Efficient synthesis of 3-sulfolenes from allylic alcohols and 1,3-dienes enabled by sodium metabisulfite as a sulfur dioxide equivalent

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ARTICLE

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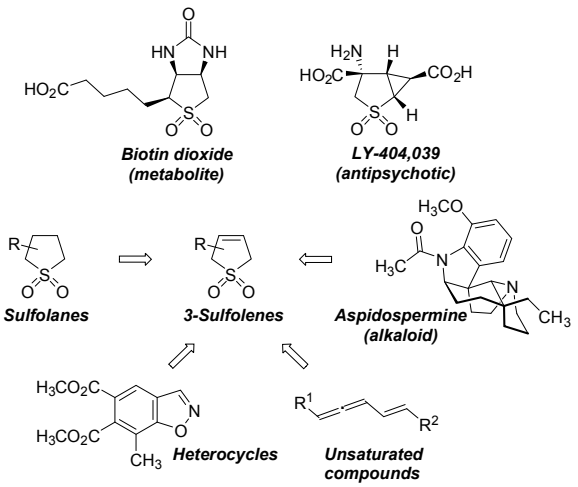
We present herein an efficient and practical method for a gram scale synthesis of 3-sulfolenes using sodium metabisulfite as a safe, inexpensive, and easy to handle sulfur dioxide equivalent. Diversely-substituted 3-sulfolenes can be prepared by reacting a variety of 1,3-dienes or allylic alcohols with sodium metabisulfite in aqueous hexafluoroisopropanol (HFIP) or in aqueous methanol in the presence of potassium hydrogen sulfate. Advantageously, the method enables conversion of allylic acohols directly to 3-sulfolenes, by-passing intermediate 1,3-dienes.

Five-membered sulfur heterocycles play important roles in organic synthesis,[1] medicinal chemistry,[2] and materials science.[3] 3-Sulfolenes[4] are key intermediates in the synthesis of sulfolanes,[5] polycyclic heterocycles,[1c] conjugated unsaturated compounds,[6] as well as in natural product synthesis (Figure 1).[7] The synthesis of 3-sulfolenes typically involves reactions with excess sulfur dioxide. Sulfur dioxide is a toxic gas,[8] and synthetic manipulations with sulfur dioxide require high pressure equipment. In addition, measurement of exact quantities of sulfur dioxide is not practical, and variabilities in quantities of sulfur dioxide used and in reaction pressures may lead to inconsistent product yields and purities. These limitations have inspired a search for reagents that can serve as practical and safe sulfur dioxide equivalents.[9] DABCO-bis(sulfur dioxide) (DABSO) is a solid and bench stable reagent that has recently been introduced by Willis as a convenient sulfur dioxide equivalent for the synthesis of sulfinates, sulfonamides, sulfones, and 3-sulfolenes.[10] Although DABSO has a number of synthetic advantages as a sulfur dioxide equivalent, it may be expensive for some applications, and the synthesis of 3-sulfolenes using DABSO requires large excess (6 equiv.) of 1,3-diene.[10a] Alternatively, use of excess boron trifluoride diethyl ether complex as an additive is necessary to sequester the Lewis basic DABCO that inhibits the cheletropic reaction with 1,3-dienes.[10c] Sodium and potassium metabisulfites have recently been used as sulfur dioxide equivalents for the synthesis of sulfones and sulfonamides.[11] Metabisulfites are bench stable, inexpensive, solid salts with one of the highest SO_2 equivalent contents (65.4% for $Na_2S_2O_5$).[12] We reasoned that sodium metabisulfite can produce sulfur dioxide in situ that will then undergo the cheletropic reaction with 1,3-dienes. In our search for appropriate reaction conditions we were guided by the studies by Faita,[13] Vogel, and Sordo[14] on the influence of solvents, as well as Brønsted and Lewis acids on the rates and the equilibrium constants of the cheletropic reaction of 1,3-dienes with sulfur dioxide.

Figure 1. Sulfolane and 3-sulfolene in organic and medicinal chemistry.



It is known that the rate of the cheletropic cycloaddition reaction increases in more polar solvents (e.g., $k = 49\times10^{-5}$ $M^{-1}sec^{-1}$ in CH_3OH, $E_T(30) = 55.5$; $k = 0.93\times10^{-5}$ $M^{-1}sec^{-1}$ in C_6H_6, $E_T(30) = 34.5$). Conversely, the rate of the cycloelimination decreases in more polar solvents (e.g., $k = 1.7\times10^{-5}$ $M^{-1}sec^{-1}$ in CH_3OH, $E_T(30) = 55.5$; $k = 4.55\times10^{-5}$ $M^{-1}sec^{-1}$ in C_6H_6, $E_T(30) = 34.5$).[13] Thus, formation of 3-sulfolenes proceeds faster and is more complete in solvents of higher polarity. On the other hand, experimental and computational studies showed that

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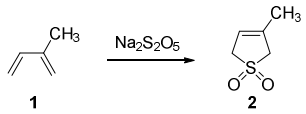
the cheletropic reaction can be accelerated by Brønsted and Lewis acids.[14]

We were therefore particularly interested in investigating the effect of hexafluoroisopropanol (HFIP) on the efficiency of the cheletropic reaction with sodium metabisulfite as a sulfur dioxide precursor. Hexafluoroisopropanol is one of the most polar ($E_T(30)$ = 65.3)[15] and acidic (pK_a = 9.3)[16] common organic solvents. These properties, in addition to the high ionizing power (Y_{OTs} = 3.79),[17] very low nucleophilicity (N_{OTs} = −4.23)[18] and high hydrogen bond donor abilities (α = 1.96)[19] have made HFIP the solvent of choice for a number of recently developed synthetic methods.[20]

Indeed, optimization studies for the reaction of diene **1** with sodium metabisulfite showed that HFIP is superior to other less polar solvents (e.g., entries 1 and 2, Table 1). The optimal ratio of HFIP and water was found to be 4 : 1. In this solvent mixture, sulfolene **2** was formed in 20% yield at 80 °C (entry 3). The yield improved to 50% at 100 °C (entry 4) with 2 equiv. of sodium metabisulfite. When the amount of sodium metabisulfite was increased to 5 equiv., complete conversion was observed, and sulfolene **2** was isolated in 97% yield (entry 7). In addition, to aqueous HFIP, we found that potassium hydrogen sulfate in aqueous methanol promoted the efficient conversion of diene **1** to sulfolene **2** in the presence of sodium metabisulfite (entries 9 and 10).

Table 1. Optimization of the 3-sulfolene synthesis from 1,3-dienes[a]



1 **2**

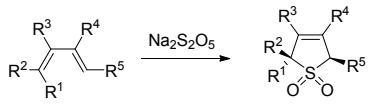
Entry	Solvent (ratio)	Reagent (equiv.)	T, °C	Yield, %[b]
1	THF/H_2O (3 : 1)	$Na_2S_2O_5$ (4)	80	3
2	HFIP/H_2O (3 : 1)	$Na_2S_2O_5$ (4)	80	19
3	HFIP/H_2O (4 : 1)	$Na_2S_2O_5$ (5)	80	20
4	HFIP/H_2O (4 : 1)	$Na_2S_2O_5$ (2)	100	50
5	HFIP/H_2O (4 : 1)	$Na_2S_2O_5$ (3)	100	60
6	HFIP/H_2O (4 : 1)	$Na_2S_2O_5$ (4)	100	65
7[c]	**HFIP/H_2O (4 : 1)**	**$Na_2S_2O_5$ (5)**	**100**	**97**
8	CH_3OH/H_2O (4 : 1)	$Na_2S_2O_5$ (3) $KHSO_4$ (1)	80	39
9[c]	CH_3OH/H_2O (4 : 1)	$Na_2S_2O_5$ (5) $KHSO_4$ (3)	100	80
10[c]	**CH_3OH/H_2O (4 : 1)**	**$Na_2S_2O_5$ (5) $KHSO_4$ (2)**	**100**	**98**

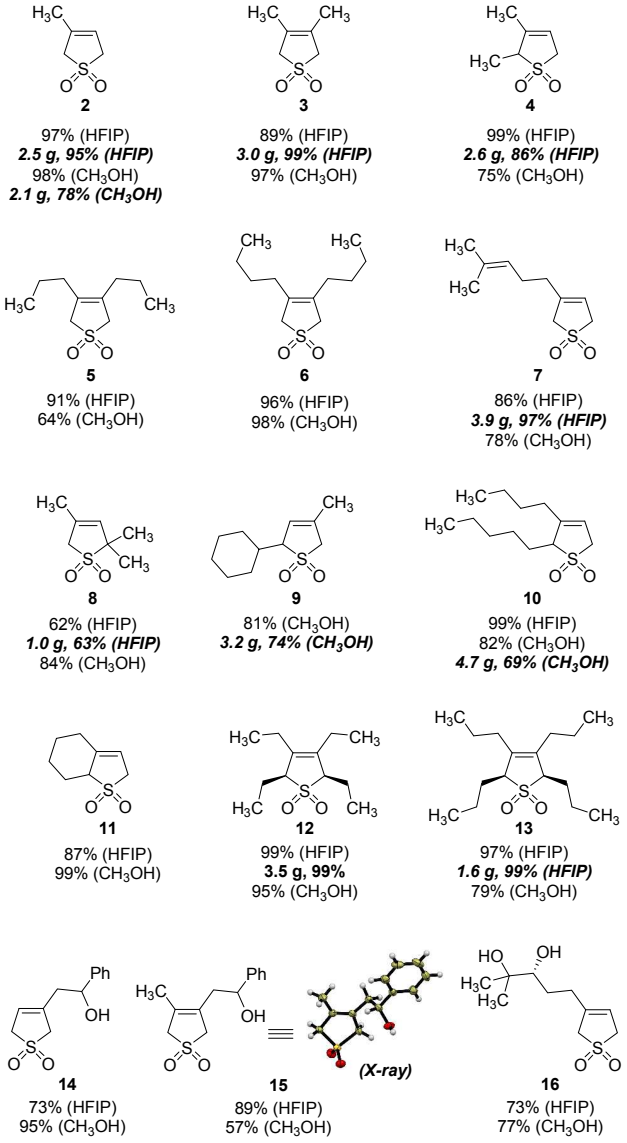
[a] Reaction conditions: 1,3-diene (2 mmol), solvent (5 mL), 16 h. [b] Yield was determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard. [c] Isolated yield.

In this case, the lower pK_a of bisulfate (pK_a = 1.99 in water)[21] can promote formation of sulfur dioxide in situ, while the increased polarity and acidity of the solution may accelerate the cheletropic reaction.

We next studied the scope of the method under both conditions, i.e., in HFIP/H_2O, and with $KHSO_4$ in CH_3OH/H_2O (Table 2). A number of substituted 1,3-dienes were subjected to the reaction with sodium metabisulfite.

Table 2. Synthesis of 3-sulfolenes from 1,3-dienes[a]



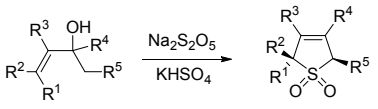


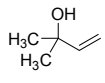
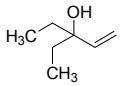
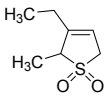
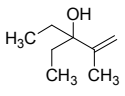
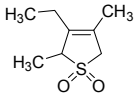
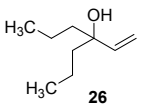
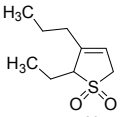
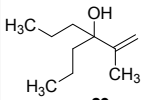
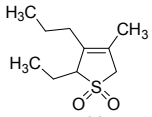
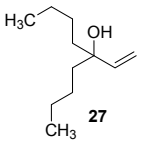
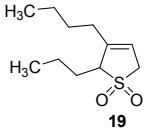
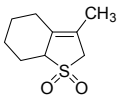
[a] Reaction conditions: HFIP: 1,3-diene (2 mmol), $Na_2S_2O_5$ (5 equiv.), HFIP/H_2O (4 : 1) (5 mL), 100 °C, 14 h. CH_3OH: 1,3-diene (2 mmol), $Na_2S_2O_5$ (5 equiv.), $KHSO_4$, (2 equiv.), CH_3OH/H_2O (4 : 1) (5 mL), 100 °C, 14 h.

In general, most of the sulfolenes were obtained in good to excellent yields in HFIP and with $KHSO_4$ in methanol (e.g., sulfolenes **2-6**). Myrcene-derived sulfolene **7**, as well as the α,α-disubstituted product **8** were also obtained in good yields. Only in the case of sulfolene **9** was a significant difference in the two protocols observed. While little product was formed in HFIP/H_2O, sulfolene **9** was formed in 81% yield on small scale, and in 75% yield on gram (3.2 g) scale in methanol and with $KHSO_4$. 2,3-Disubstituted sulfolenes **10** and **11** were produced in good yields as well. In addition, the tetrasubstituted sulfolenes **12** and **13** were readily accessed using both reaction conditions.

Furthermore, the acid-sensitive benzylic alcohol functionality was not affected during the synthesis of sulfolenes **14** and **15**. Similarly, the myrcene-derived diol sulfolene **16** was readily prepared in 73% (in HFIP/H_2O) and 77% (in CH_3OH/H_2O with $KHSO_4$). In none of the cases was polymerization of the 1,3-dienes or isomerization to 2-sulfolenes observed. The reaction can also be readily carried out on gram scales. For example, sulfolenes **2-4**, **7-10**, as well as **12** and **13** were prepared in gram quantities (1–4.7 g), and both reaction conditions are equally amenable to scale up.

Table 3. Synthesis of 3-sulfolenes from allylic alcohols[a]



Substrate	Product	Substrate	Product
 **23**	 **2** 86%	 **24**	 **11** 63%
 **25**	 **17** 83% ***1.5 g, 67%***	 **28**	 **20** 87%
 **26**	 **18** 74%	 **29**	 **21** 73%
 **27**	 **19** 75%	 **30**	 **22** 62%

[a] Reaction conditions: allylic alcohol (0.42–1 mmol), $Na_2S_2O_5$ (3–5.5 equiv.), $KHSO_4$ (4–7.3 equiv.) HFIP/H_2O (2 : 1 or 3 : 1) (5 mL), 100 °C, 36 h.

The structure of sulfolene **15** was confirmed by single crystal X-Ray crystallographic analysis.

Due to the relatively low boiling point of HFIP (58.6 °C), it can be easily recovered by distillation and reused for the synthesis of sulfolenes. For example, a synthesis of sulfolene **3** was repeated consecutively three times using recycled HFIP without any noticeable deterioration of yields.

The metabisulfite-mediated sulfolene synthesis proceeds with better yields and produces lower headspace pressure than the protocol that is based on the use of condensed sulfur dioxide generated ex situ. For example, the headspace pressure was 18 psi under the HFIP/H_2O conditions, and 10 psi using the CH_3OH/H_2O with $KHSO_4$ conditions. In both cases the yield of sulfolene **7** was >75%. When sulfur dioxide was generated ex situ by reacting sodium metabisulfite (10 equiv.) with 12M hydrochloric acid (20 equiv.), the headspace pressure was 32 psi, while the yield of sulfolene **7** was only 48% with methanol as a reaction solvent.

Allylic alcohols serve as precursors to a number of 1,3-dienes.[22] A method that allows for a synthesis of 3-sulfolenes directly from allylic alcohols will significantly improve the efficiency of 3-sulfolene synthesis by obviating isolation of intermediate 1,3-dienes that can be volatile and prone to polymerization. Martial and Bischoff recently showed that the DABSO/BF_3·OEt_2 system can be used to convert allylic alcohols to 3-sulfolenes.[10c] We were therefore interested in developing a metabisulfite-based method for this transformation. Indeed, we found that a number of 3-sulfolenes, e.g., **2**, **11**, and **17-22** can be prepared from readily available allylic alcohols under modified reaction conditions in HFIP/H_2O in the presence of $KHSO_4$ (Table 3). Thus, sulfolenes **2** and **11** were produced from commercial allylic alcohols **23** and **24** in 86% and 63% yields, respectively. For the synthesis of sulfolenes **17-22**, alcohols **25-30** were conveniently prepared by the reaction of the corresponding ketones with vinyl- or isopropenylmagnesium bromide, and used without purification in the reaction with sodium metabisulfite. This way, sulfolenes **17-22** were prepared in >60% yield. The synthesis of sulfolene **17** was successfully carried out on a gram scale.

Conclusions

In conclusion, this paper describes the development of a simple and efficient method of preparation of 3-sulfolenes from 1,3-dienes and allylic alcohols. The reaction development was enabled by a mechanism-driven optimization of the reaction conditions. The reactions can be carried out on gram scales with sodium metabisulfite as a bench stable and inexpensive sulfur dioxide equivalent in aqueous hexafluoroisopropanol (HFIP) or in aqueous methanol in the presence of potassium hydrogen sulfate. Advantageously, the method enables conversion of allylic alcohols directly to 3-sulfolenes, by-passing isolation of intermediate 1,3-dienes. The new method is expected to find applications in natural product synthesis, medicinal chemistry, and organic synthesis.

Experimental

General Procedure 1 (GP1) for the synthesis of sulfolenes in hexafluoroisopropanol (HFIP)

A 75 mL glass pressure vessel was charged with a 4 : 1 v/v mixture of HFIP (4 mL) and water (1 mL). The stirred mixture was degassed by bubbling argon for 5 min, then 1,3-diene (2 mmol) and sodium metabisulfite (10 mmol, 5 equiv) were added. The vessel was sealed, and the reaction mixture was stirred at 100 °C for 14 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to remove HFIP. Ethyl acetate was added, and the solution was dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure to afford the sulfolene product.

General Procedure 2 (GP2) for the synthesis of sulfolenes in methanol with $KHSO_4$

A 75 mL pressure vessel was charged with a 4 : 1 v/v mixture of methanol (4 mL) and water (1 mL). The stirred mixture was degassed by bubbling argon for 5 min, then $KHSO_4$ (4 mmol, 2 equiv.), diene (2 mmol) and sodium metabisulfite (10 mmol, 5 equiv.) were added. The vessel was sealed, and the reaction mixture was stirred at 100 °C for 14 h. The reaction mixture was cooled to room temperature and concentrated. Ethyl acetate was added, and the solution was dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure to afford the sulfolene product.

General Procedure 3 (GP3) for the synthesis of allylic alcohols

To a solution of ketone (5 mmol) in tetrahydrofuran (10 mL) was added 1M vinylmagnesium bromide or isopropenylmagnesium bromide solution in THF (8 mmol, 1.6 equiv.) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. Saturated solution of ammonium chloride (3 mL) was added, and the mixture was extracted with ethyl acetate (4 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The purity of the crude allylic alcohol was assayed by means of ^{1}H NMR spectroscopy with 1,4-dimethoxybenzene as an internal standard, and the crude allylic alcohol was immediately used for the preparation of 3-sulfolenes (GP4).

General Procedure 4 (GP4) for the synthesis of sulfolenes from allylic alcohol

To a 48 mL pressure vessel charged with allylic alcohol (0.6−1 mmol) was added a 2 : 1 or 3 : 1 v/v mixture of degassed HFIP and water (5 mL). Sodium metabisulfite (3 mmol, 3−5 equiv.) and $KHSO_4$ (4 mmol, 4−7.3 equiv.) were added. The vessel was sealed, and the reaction mixture was stirred at room temperature for 15 minutes. The reaction mixture was then allowed to stir at 100 °C for 36 h. The reaction mixture was cooled to room temperature, ethyl acetate was added, and the solution was dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure and purified by flash chromatography (silica gel, ethyl acetate/ hexane) to afford the 3-sulfolene product.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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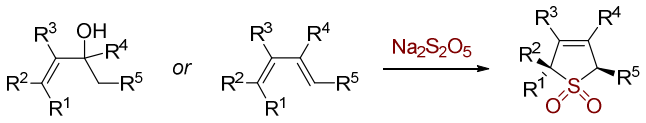
Table of Contents Entry



- sodium metabisulfite as a sulfur dioxide equivalent
- direct synthesis of 3-sulfolenes from allylic alcohols
- diversely substitited 3-sulfolenes on gram scales
- mild reaction conditions and broad scope

Sentence highlighting the novelty of the work:

The new method enables a simple and efficient synthesis of 3-sulfolenes from 1,3-dienes and allylic alcohols using sodium metabisulfite.