaneously disproportionate to yield the corresponding disulfide and thiosulfonate,[17] which eventually react with thiols to form disulfides. We also carried out a crossover experiment with **6c** and **17b** to bolster evidence of the intermediate sulfenic acid **12** (see Supporting Information). In addition to the two self-conjugated thiosulfinates, we observed the formation of mixed thiosulfinates. This further supports the proposed mechanism.

The reaction pathway shown in Scheme 5 explains the instability of α-siloxy sulfoxides and the formation of silanol, disulfide, and sulfinic acid as final products. To further demonstrate the mechanism, we prepared three analogs with similar structure and properties to α-siloxy sulfoxides, i.e. **14**–**16** (Figure 1). These compounds were exposed to the same conditions which degraded **6c** to evaluate their stability and thus gain mechanistic insight.

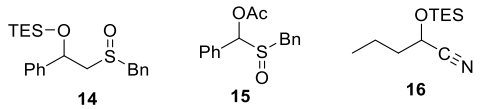


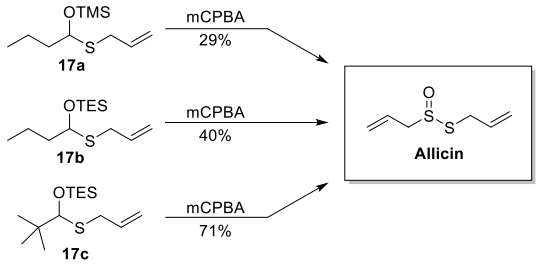
Figure 1. Structures of analogs.

One carbon homologue **14** was used to investigate the stability of the secondary siloxy group. With the siloxy group moved to the β-position of sulfoxide, this compound was found to be stable and no degradation was noted. This indicated the instability of α-siloxy sulfoxides was not simply derived from a trigger labile to the mCPBA oxidation. Although the sulfoxide of compound **14** may form a six-member ring with the siloxy group for the silyl migration, the process should not be productive, as it will not lead to break down of the molecule to drive the reaction. Compound **15** was prepared to test the inherent stability of α-oxyl sulfoxides. This α-acetoxy sulfoxide was found stable under the reaction conditions. Apparently in this case sulfoxide could not promote intramolecular acyl migration to remove the protection group on the oxygen atom and cause degradation. As such the stability of α-oxyl sulfoxides is not a problem. **14** and **15** did not examine the stability of the *O*-silyl protecting group with an α electron-withdrawing/-leaving group under the oxidation conditions. It is plausible that the instability of the α-siloxy sulfoxide was due to a combination of electronic and entropic effects. These contributions were probed via analog **16** which features cyanide as an electron-withdrawing group and potential leaving group with similar electronic characteristics to the sulfoxide. The α-proton's pK_a of nitrile and sulfoxide are approximately 30 and 35 in DMSO, respectively. The nitrile is slightly more electron-withdrawing but not significantly so. When considered as leaving groups via their pK_a they are quite similar. The pK_a of HCN is 9 while sulfenic acids possess values of 5–10. The difference between them is their ability to attack the siloxy group. Upon exposure to the oxidative and acidic conditions used previously, the cyano analog **16** proved stable. This indicates the instability is not simply due to the electronic and entropic driving forces provided by an α leaving group.

Stability studies on **14**–**16** further confirmed our understanding of the silyl migration-triggered degradation of α-siloxy sulfoxides. This migration ultimately unmasks the parent aldehyde, indicating the α-siloxy sulfide may be used in an oxidant-triggered aldehyde deprotection strategy. Since this process led to the formation of RSOH and subsequently the thiosulfinate, we believed this reaction could be used as a unique oxidation-triggered strategy for thiosulfinate production. Although in general thiosulfinates are unstable, some plant-derived thiosulfinates are biologically relevant. Allicin is the main active component in garlic and possesses interesting benefits for oxidative stress related diseases such as cancer and drug withdrawal syndrome. Allicin (and thiosulfinates in general) is typically prepared by treating allyl disulfide with a strong peroxy acid, which is not a biocompatible process. However, delivery to cells exhibiting oxidative stress could prove beneficial as a therapeutic by increasing antioxidant response. As such, oxidation-triggered allicin donors would be interesting.

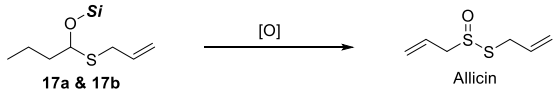
Based on the new silyl migration mechanism, it was expected that allyl thioethers **17a**–**c** (Scheme 6) would be the proposed

Scheme 6. Oxidation-Triggered Allicin Formation



allicin donors. These are stable compounds that can be administered as needed. They serve as allicin releasing prodrugs only when appropriate oxidants are present, therefore, achieving release upon demand. **17a**–**c** were then prepared and tested under mCPBA oxidation. As expected, the formation of allicin (29–71%) was observed. Interestingly, the more stable protecting group led to higher conversion.

To further understand the scope of this reaction, other oxidation conditions were examined (Figure 2). H_2O_2 is a biologically relevant oxidant. It is known to be a central redox



entry	[O]	s.m.	[17]	solvent	temp	time	yield
1	H_2O_2	**17a**	25 mM	THF/H_2O	37°C	30 min	>90%[a]
2	H_2O_2	**17a**	25 mM	THF/H_2O	37°C	4 h	48%[a]
3	H_2O_2	**17b**	25 mM	THF/H_2O	37°C	30 min	>90%[a]
4	H_2O_2	**17b**	25 mM	THF/H_2O	37°C	4 h	43%[a]
5	NaOCl	**17a**	25 mM	THF/H_2O	37°C	24 h	N/A
6	MMPP	**17a**	100 mM	THF/H_2O	0°C	1 h	31%
7	MMPP	**17b**	100 mM	THF/H_2O	0°C	1 h	74%
8	$NaIO_4$	**17b**	20 mM	MeOH/H_2O	0°C	8 h	N/A

Figure 2. Effects of oxidation conditions on allicin formation. [a]Yields determined by HPLC with external reference.

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signaling molecule and a metabolite consequent of an oxidative stress condition. H_2O_2 was found to produce allicin from **17a/b** very effectively. >90% Allicin was formed in 30 min, and the yields dropped afterward due to the degradation of allicin. Compounds like **17** may thus claim a role as biologically relevant oxidant-triggered allicin donors. NaOCl is another biologically relevant oxidant, although it did not produce allicin. Two other oxidants, magnesium monoperoxyphthalate (MMPP) and $NaIO_4$, were also utilized to explore the reaction scope. Of these, only MMPP produced allicin.

In summary, in our attempts to develop O to S relay deprotection-based RSOH donors we discovered a unique O-to-O silyl migration on sulfoxide substrates. This process led to the formation of thiosulfinates, likely via the RSOH intermediate (as shown in Scheme 5). Therefore, the sulfoxide substrates may still be considered as RSOH precursors. However, since we were unable to trap the RSOH intermediate with dimedone and methyl iodide, more studies may be needed to further confirm the mechanism. Nevertheless, this reaction was applied to develop an oxidation-triggered allicin formation strategy. Given the known medicinal benefits of allicin, these oxidation-triggered allicin donors may be useful in certain situations. It should be noted that besides allicin this process also produces several side products such as aldehyde and silanol. Their potential side-effects could be a limitation of the method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01149.

Experimental and characterization of each compound (PDF)

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Notes

The authors declare no competing financial interest.

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