Sulfoxide Synthesis from Sulfinate Esters under Pummerer-like Conditions

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Abstract: A facile synthetic method of allyl sulfoxides by *S*-allylation of sulfinate esters through sulfonium intermediates has been developed without [3,3]-sigmatropic rearrangement and further Pummerer-type reactions of the resulting allyl sulfoxides. On the basis of the plausible reaction mechanism involving sulfonium salt intermediates, *S*-alkynylation and *S*-arylation were also accomplished.

Organosulfur compounds have gained attention in a broad range of research fields such as pharmaceutical sciences, agrochemistry, and materials science.[1,2] The recent remarkable successes of synthetic chemistry using sulfoxides have enhanced the accessibility of highly functionalized compounds by virtue of the significant transformability of sulfoxides.[3–8] For example, the preparations of diverse compounds **2**–**5** were achieved by a variety of transformations of allyl aryl sulfoxides **1** through C–S bond cleavage (Figure 1A).[6,7,8h,8j] In particular, multisubstituted aromatic sulfides **4** and **5** were synthesized from sulfoxides **1** by a reaction with aryne intermediate **I** in the presence of electrophiles and the [3,3]-sigmatropic rearrangement of allyl sulfonium intermediate **II**, respectively.[6,7] Similar interrupted Pummerer reactions of sulfoxides **6** and **8** with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of allyltrimethylsilane were also accomplished through the [3,3]-sigmatropic rearrangement, showing the notable reactivity of allyl sulfonium intermediates **III** and **IV** (Figures 1B and 1C).[4c,4f] Herein, we describe an efficient synthesis of various allyl sulfoxides by allylation of sulfinate esters[9] using allyltrimethylsilane under the Pummerer-like conditions[4] through sulfonium intermediate **V** having a methoxy group, enabling to avoid the [3,3]-sigmatropic rearrangement and further Pummerer-type reactions of the resulting allyl sulfoxides (Figure 1D).

We envisioned that the Pummerer-type activation of sulfinate esters **10** in the presence of allylsilanes **11** and stability of methoxy sulfonium intermediates[10] would allow for the facile synthesis of allyl sulfoxides **12**, considering that the hydrolysis of methoxy sulfonium intermediates **V'** can afford sulfoxides (Figure 2A). As a result of screening the reaction conditions, we found that treatment of methyl benzenesulfinate (**10a**) with Tf_2O in the presence of allyltrimethylsilane (**11a**) followed by addition of aqueous sodium bicarbonate provided allyl phenyl sulfoxide (**12a**) in high yield (Figures 2A and 2B). Examinations using a variety of acid anhydrides or Lewis acids showed the remarkable reactivity of Tf_2O in the *S*-allylation of sulfinate ester **10a**.[11] A wide range of allyl sulfoxides **12b**–**12j** were prepared by the *S*-allylation under the Pummerer-like conditions, where *C*-allylation products through the [3,3]-sigmatropic rearrangement were not obtained. Indeed, not only electron-rich aromatic sulfinate esters bearing methyl and methoxy groups but also electron-deficient substrates with chloro and nitro groups were efficiently allylated to furnish sulfoxides **12b**–**12e**. Sulfoxides **12f** and **12g** were obtained uneventfully by the reactions of bulky 2-bromo- and 2,6-dimethyl-substituted benzenesulfinate esters. Furthermore, *S*-allylations of 2-naphtyl-, benzyl-, and *n*-pentyl-substituted sulfinate esters also took place smoothly to provide sulfoxides **12h**–**12j**.

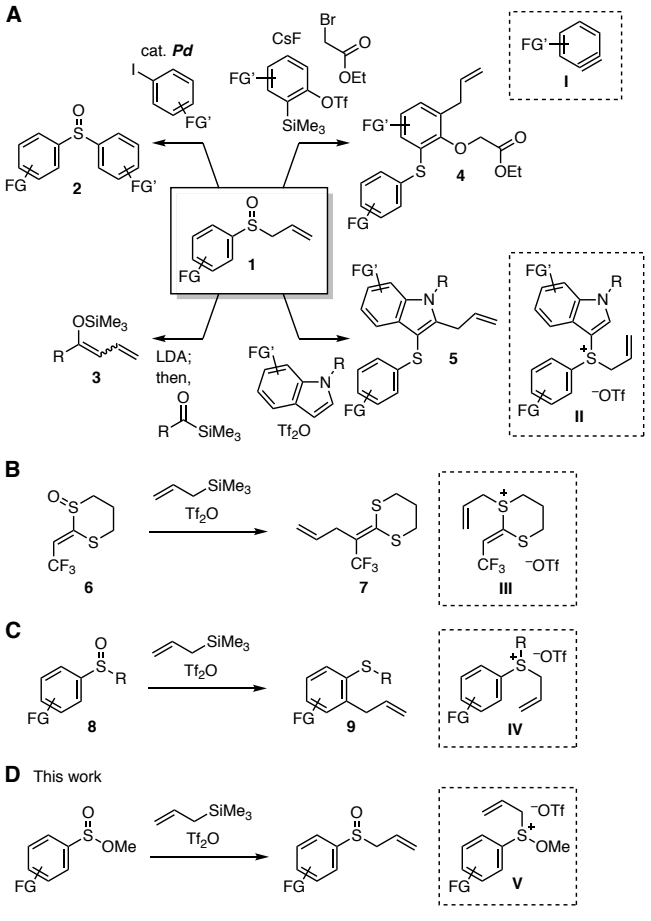

Figure 1. Transformations through the Pummerer-type activation of sulfoxides and sulfinate esters. (A) Versatile transformations using allyl sulfoxides **1**. (B) Interrupted Pummerer reaction of ketene dithioacetal monoxide **6**. (C) Interrupted Pummerer reaction of aromatic sulfoxide **8**. (D) This work.

Various functionalized allylsilanes **11** participated in the *S*-allylation of sulfinate ester **10a** (Figures 2A and 2C). Sulfoxides

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12k and **12l** were efficiently synthesized by 2-methyl- and 2-phenylallylation, respectively. It is worth noting that the C–S bond formation enabled to prepare allyl chloride **12m**, allyl acetate **12n**, ester **12o**, and bromoalkene **12p** leaving highly electrophilic functional groups untouched, while it is not easy to synthesize sulfoxides having electrophilic moieties by the conventional allyl sulfoxide synthesis via allylation of thiols and subsequent oxidation. Moreover, transformable sulfoxides **12q** and **12r** possessing a silyl and boryl groups were obtained in moderate to good yields without damaging these reactive functional groups.

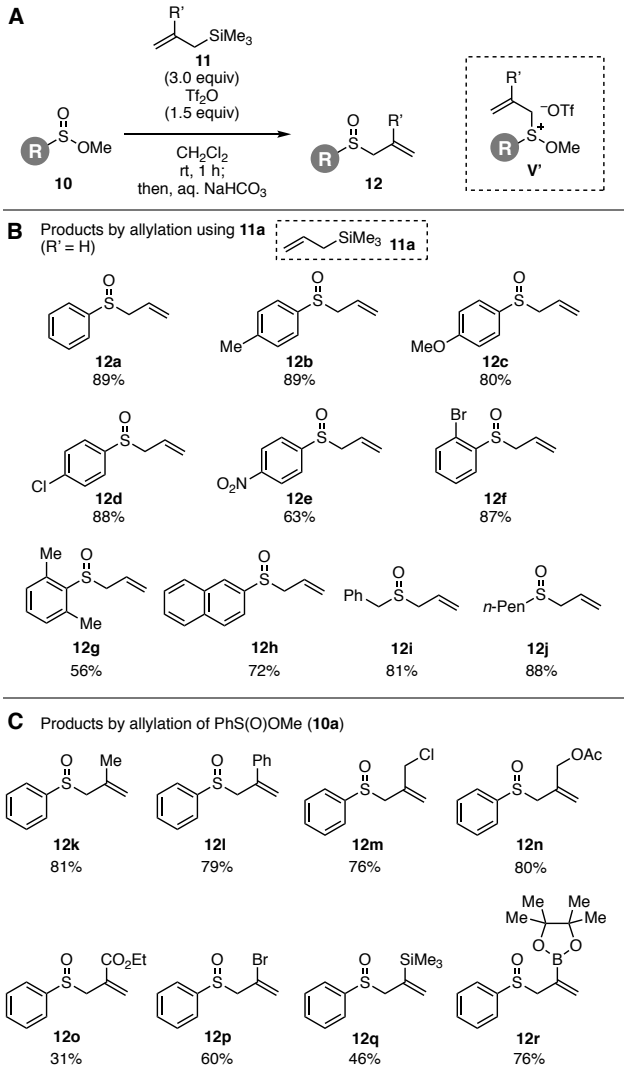

Figure 2. Allyl sulfoxide synthesis from sulfinate esters **10** and allylsilanes **11**. (A) General scheme. (B) Results using various sulfinate esters **10** with **11a**. (C) Results using allylsilanes **11** with **10a**.

To gain insight into the reaction mechanism of the *S*-allylation of sulfinate esters under the Pummerer-like conditions, we then examined control experiments (Figure 3). Firstly, the reaction using $[^{18}O]H_2O$ in the hydrolysis using aqueous sodium bicarbonate was conducted to clarify the origin of the oxygen atom of sulfoxide **12a** (Figure 3A). The result showed that ^{18}O-incorporated **12a'** was obtained selectively, indicating that the sulfoxide oxygen was derived from water in the hydrolysis. We then attempted to isolate sulfonium intermediate **13** (Figure 3B). As a result, after sulfinate ester **10a** was treated with Tf_2O in the presence of allylsilane **11a**, an addition of solid sodium bicarbonate, filtration of the resulting mixture, removal of the solvent of the filtrate, and washing with diethyl ether afforded sulfonium salt **13** quantitatively. Hydrolysis of sulfonium salt **13** with aqueous sodium bicarbonate underwent uneventfully to give sulfoxide **12a**. In addition, reduction of sulfonium salt **13** with sodium borohydride successfully provided allyl phenyl sulfide (**14**) in good yield.[10c] On the basis of these results, we proposed a reaction mechanism of the *S*-allylation (Figure 3C). The Pummerer-type activation of sulfinate ester by virtue of the remarkable reactivity of Tf_2O,[10c] and following *S*-allylation of the resulting sulfonium intermediate **VI** would furnish sulfonium intermediate **13** along with trimethylsilyl triflate. Then, hydrolysis of sulfonium salt **13** with aqueous sodium bicarbonate involving the nucleophilic attack of external water to the sulfur atom leads to sulfoxide **12a**. Although the role of methoxy group is still unclear, the stability of sulfonium salt **13** would achieve the sulfoxide synthesis without [3,3]-sigmatropic rearrangement or the Pummerer-type reactions of allyl sulfoxide **12a** and further Pummerer-type reactions of the resulting allyl sulfoxides.

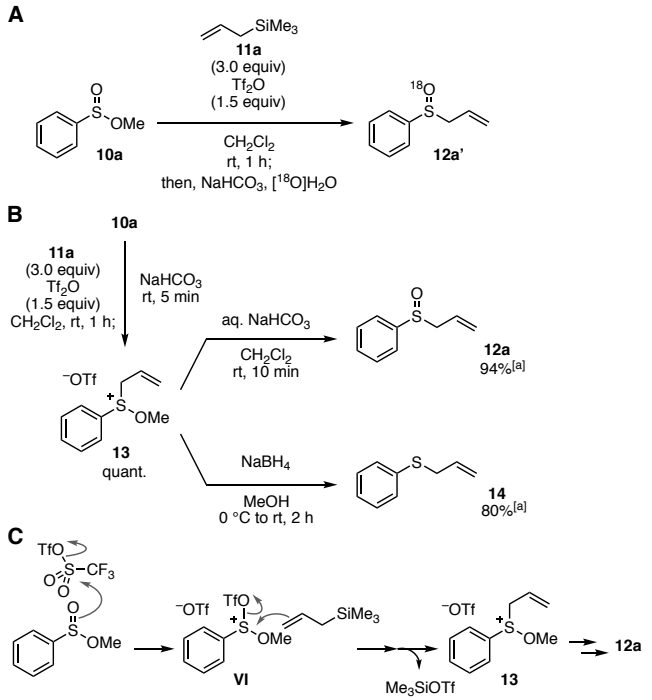

Figure 3. Control experiments. (A) Reaction using $[^{18}O]H_2O$. (B) Isolation of sulfonium salt **13**, hydrolysis of **13**, and reduction of **13**. (C) Plausible reaction mechanism. [a] ^1H NMR yield.

Our attention then directed toward novel transformations through the cationic intermediates generated by the Pummerer-type activation of sulfinate esters with Tf_2O (Figure 4). In this context, we have developed a facile synthetic method of alkynyl sulfoxides **16** using alkynyl silanes **15** (Figure 4A). Indeed,

treatment of sulfinate ester **10a** dissolved in nitromethane with Tf_2O in the presence of ethynylsilanes **15** at –20 °C furnished alkynyl sulfoxides **16** in moderate to high yields. This novel transformation enabled the preparation of alkynyl sulfoxides **16a**–**16c** having a methyl, phenyl, and 4-anisyl group. Since alkynyl sulfoxides serve in a variety of reactions including carbometallation, [2+2] cycloaddition, and cyclopropanation, the alkynyl sulfoxide synthesis developed in this study would allow for the preparation of a range of organosulfur compounds.[4x,13] In addition, Friedel–Crafts-type arylation of sulfinate ester **10a** also took place smoothly to afford a regioisomeric mixture of diaryl sulfoxides **18** and **18'** in good yield (Figure 4B).[9a]

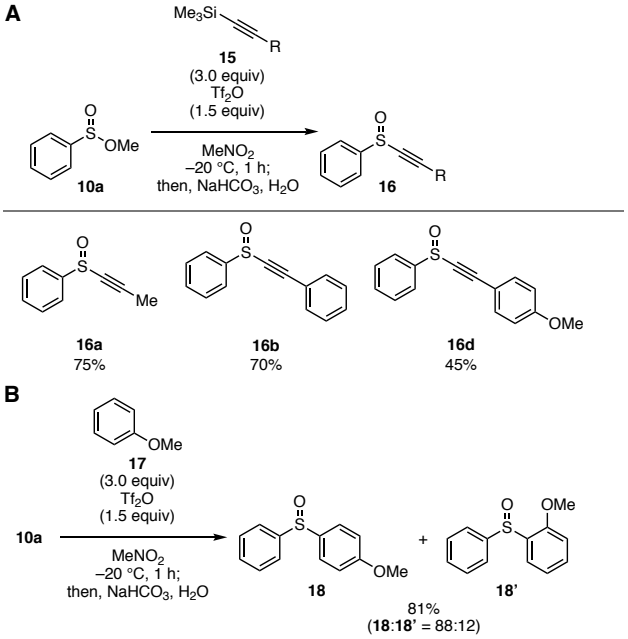

Figure 4. Alkynylation and arylation of sulfinate ester **10a**. (A) Alkynylation with alkynylsilanes **15**. (B) Arylation with anisole (**17**).

Wide transformability of allyl aryl sulfoxides synthesized from sulfinate esters was showcased by the syntheses of multisubstituted aromatic compounds (Figure 5). Modifying the conditions for the trifunctionalization of aryne intermediates reported by Li and coworkers[6] (Figure 1A, **1** to **4**), we found that 2,3,6-trisubstituted phenol **20a** was obtained in moderate yield with avoiding further arylation between phenol **20a** and 3-methoxybenzyne when the aryne trifunctionalization was performed in hot 1,4-dioxane[5e] in the absence of electrophiles such as ethyl bromoacetate (Figure 5A). Iodine-mediated cyclization of the resulting phenol **20a** and subsequent elimination with a base successfully furnished benzofuran **21**.[14] Methallylation of sulfinate ester **10d** followed by the aryne trifunctionalization led to the synthesis of highly functionalized phenol **20b** (Figure 5B). Furthermore, tetrasubstituted indole **23** was prepared through 2-bromoallylation of sulfinate ester **10c** and following 2,3-difunctionalization of indole **22** according to the reports by Procter and coworkers[7] (Figure 5C). Functionalized allyl aryl sulfoxide **12t** and indole **22** bearing *o*-silylaryl triflate moiety[15] for the aryne generation participated in the 2,3-disubstituted indole synthesis leaving the reactive functional groups intact. Thus, a wide variety of indoles would be synthesized by *S*-allylation of sulfinate esters, 2,3-difunctionalization of indoles, and further transformations through indolyne intermediates with a number of arynophiles.[15,16]

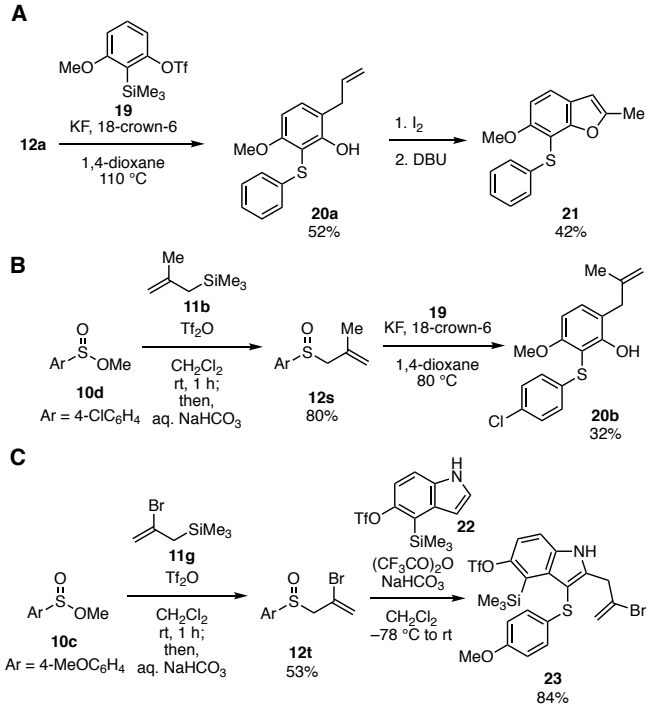

Figure 5. Transformations of allyl sulfoxides. (A) Benzofuran synthesis. (B) Trisubstituted phenol synthesis. (C) Multisubstituted indole synthesis.

In summary, we have developed a facile synthetic method of allyl sulfoxides by *S*-allylation of sulfinate esters through sulfonium intermediates without [3,3]-sigmatropic rearrangement and further Pummerer-type reactions of the resulting allyl sulfoxides. On the basis of the plausible reaction mechanism, *S*-alkynylation and *S*-arylation were also accomplished. Further studies to expand the scope of these transformations using sulfinate esters under the Pummerer-like conditions and the applications to the synthesis of bioactive compounds are now in progress.

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Keywords: sulfoxide • sulfinate ester • sulfonium salt • cationic intermediate • allylation

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