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Alkyldisulfanium Salts: Isolable, Electrophilic Sulfur Reagents Competent for Polyene Cyclizations

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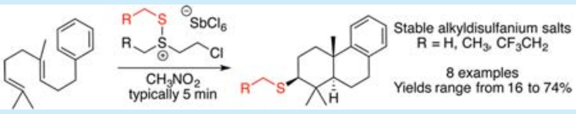
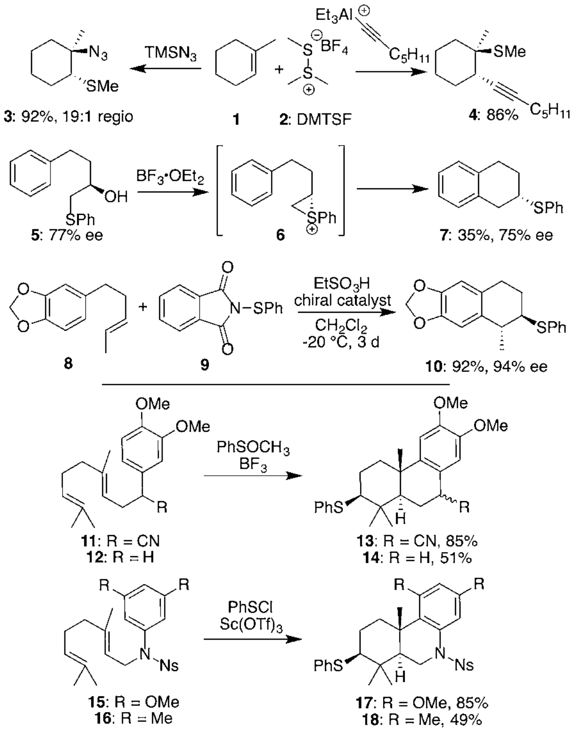
Supporting Information

ABSTRACT: Tools that can effect electrophilic sulfur-promoted cation−π cyclizations are generally lacking, especially using alkylsulfide-based reagents. Herein we report that combining three different 1,2-dithioethers with Cl_2 and $SbCl_5$ generates isolable alkyldisulfanium salts that can effect such reactions. These new reagents can install −SMe, −SEt, and $-SCH_2CH_2CF_3$ in modest, moderate, or good yield on diverse frameworks, including polyenes that terminate with electron-deficient groups. We also show that reagents such as dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) can accomplish similar chemistry.



Synthetic chemists have long been interested in using varied electrophiles to transform alkenes into new, and potentially more valuable, building blocks for applications ranging from materials science to pharmaceuticals.[1] Among those electrophile choices, sulfur-based species have long been of general interest given that the intermediate thiiranium ions can be opened by a wide range of nucleophiles to afford new products.[2] With simple alkenes, a number of processes have been developed with aryl and alkylsulfide electrophiles using heteroatom-based nucleophiles both inter- and intramolecularly;[2] the conversion of **1** into **3** (Scheme 1) using dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF, **2**)[3] is representative, noting that differential regiochemistry can be achieved based on reaction conditions.[4] In limited cases, such as the conversion of **1** to **4**, carbon-based nucleophiles can add as well.[5] Enantiospecific variants of some of these transformations constitute more recent advances, with key discoveries being the development of approaches to forge chiral sulfonium species *in situ* (as in the conversion of **5** into **7**)[6,7] and more recent, and pioneering, findings from Denmark et al. to effect exogenous chiral additions of sulfur electrophiles onto alkenes such as **8** with catalytic amounts of appropriate chiral promoters.[8] However, despite these and other advances,[9] limitations remain. One of these is the ability to utilize electrophilic sulfur sources effectively with polyene substrates, such as for cation−π cyclizations. Indeed, only a few examples of these reactions are known. For example, in studies performed several decades ago, the Livinghouse group showed that the process was achievable using an aryl thiiranium species with electron-rich aryl-terminating substrates such as **11** and **12**, but that the addition of electron-withdrawing groups on the intervening chain (such as the nitrile of **11**) was necessary to enhance synthetic yields by achieving superior chemoselectivity between the two alkenes present;[10] in a more recent publication, Shaw et al. developed an optimized version of those original conditions to achieve the same type of process on *N*-linked substrates such as **15** and **16**, accessing a unique collection of

Scheme 1. Key Precedent for Electrophilic S-Promoted Polyene Cyclizations and the Forefront in Terms of Asymmetric Cyclizations Using Monoalkene-Containing Substrates



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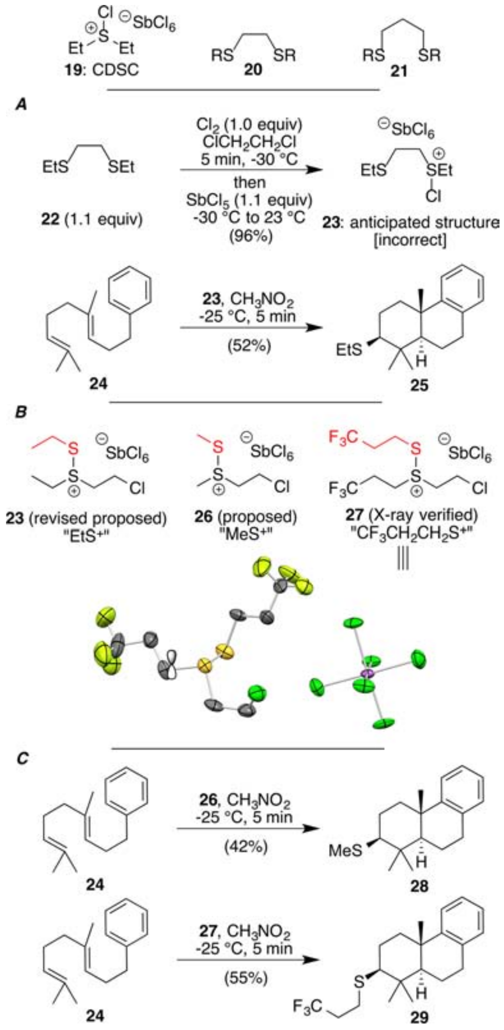
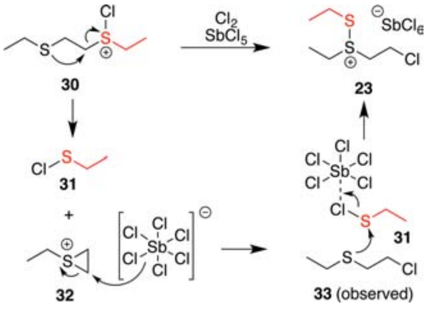
Scheme 2. Attempts to Develop More Reactive Chloronium Sources Led to the Discovery of a Collection of Reagents (23, 26, and 27) That Are Potent Electrophilic Sulfur Sources (A and B); Initial Application to Substrate 24 (A and C)



heterocycles in the form of **17** and **18**.[11,12] In both cases, however, only PhS-based cyclization products were generated.[13] Here, we report the identification of three isolable and stable alkyldisulfanium salts that can serve as competent alkyl-based sulfur electrophiles. These reagents are capable of cyclizing, with various levels of success, eight different substrates, five of which are polyenes with different terminating groups. As such, the means to incorporate distinct alkylthio groups onto other substrates may exist, affording useful structural diversity, especially given the prevalence of sulfur in pharmaceutical agents.[14]

Our interest in this area derived from our efforts to identify highly reactive halonium electrophiles that could broadly effect polyene cyclizations.[15] As documented, we found that the combination of Et_2S, molecular halogen, and $SbCl_5$ produces isolable, but highly effective forms of Cl^+, Br^+, and I^+ that can achieve such processes on a range of materials. Among these tools, however, the one based on molecular chlorine (CDSC, **19**, Scheme 2)[15b] possesses more modest capabilities in terms of yield and diastereoselectivity than its halogen cousins despite being determined to be a highly reactive chloronium source relative to other commercially available tools.[16]

Scheme 3. Proposed Mechanism to Account for the Formation of the Electrophilic Alkyldisulfanium Salts (Shown with 23)



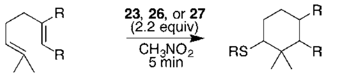
In an effort to improve upon that reactivity, we sought to explore the properties of such reagents as generated from bidentate sulfur ligands of type **20** and **21**, leading us to prepare reagent **23** as shown from disulfide **22** using molecular Cl_2 and $SbCl_5$ in 1,2-dichloroethane. Its structure as drawn could not be verified, as the solid formed from this process quickly hydrolyzed in most organic solvents, thereby precluding NMR and IR analysis. Nevertheless, we decided to test its reactivity, and to our surprise, when we exposed polyene **24** to 2.0 equiv of that new material (i.e., **23**), the product of a chloronium-induced cyclization was not observed; instead, the major adduct obtained in 52% isolated yield was **25** wherein EtS^+ had served as the electrophile inducing polyene cyclization.

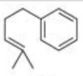
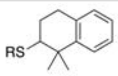
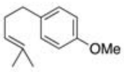
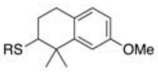
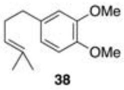
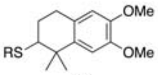
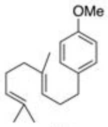
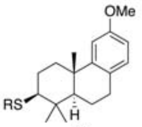
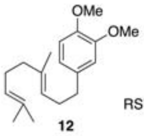
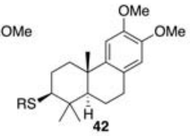
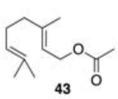
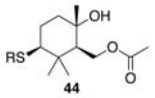
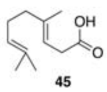
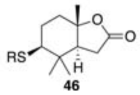
Given this outcome, coupled with the absence of examples of alkyl sulfide-induced polyene cyclizations in more general terms, we sought to determine the actual structure of reagent **23** and to identify additional tools of similar structure that would also be competent in such chemistry. Following probes of several different disulfides of types **20** and **21** (cf. Scheme 2),[17] we identified two other reagents (**26** and **27**)[18] that were effective sources of electrophilic alkyl sulfides in terms of cyclizing substrate **24**, affording **28** and **29** in 42% and 55% yield, respectively. The latter of these reagents was successfully diffracted using X-ray crystallographic analysis, revealing that its structure is an alkyldisulfanium salt. We presume, based on analogy, that both **23** and **26** possess similar connectivities (Scheme 2).

A proposal to account for the formation of these tools is shown in Scheme 3 using reagent **23** for purposes of illustration. As shown, we believe that, following chlorination of one of the sulfides within **22** to generate **30**, internal nucleophilic displacement by the other sulfide could generate a mixture of both chlorosulfide **31** and reactive thiiranium **32**. Attack by chloride from the $SbCl_6^-$ counterion in solution could then convert this latter species into **33**, with its subsequent attack onto **31** and $SbCl_6^-$ regeneration then affording the final reagent. This proposal is based on several key observations. First, we were able to detect (2-chloroethyl)(ethyl)sulfane (**33**) by ^1H NMR analysis of the crude material obtained during our initial probes of reagent **23**, indicating that it is a likely intermediate.[19] Second, while various thioether substituents such as Et, Me, Bn, *i*-Pr could lead to isolable alkyldisulfanium salts, only those with fully linear alkyl groups (i.e., Et and Me) effectively promoted polyene cyclization with **24**, suggesting that sterics is important as would be expected based on the mechanism proposed with several nucleophilic operations.[20] Finally, efforts to use other, shorter CF_3-based alkyl chains failed, presumably because closer proximity of the electron-withdrawing group to the reactive sulfur centers prevented thiiranium formation.

With these three tools in hand, we then sought to probe their overall power with a variety of substrates including both monoalkene-containing materials as well as other polyenes with varying degrees of electron density in their terminating groups. The results are shown in Table 1, with typically 5 min of reaction time and 2.2 equiv of electrophilic sulfur source used at temperatures based on the electron wealth of the nucleophilic component as indicated.

Table 1. Exploration of the Scope of the "RCH_2S^+" Sources on Both Monoalkenes and Polyenes of Varying Electron Wealth

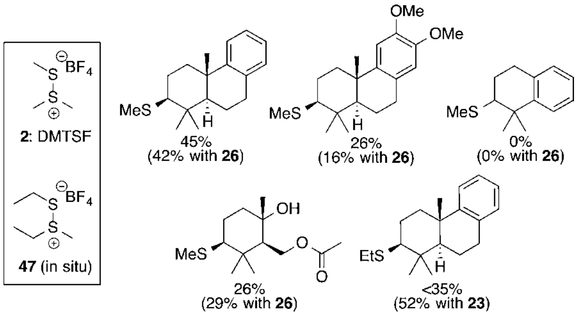


entry	starting material	product	reagent **23** "EtS+" yield (%)[a]	reagent **26** "MeS+" yield (%)[a]	reagent **27** "$CF_3CH_2CH_2S^+$" yield (%)[a]
1	 **34**	 **35**	0[b]	0[b]	32-74[cd]
2	 **36**	 **37**	0[e]	65[f]	72[c]
3	 **38**	 **39**	52[g]	57[g]	70[c]
4	 **40**	 **41**	50[c]	0[b]	46[c]
5	 **12**	 **42**	29[h]	16[i]	52[c]
6	 **43**	 **44**	35[j]	29[j]	43[j]
7	 **45**	 **46**	20[j]	41[j]	47[jk]

[a] Isolated yields. [b] Decomposition was observed. [c] 2.2 equiv of reagent were used for 5 min at −25 °C. [d] Contains an additional 7% of (2-chloroethyl)(3,3,3-trifluoropropyl)sulfane. [e] Traces of product observed. [f] 4.0 equiv of reagent were used for 5 min at −25 °C, then 23 °C for 1 h. [g] 2.2 equiv of reagent were used for 5 min at −25 °C, then 23 °C for 5 min. [h] 3.0 equiv of reagent were used for 5 min at −25 °C. [i] 4.0 equiv of reagent were used for 5 min at −25 °C, then 23 °C for 30 min. [j] 2.2 equiv of reagent were used for 5 min at 0 °C. [k] Contains an additional 15% of an inseparable byproduct; UV inactivity made purification challenging.

Globally, given the ability of the alkyl chains within **23**, **26**, and **27** to differentially stabilize the incipient electrophilic character of their key sulfur atoms based on their inductive properties, we expected that reagent **27** should be the most reactive, while **23** would be the least electrophilic. As shown by the outcomes in entries 1−3 using substrates with a single pendant alkene and aromatic rings of varying nucleophilicity to intercept the intermediate thiiranium ion formed, that supposition proved true. Indeed, only **27** could cyclize the electron neutral **34** through a terminating Friedel−Crafts reaction, with the addition of extra electron density enabling product formation from the other tools in good to moderate yield.[21] For polyene substrates with greater electron density than that already probed in the form of **24** (cf. Scheme 2), both reagents **23** and **27** worked reasonably well (entries 4 and 5), though for reasons that are not clear at present, MeS^+ source **26** afforded either no product or very low yield of product in these two cases. Pleasingly, however, substrates with more modest electron density such as **43** and **45** bearing different terminating groups in the form of a carbonyl and a carboxylic acid, respectively, were competent with all three tools, affording products **44** and **46** in yields ranging from 20% to 47%. Although it could be argued that these numbers from a yield perspective may be nonoptimal, they serve as an important initial proof of principle for the ability to incorporate alkylsulfides in polyene cyclizations, especially with substrates that historically have proven more difficult to cyclize due to the electron deficiency within their terminating groups. Indeed, those outcomes more broadly proceed with levels of efficiency similar to the electrophilic arylsulfides that are arguably more reactive/stable as documented in part in Scheme 1.

Scheme 4. Attempted Polyene Cyclizations Using 2 and 47



Finally, given the homology of our reagent structures to that of DMTSF (**2**, cf. Scheme 1),[22] we sought to determine if these reagents (some being commercial) were equally competent for polyene cyclization; we note that to the best of our knowledge only one example of a diene-containing molecule (nonterpene based) had ever been exposed to such tools.[23] This reagent, as well as its *in situ* generated ethyl sulfide analog (**47**), gave similar results (Scheme 4). Thus, we show for the first time that these alternate reagents can effect polyene cyclizations as well, where the superior yield in the final case with **23** might reflect the ability to obtain that reagent as a discrete solid. More globally, the potential advantage of our approach from a reagent preparation standpoint, especially for new alkyl sulfides, is that it requires only alkylating a dithiol followed by chlorine treatment; by contrast, reagents such as **2** and **47** require access to a disulfide precursor, a facet which might preclude access to transfer reagents like **27**.

In summary, we have identified three new isolable and storable reagents in the form of alkyldisulfanium salts that are competent alkyl-based S-electrophiles capable of effecting a diverse range of cyclizations in racemic form. Their connectivities have, in one case, been verified by X-ray crystallography, and a mechanism to account for their formation has been advanced based on many observations of the process in general terms. We have also shown that reagents of related structure, such as DMTSF, can also effect these processes. Collectively, these tools document that alkylsulfur groups can serve as competent electrophiles for processes previously achieved only with activated arylsulfide

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reagents, indicating that an enhanced range of substrates can likely be accessed via other S-promoted cyclizations as well.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02059.

Full experimental details, copies of spectral data, X-ray crystal structures (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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(17) These efforts included a number of different alkyl-based side chains on a 1,2-ethanedithiol core as well as efforts to change that 1,2-ethanedithiol core with longer chains as well as further substitution on the intervening carbon chain.

(18) The alkyldisulfanium salts are stable for several weeks when stored at −20 °C (samples of **23** have been stored for up to 6 months with no loss in reactivity), but they are unstable at 23 °C, decomposing over the course of 12 h. They also show instability when dissolved in standard organic solvents at 23 °C, making NMR analysis challenging. However, **23**, **26**, and **27** all have readily measured melting points. See the Supporting Information for all their properties as discerned thus far.

(19) Given the volatility of **33**, efforts were not made to isolate it.

(20) Both the Bn and *i*-Pr reagents did afford trace amounts of cyclized product, but the yields were less than 10% at best.

(21) The yield for this particular product proved to be fairly variable, with sulfhydrin alkene addition products being formed in some additional runs. For the other products listed in Table 1, yields were reproducible.

(22) We thank a referee for his/her comments that induced these additional explorations.

(23) Haufe, G.; Alvernhe, G.; Anker, A.; Laurent, A.; Saluzzo, C. *Tetrahedron Lett.* **1988**, *29*, 2311.