Radical Reactions

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# Regioselective Hydroxysulfenylation of α,β-Unsaturated Imines: Enhanced Stability of an Intermediate Radical**

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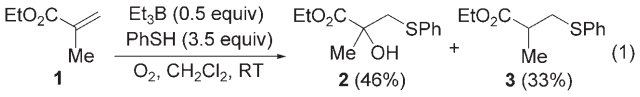
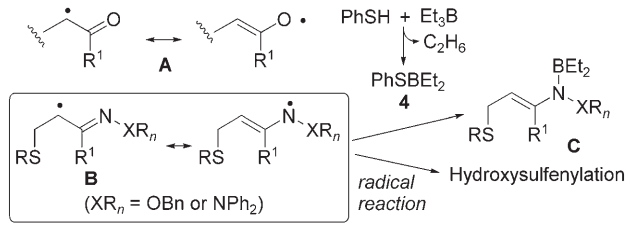
Free-radical-mediated hydroxysulfenylation reactions, which are traditionally called thiol–oxygen cooxidation reactions,[1] have been developed as attractive routes toward valuable functionalized products.[2–4] However, the diversity of hydroxysulfenylation reactions is constrained by the use of electron-rich olefins as radical acceptors. Less is known about the hydroxysulfenylation reactions of electron-deficient olefins,[5] probably because competitive Michael addition of the thiol might impede the radical process. Hydroxysulfenylation reactions are frequently plagued by low regioselectivity and chemical efficiency.[4] We anticipated that electron-deficient olefins should have the potential to induce hydroxysulfenylation pathways with good regioselectivity, since the thiyl radical has both electrophilic and nucleophilic character.[2,6] Indeed, on our first attempt, the reaction of methacrylate **1** with thiophenol gave the unfavorable Michael adduct **3**, although the hydroxysulfenylation product **2** was also produced with high regioselectivity [Eq. (1)].[7] The main limitation of this reaction is assumed to be the insufficient stability of the intermediate carbonyl-stabilized radical and the competition with the nonradical Michael addition reaction; therefore, we expected that the hydroxysulfenylation could become the major reaction by enhancing the stability of the intermediate radical and by reducing the ability of the Michael acceptor to undergo the ionic process.

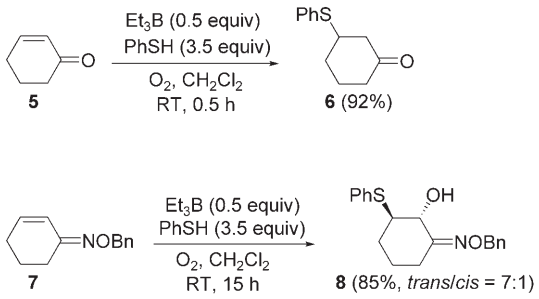



In contrast to the rich chemistry of α-carbonyl radical **A**,[8] the reactivity of the α-imino radical **B** has been unexplored; thus, our research group was interested in developing new transformation of α-imino radicals (Scheme 1).[9] We considered that the stability of the intermediate radical would be increased by converting the carbonyl group of α,β-unsaturated aldehydes or ketones into the imino group, in particular under triethylborane-induced reaction conditions.[10] This concept is supported by the lower dissociation energy of the N–B bond than the O–B bond, which is related to the trapping process of the intermediate radicals **A** and **B** by the organoborane.[11] The ability of triethylborane to trap **B** was suppressed by the formation of $PhSBEt_2$ (**4**) as a result of rapid reaction with the thiol.[12,13] Radical **B** can also be stabilized by the β-sulfenyl group.[14] Herein, we describe the regioselective hydroxysulfenylation of electron-deficient olefins by taking advantage of α-imino radicals.[7]




***Scheme 1.*** Outline for hydroxysulfenylation via an α-imino radical. Bn = benzyl.

We first probed the utility of the α-imino radical and a highly promising result was obtained after cyclohexanone **5** was replaced by oxime ether **7** (Scheme 2).[15]. Michael adduct




***Scheme 2.*** Michael addition and hydroxysulfenylation reactions.

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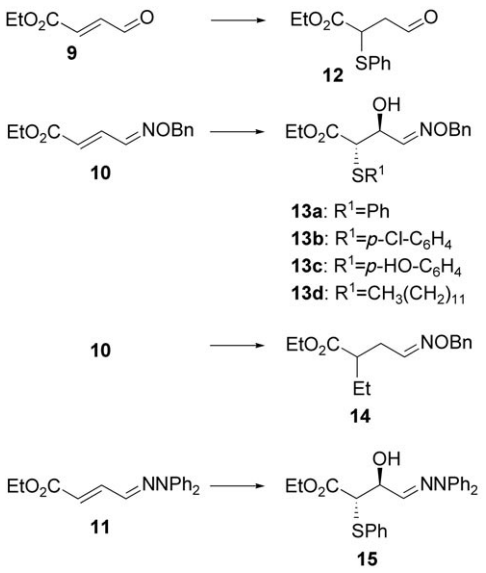
**6** was obtained exclusively from **5**. In marked contrast, hydroxysulfenylation of **7** proceeded with excellent regioselectivity to give the β-hydroxysulfide **8** in 85% yield, without the formation of the simple Michael adduct. These observations suggest that the enhanced stability of the intermediate α-imino radical offers a complementary radical reaction pathway and oxidative interception with molecular oxygen. It is also important to stress that the ionic Michael addition reaction was suppressed by converting the ketone into an oxime ether, which is weakly electron-withdrawing; thus, the Michael adduct from **7** was not formed even in the absence of triethylborane.

Next, the pathway of the hydroxysulfenylation reaction was investigated under different reaction conditions (Scheme 3). The substrate of choice was α,β-unsaturated



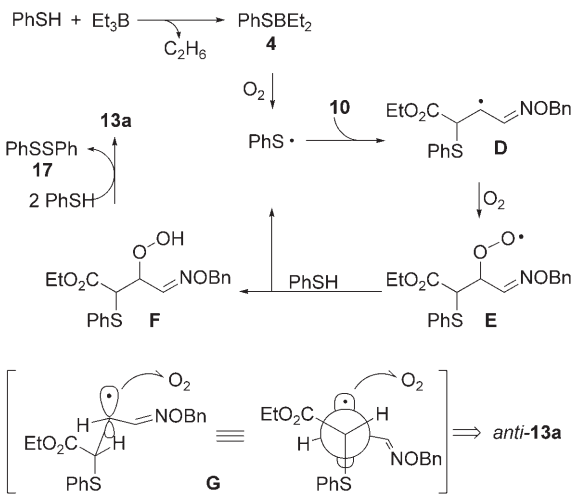

***Scheme 3.*** The hydroxysulfenylation reactions of oxime ether **10** and hydrazone **11**.

oxime ether **10**, as it has excellent reactivity towards the nucleophilic ethyl radical generated from triethylborane.[9] In other words, we expected that the direct comparison of the thiyl radical addition with the ethyl radical addition would be informative with respect to the reaction mechanism. As expected, introduction of the oxime ether group promoted the hydroxysulfenylation, whereas the reaction of aldehyde **9** gave the simple Michael adduct **12** (Table 1, entries 1 and 2).[16] The ester group of **10** did not affect the regioselectivity. Thiyl radical addition took place exclusively at the β position to give product **13a** (Table 1, entry 3). The use of more than 3.0 equivalents of thiophenol was necessary to achieve good conversions (Table 1, entries 3–7).[17] This improved conversion occurs because the thiophenol acts as an agent to reduce the hydroperoxide **F** to give the product **13a** and diphenyl disulfide **17** (Scheme 4).[18,19] The amount of triethylborane used has an impact on the chemical efficiency and reaction products.[20] Decreasing the amount of triethylborane to 0.1 equivalent resulted in a lower yield (Table 1, entry 8). The formation of the ethyl radical addition product **14** was

***Table 1:*** Reaction of **9**–**11** with selected thiols.

| Entry | Substrate | Thiol (equiv) | Borane (equiv) | Product (yield [%])[a] |
|---|---|---|---|---|
| 1[b] | **9** | PhSH (3.5) | none | **12** (92) |
| 2[b] | **9** | PhSH (3.5) | $Et_3B$ (0.5) | **12** (84) |
| 3[c] | **10** | PhSH (1) | $Et_3B$ (0.5) | **13a** (31)[e,f] |
| 4[c] | **10** | PhSH (2) | $Et_3B$ (0.5) | **13a** (63)[e] |
| 5[c] | **10** | PhSH (3) | $Et_3B$ (0.5) | **13a** (72)[e] |
| 6[c] | **10** | PhSH (3.5) | $Et_3B$ (0.5) | **13a** (75)[e] |
| 7[c] | **10** | PhSH (4) | $Et_3B$ (0.5) | **13a** (71)[e,g] |
| 8[c] | **10** | PhSH (3.5) | $Et_3B$ (0.1) | **13a** (42)[e] |
| 9[d] | **10** | PhSH (3.5) | $Et_3B$ (10) | **14** (63) |
| 10[c] | **10** | PhSH (3) | $PhSBEt_2$ (0.5) | **13a** (73)[e] |
| 11[c] | **10** | PhSSPh (2) | $Et_3B$ (0.5) | n.d.[h] |
| 12[c] | **10** | PhSSPh (2) | $Et_3B$ (5) | n.d.[i] |
| 13[c] | **11** | PhSH (3.5) | $Et_3B$ (0.5) | **15** (71)[j] |
| 14[c] | **10** | *p*-Cl-$C_6H_4SH$ (3.5) | $Et_3B$ (0.5) | **13b** (78)[e] |
| 15[c] | **10** | *p*-HO-$C_6H_4SH$ (3.5) | $Et_3B$ (0.5) | **13c** (64)[e] |
| 16[c] | **10** | $CH_3(CH_2)_{11}SH$ (3.5) | $Et_3B$ (0.5) | **13d** (44)[e] |

[a] Yield of the isolated product. [b] Reaction time was 0.5 h. [c] Reaction time was 15 h. [d] Reaction time was 3 h. [e] **13a–d** were obtained as an *E*/*Z* mixture with *anti*/*syn* = 7:1–6:1. [f] **10** was recovered in 30% yield. [g] The Michael addition product was obtained in 3% yield. [h] **10** was recovered in 59% yield. [i] Ethyl radical addition was observed. [j] **15** was obtained as an *E*/*Z* mixture with *anti*/*syn* = 4:1. n.d. = not detected.

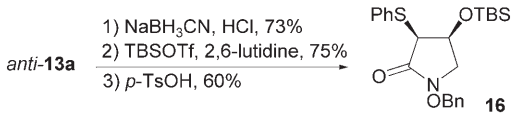



***Scheme 4.*** Proposed hydroxysulfenylation reaction pathway.

observed when a large amount of triethylborane was used (Table 1, entry 9). In these reactions, triethylborane immediately reacted with thiophenol to give **4**,[12,13] which would act as a radical initiator for the reaction with triplet oxygen. The use of preformed **4**, instead of triethylborane, led to **13a** in good yield (Table 1, entry 10). Hydroxysulfenylation did not proceed when diphenyl disulfide (**17**) was used as the thiyl radical source (Table 1, entries 11 and 12); thus, regeneration of the thiyl radical from **17** was excluded in the reaction mechanism. The reaction of hydrazone **11** was also efficient, albeit with slightly lower diastereoselectivity (Table 1, entry 13). Other thiols such as aryl mercaptans (including one with a free hydroxy group) and an aliphatic thiol worked well (Table 1, entries 14–16).

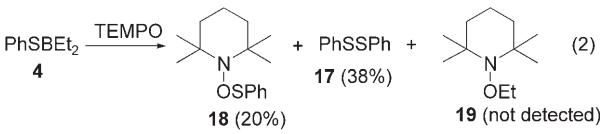
  

The relative configurations of *anti*-**13a** and *syn*-**13a** were elucidated by NOESY experiments of γ-lactam **16**,[21] which was prepared from the major isomer of β-hydroxysulfide **13a** by reduction of the oxime ether group, TBS protection of the hydroxy group, and cyclization by treatment with *p*-TsOH (Scheme 5). The preferential formation of the *anti* isomer can be explained by invoking conformer **G**, in which the carbon–sulfur bond is eclipsed by the p orbital of the radical center, because electronic and steric effects (Scheme 4).[14]



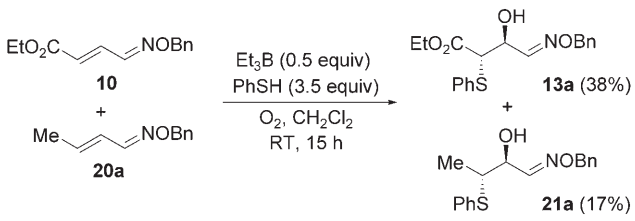

***Scheme 5.*** Preparation of γ-lactam **16**. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, Ts = toluenesulfonyl.

The ability of **4** to act as a radical initiator is assumed to be lower than triethylborane. To explore the validity of this mechanistic hypothesis, an experiment using TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) was performed [Eq. (2)]. The products **18** and **17** were obtained without the formation of **19**. This observation indicates that **4** undergoes bimolecular homolytic cleavage of the B–S bond by reaction with triplet oxygen at the boron atom to give a thiyl radical.



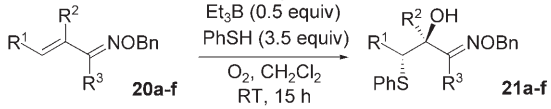

A competition experiment was conducted to study the influence of the ester group of **10** on reactivity towards the thiyl radical (Scheme 6). Although oxime ether **10** exhibited slightly higher reactivity in the formation of **13a**, β-hydroxysulfide **21a** was also formed from the crotonaldehyde derivative **20a**. This result suggests that our hydroxysulfenylation can be applied to a wide range of α,β-unsaturated oxime ethers.

On the basis of these results, we next investigated the hydroxysulfenylation reaction of acyclic oxime ethers **20a–f** (Table 2). Good yields were obtained for the reactions of **20b**, having a phenyl group at the β position, and **20c**, having a *tert*-butyl ester group (Table 2, entries 2 and 3). Oxidative interception with molecular oxygen was efficient in the reaction of the α methylated oxime ether **20d** to give **21d**, which is fully substituted at the $sp^3$ carbon centers (Table 2, entry 4). Excellent *anti*/*syn* selectivity was observed in the reaction of ketoxime ether **20e** (Table 2, entry 5). Thioacetal **21f** could be prepared from **20f**, which has a phenylthio substituent (Table 2, entry 6).




***Scheme 6.*** Competition experiment.

***Table 2:*** Reaction of **20a–f** with thiophenol.




| Entry | Substrate | $R^1$ | $R^2$ | $R^3$ | Product | Yield [%][a] (*anti*/*syn*) |
|---|---|---|---|---|---|---|
| 1[b] | **20a** | Me | H | H | **21a** | 61 (5:6) |
| 2[b] | **20b** | Ph | H | H | **21b** | 69 (3:1) |
| 3[b] | **20c** | $CO_2t$Bu | H | H | **21c** | 70 (10:1) |
| 4[b] | **20d** | $CO_2$Et | Me | H | **21d** | 72 (3:2) |
| 5[b] | **20e** | Me | H | Me | **21e** | 63 (20:1) |
| 6[c] | **20f** | SPh | H | H | **21f** | 72 |

[a] Yield of the isolated product. [b] Reaction was carried out with $Et_3B$ (0.5 equiv) and PhSH (3.5 equiv) under air. [c] Reaction was carried out with $Et_3B$ (1 equiv) and PhSH (4 equiv) under $O_2$.

The hydroxysulfenylation method was extended to a series of complex substrates **22–27** (Table 3). Good diastereoselectivity was obtained using **22**, which bears Oppolzer's camphorsultam (Table 3, entry 1).[22] Hydroxysulfenylation of the cyclopentenone derivative **23** also worked well (Table 3, entry 2). However, exomethylene **24** had limited success and predominantly gave Michael adduct **30b**, thus resulting in a decreased yield of β-hydroxysulfide **30a** (Table 3, entry 3). The reaction conditions were modified for the hydroxysulfenylation of bulky oxime ethers **25–27**.[21] The reaction of **25** gave the β-hydroxysulfide **31** with low *trans*/*cis* selectivity (Table 3, entry 4). In contrast, the reaction of **26** gave β-hydroxysulfide **32** as a single diastereomer (Table 3, entry 5). The reaction of **27** also proceeded with high stereoselectivity,[23] and β-hydroxysulfides **33** and **34** were isolated under modified reaction conditions (Table 3, entry 6). The selective formation of **34** was achieved by using 4.5 equivalents of thiophenol (Table 3, entry 7).

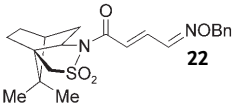
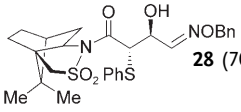
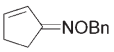
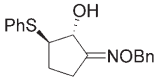
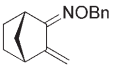
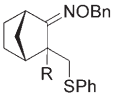
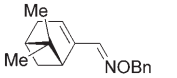
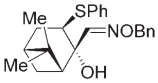
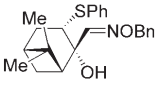
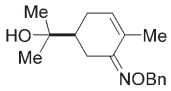
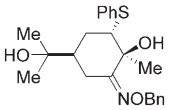
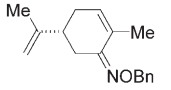
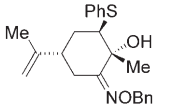
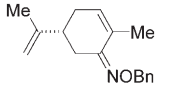
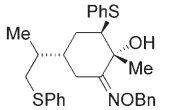
In conclusion, we have developed a highly regioselective hydroxysulfenylation reaction of α,β-unsaturated imines. The reaction is characterized by mild conditions, is straightforward, and allows for regio- and stereoselective construction of a carbon–sulfur bond and a carbon–oxygen bond, thus providing a highly efficient synthetic approach to β-hydroxysulfides.

## Experimental Section

General procedure for the hydroxysulfenylation reaction: Thiol (1.75 mmol) and $Et_3B$ (1.0 M in hexane, 0.25 mL, 0.25 mmol) were added to a solution of α,β-unsaturated (*E*)-oxime ether (0.5 mmol) in $CH_2Cl_2$ (6 mL) under an atmosphere of dry air at room temperature. After stirring the reaction mixture for 15 h, it was concentrated under reduced pressure. Purification of the residue by medium-pressure

***Table 3:*** Hydroxysulfenylation of oxime ethers **22–27**.

| Entry | Substrate | | Product (yield [%][a], ratio) |
|---|---|---|---|
| 1[b] |  | **22** |  **28** (70%, *anti*/*syn* = > 10:1, > 10:1 d.r.) |
| 2[b] |  | **23** |  **29** (78%, *trans*/*cis* = 10:1) |
| 3[b] |  | **24** |  **30a**: R = OH (15%, > 20:1 d.r.)<br>**30b**: R = H (70%) |
| 4[c] |  | **25** |  **31** (51%, *trans*/*cis* = 3:2)<br>  |
| 5[c] |  | **26** |  **32** (58%, *trans*/*cis* = > 20:1) |
| 6[c] |  | **27** |  **33** (34%, *trans*/*cis* = > 20:1) |
| 7[d] |  | **27** |  **34** (31%, *trans*/*cis* = > 20:1)<br>**34** (50%, *trans*/*cis* = > 20:1) |

[a] Yield of the isolated product. [b] Reaction was carried out with $Et_3B$ (0.5 equiv) and PhSH (3.5 equiv) under air. [c] Reaction was carried out with $Et_3B$ (1 equiv) and PhSH (4 equiv) under $O_2$. [d] Reaction was carried out with $Et_3B$ (1 equiv) and PhSH (4.5 equiv) under $O_2$.

column chromatography (*n*-hexane/AcOEt = 10:1–4:1) afforded the corresponding β-hydroxysulfide.

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**Keywords:** hydroxysulfenylation · oxime ethers · oxygen · radicals · thiols

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