Synthetic Methods

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Stereoselective Synthesis of Vinyl Triflones and Heteroaryl Triflones through Anionic O→C_{vinyl} and N→C_{vinyl} Trifluoromethanesulfonyl Migration Reactions**

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Vinyl triflone (trifluoromethanesulfone) is a simple, unique, and useful structural unit which takes advantage of the strong electron-withdrawing power[1] and the manifold reactivity[2] of the triflyl (trifluoromethanesulfonyl; SO_2CF_3) group. Research on vinyl triflone began about two decades ago.[3] Although vinyl triflones have some potential with applications in medicinal chemistry and material science, they are not widely available.[4] There are mainly two methods to synthesize vinyl triflones: direct condensation of triflyl-containing building blocks with aldehydes[4f,5] and indirect transformation from alkynyl triflones[6] or alkyl triflones.[3a,4d,7] Although these methods are efficient, they suffer from either comparably narrow substrate scope or multiple reaction steps. Critically, they require precursors which already contain a carbon–triflyl moiety, that is, C–SO_2CF_3. To meet the increasing demand of organofluorine compounds in agrochemicals, pharmaceuticals, and materials,[8] it is highly desirable to develop straightforward methods for the synthesis of vinyl triflones by direct C_{vinyl}–$S_{triflyl}$ bond formation (Figure 1).

The anionic Fries rearrangement, developed in the 1980s,[9] has become a common concept in the synthesis of polysubstituted aromatics.[10] The anionic thia-Fries rearrangement, uncovered by Lloyd-Jones in 2003, has been widely applied in the synthesis of various aryl triflones.[11] Recently, our group reported the regioselective synthesis of various heteroaryl triflones by anionic thia-Fries rearrangement.[12] Next we were wondering if we could extend its application to the synthesis of vinyl triflones. However, the

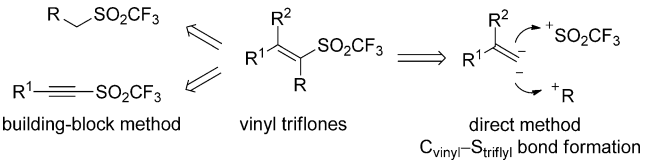
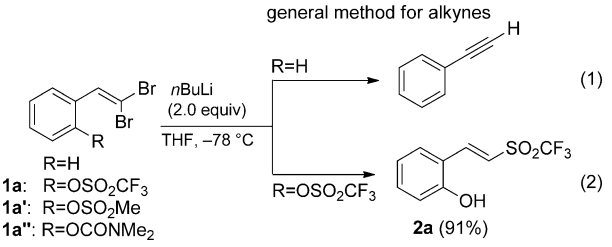


Figure 1. Strategies for substituted vinyl triflones: a building block method and a direct method (C_{vinyl}–$S_{triflyl}$ bond formation).

O_{aryl}→C_{vinyl} sulfonyl migration reaction is still a challenge. As in these remote anionic Fries-type rearrangement reactions,[13] the chemo-, regio-, and stereoselectivity must be simultaneously considered. Thus, to date, only few examples have been reported, and the substrates were limited to a special structure.[14] In continuation of our recent research interest in triflone chemistry,[12,15] we report herein our original results about stereoselective synthesis of substituted vinyl triflones from easily accessible *gem*-bromovinyl substrates through an anionic thia-Fries-type rearrangement. A C_{vinyl}–$S_{triflyl}$ bond formation was realized with the help of an intramolecular migration reaction.

The reaction of *gem*-dibromovinyl substrates with *n*BuLi (2.0 equiv) is well known as the general method for preparing alkynes [Eq. (1), Scheme 1].[16] We were pleased to find that



Scheme 1. Reactions of *gem*-dibromovinylbenzenes with *n*BuLi. General method for alkynes [Eq. (1)] and our new method for vinyl triflone [Eq. (2)]. Yield was determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. THF = tetrahydrofuran.

the situation was totally different for our designed compound **1a**, having an *ortho* OTf substituent. The O→C_{vinyl} triflyl migration reaction proceeded, thus giving the *E*-vinyl triflone **2a**, in 91% yield, stereoselectively [Eq. (2), Scheme 1]. Interestingly, the amount of base is critical. When 1.0 equivalent of *n*BuLi was added, about half of **1a** was converted and the desired product **2a** was obtained in low yield (22%). The

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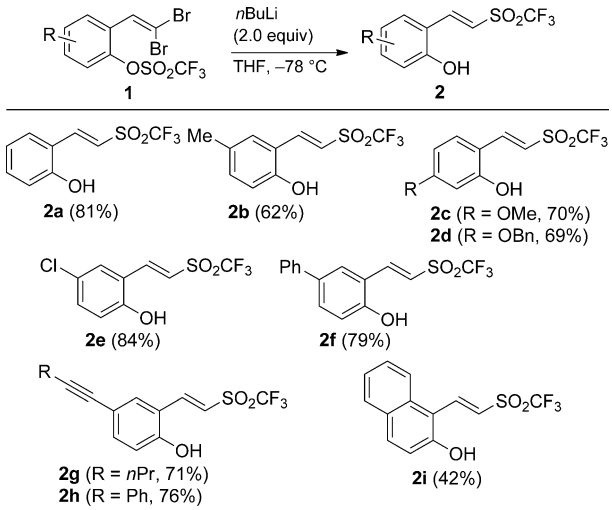
reaction conditions, including base, solvent, and temperature, were further screened, but no better result was obtained (see Table S1 in the Supporting Information). It should be noted that the triflyl group plays an important role in ensuring that the migration process takes place in this intramolecular rearrangement reaction. Starting from compounds **1a′** or **1a″**, the respective methanesulfonyl or carbamoyl migration reactions could not be detected at all.

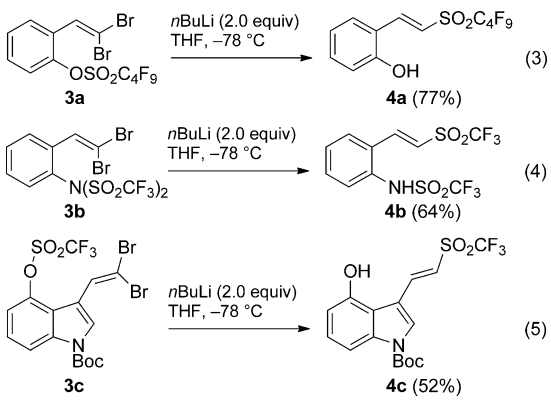
The scope of this anionic O→C_{vinyl} triflyl migration was then investigated with various *ortho-gem*-dibromovinylphenyl triflates (**1**). The results are summarized in Scheme 2. All the triflates **1b–h**, bearing either electron-donating or electron-withdrawing substituents in different positions, underwent remote triflyl migration to give the corresponding vinyl triflones **2b–h** in moderate to good yields. In the case of the naphthyl triflate **1i**, although the reaction mixture was a bit complex, the desired compound **2i** was obtained in acceptable yield. Based on all of the olefinic ^{1}H–^{1}H coupling constants (15.0–15.6 Hz) in the ^{1}H NMR spectra, the products **2a–i** were assigned as *E* isomers.[17]



Scheme 2. Stereoselective synthesis of vinyl triflones. Reactions of *ortho-gem*-dibromovinyl phenyl triflates **1** with *n*BuLi. Yields are of the isolated products.

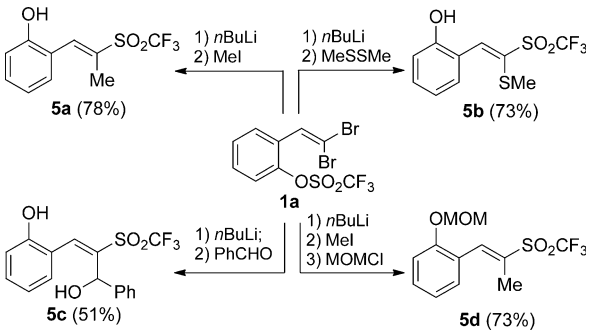
Fortunately, this O→C_{vinyl} triflyl migration strategy was successfully extended to three types of reactions (Scheme 3). First, not only the triflyl group, but also the nonaflyl (nonafluorobutanesulfonyl) group could undergo this migration process. Under the same reaction conditions, the compound **3a** was converted into the vinyl nonaflone **4a** in 77% yield [Eq. (3), Scheme 3]. Second, the N→C_{vinyl} triflyl migration in compound **3b** also proceeded well, thus giving a new type of vinyl triflone, **4b**, in 64% yield [Eq. (4), Scheme 3]. The last extension was a 1,6-triflyl migration. Starting from the indole derivative **3c**, the vinyl triflone **4c** was obtained in 52% yield [Eq. (5), Scheme 3]. To the best of our knowledge, this is the first example of anionic 1,6-migration reaction.

After obtaining the above disubstituted vinyl triflones, the reaction conditions were further optimized for the synthesis



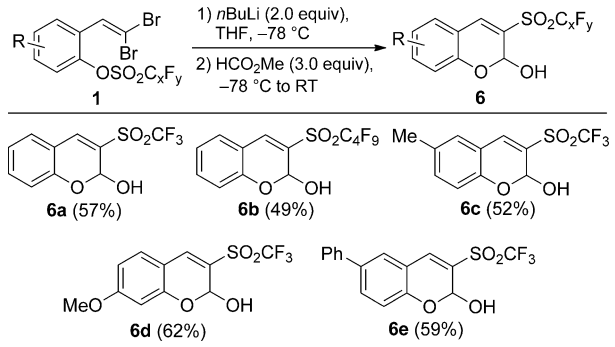
Scheme 3. Extension of intramolecular migration reactions. Boc = *tert*-butoxycarbonyl.

of trisubstituted vinyl triflones. Recently, the tandem reactions of *gem*-dibromovinyl systems have been widely applied in the synthesis of bifunctionalized compounds.[18] Influenced by this concept, a one-pot procedure was designed (Scheme 4). Different electrophiles were added to the reaction mixture after the addition of *n*BuLi. When the electrophiles were MeI, MeSSMe, and PhCHO, the corresponding trisubstituted vinyl triflones **5a–c** were obtained in moderate to good yields with excellent stereoselectivities. A one-pot, three-step reaction was also developed, wherein *n*BuLi, MeI, and MOMCl, were added sequentially to the reaction mixture of **1a**. After column chromatography the protected trisubstituted vinyl triflone **5d** was obtained in 73% yield. The structure of the compounds **5** was confirmed by X-ray crystallographic analysis of **5a**.[19]



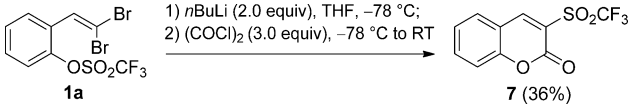
Scheme 4. Stereoselective synthesis of substituted vinyl triflones. Tandem reactions by treatment of **1a** with *n*BuLi and subsequent reaction with different electrophiles. MOM = methoxymethyl.

We were next interested in the synthesis of heteroaryl triflones from a biological point of view.[15] In this tandem reaction system, when the electrophile was HCO_2Me, intramolecular cyclization happened after the rearrangement/substitution steps (Scheme 5). The biologically attractive heteroaryl triflones, 3-triflyl- and 3-nonaflyl-2-hydroxy-2*H*-chromenes (**6a–e**), were obtained in good yields. Different functional groups, such as methyl, methoxy, and phenyl, were all well tolerated.



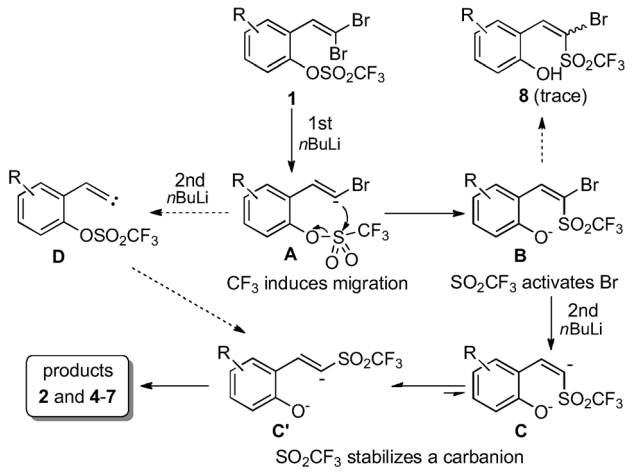
Scheme 5. Synthesis of heteroaryl triflones **6** by a rearrangement/substitution/cyclization reaction sequence.

Another type of heteroaryl triflone, the coumarin derivative **7**, was also synthesized in the one-pot rearrangement/substitution reaction with oxalyl chloride as the electrophile (Scheme 6). The formation of **7** may be explained by an additional intramolecular cyclization step.[5d]



Scheme 6. Synthesis of coumarin triflone **7** by a tandem reaction.

According to the above results, a mechanism for these rearrangement reactions is proposed in Scheme 7. When **1** reacted first with *n*BuLi, the common lithium–bromine exchange gave the intermediate **A**, which then underwent triflyl migration to afford **B**. The intermediate **B** then was converted into **C** by a second lithium–bromine exchange reaction. The second lithium–bromine exchange reaction should be faster than that of the first *n*BuLi reaction since 1) 2 equivalents of *n*BuLi are required for complete conversion, and 2) a trace amount of the brominated vinyl triflone **8** was detected even when 1 equivalent of *n*BuLi was used.



Scheme 7. A proposed reaction mechanism.

These facts can be explained by the strong electron-withdrawing power of the triflyl group in **B**, because it activates the reactivity of Br more towards *n*BuLi than the reactivity of Br in **1**. The intermediate **C**, which formed rapidly, isomerized to generate the more thermodynamically stable intermediate **C′**.[20] This in situ isomerization led to the stereoselective formation of the final products **2** and **4**–**7**, which were obtained from the subsequent reaction with different electrophiles. It is noteworthy that the strong electron-withdrawing power of the triflyl group stabilized the adjacent carbanion in **C′**. Above all, six transformations are involved in this reaction system: lithium–bromine exchange, 1,5-triflyl migration, lithium–bromine exchange, *Z* to *E* isomerization, and reactions of a carbanion or phenolate oxygen atom with electrophiles. Although the intermediate **D** can also be produced by competing α-elimination reactions from **A**, the migration process from **A** to **B** should be predominant since the strong electron-withdrawing trifluoromethyl[1b] substituent of the sulfonyl group remarkably enhances its electrophilic reactivity.

In conclusion, we have developed a new approach for the stereoselective synthesis of various vinyl triflones. Starting from *gem*-dibromovinyl substrates, several types of disubstituted vinyl triflones were conveniently obtained by remote $O\rightarrow C_{vinyl}/N\rightarrow C_{vinyl}$ triflyl migration reactions. Different trisubstituted vinyl triflones, including two types of novel heteroaryl triflones, were also synthesized by a one-pot rearrangement/substitution sequence. Further studies to expand the substrate scope and to develop applications are in progress.

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