Synthesis of a Stable Sulfenic Acid by Oxidation of a Sterically Hindered Thiol (Thiophenetriptycene-8-thiol)[1] and Its Characterization

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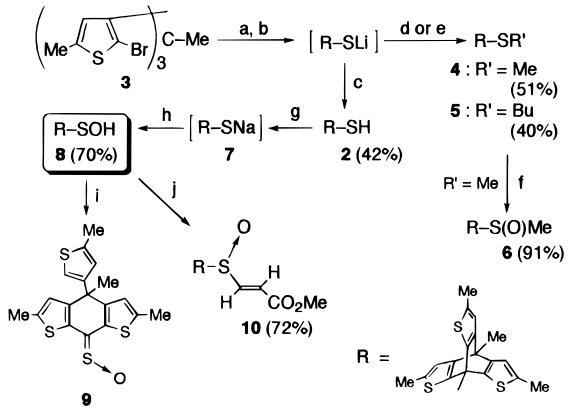
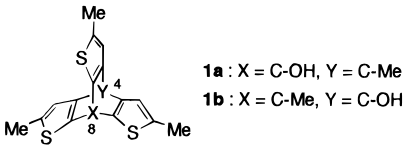
We report here the first example of the preparation of an isolable sulfenic acid by peroxy acid oxidation of a thiolate, where the sulfur atom is bound to the sp^3 carbon atom.[2] The chemistry of sulfenic acids has been investigated in details.[3,4] Although most sulfenic acids are extremely reactive intermediates, some sulfenic acids stabilized by intramolecular interactions and steric protection or electronic effects of substituents have been isolated.[5−16] The isolable sulfenic acids were, in most cases, synthesized by solvolysis of sulfenate esters[5,6a] or β-elimination of sulfoxides.[9−11,12a,15] The most straightforward method to synthesize sulfenic acids, however, would be direct oxidation of thiols. While oxidation of cysteinyl residues in a protein with mild oxidants gives the corresponding sulfenic acid,[17] that of simple thiols with MCPBA (*meta*-chloroperoxybenzoic acid),[18] an oxaziridine derivative,[3b] or dimethyldioxirane[19] has been reported to furnish sulfenic acids being only recognized as highly reactive intermediates. Recently, we have reported the synthesis of a thiophene analog (thiophenetriptycene, **1**) of triptycene,[20,21] in which the environment around the bridgehead in the same side of three thiophene sulfur atoms (the 8-position) is more hindered than that around the other one (the 4-position);[20b,21b] hydrogen bonding of the hydroxy group of thiophenetriptycen-8-ol (**1a**) is hampered to a larger extent than that of the regioisomer **1b**.[20b] Therefore, we investigated to utilize the 8-thiophenetriptycyl group as a steric protection group for the sulfenic acid resistant to further oxidation.

Scheme 1[a]



[a] Reaction conditions: (a) *t*-BuLi, THF, −78 °C; (b) S=C(OEt)$_2$, −78 °C to reflux; (c) aqueous NH_4Cl; (d) MeI; (e) BuBr; (f) MCPBA, CH_2Cl_2, 0 °C; (g) NaH, THF, room temperature; (h) MCPBA, 0 °C; (i) $h\nu$, Δ, or H^+; (j) HC≡CCO$_2$Me, CH_2Cl_2, room temperature.



Thiophenetriptycene-8-thiol (**2**) was prepared as follows (Scheme 1). 1,1,1-Tris(2-bromo-5-methyl-3-thienyl)ethane (**3**)[20] was lithiated with *t*-BuLi (6 mol equiv) in THF at −78 °C, and the resulting trilithium salt was treated with S=C(OEt)$_2$[22] at −78 °C. The reaction mixture was stirred at this temperature for 15 min and then rapidly warmed to reflux. Quenching the reaction with aqueous ammonium chloride gave the thiol **2** in 42% yield. When the reaction was quenched by addition of MeI or BuBr, the corresponding sulfides **4** and **5** were obtained in 51 or 40% yield, respectively.[23]

We first examined oxidation of the thiol **2** with MCPBA. Surprisingly, the oxidation in CH_2Cl_2 at 0 °C or at the refluxing temperature resulted in quantitative or 85% recovery of the starting compound, respectively. Incidentally, sulfide **4** was readily oxidized with MCPBA in CH_2Cl_2 at 0 °C to give the sulfoxide **6** in 91% yield. This contrast would be ascribed to the intrinsically lower nucleophilicity of the thiol sulfur in **2** than that of the sulfenyl sulfur in **4** in addition to the large steric hindrance of the 8-thiophenetriptycyl group. Therefore, the thiol

(1) We call 2,4,5′,6-tetramethyl-4,8-dihydro-4,8[3′,2′]thiophenobenzo-[1,2-*b*:5,4-*b*′]dithiophene "thiophenetriptycene" for convenience.

(2) Recently, the preparation of an arenesulfenic acid by oxidation of the corresponding arenethiol was reported: Goto, K.; Michel, H.; Okazaki, R. In *Abstracts II of the 70th Spring Annual Meeting of the Chemical Society of Japan*; The Chemical Society of Japan: Tokyo, 1996; p 1245 (3H5 34).

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(23) All new compounds gave satisfactory analytical data. Thiol **2**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.14 (s, 3H, bridgehead-Me), 2.31 (s, 9H, arom-Me), 2.94 (s, 1H, S-H), 6.63 (q-like, J = 0.8 Hz, 3H, arom-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.8 (CH_3), 15.3 (CH_3), 50.0 (C), 51.5 (C), 120.2 (CH), 134.0 (C), 153.2 (C), 156.8 (C); MS *m*/*z* 360 (M^+, 100), 345 (13), 301 (89); IR (KBr) 2544 (SH) cm^{-1}.

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2 was converted to the corresponding thiolate to increase the nucleophilicity. Thus, thiol **2** was treated with a 1.5 molar amount of NaH in THF at room temperature and the resulting sodium salt **7** was oxidized with a 1.3 molar amount of MCPBA to give the desired sulfenic acid **8** in 70% yield. Under these conditions, neither the corresponding disulfide nor thiosulfinate was formed.[24]

The structure of **8** was elucidated by its spectroscopic data[25] and X-ray single-crystal structure analysis.[26] The ^{1}H NMR measurements of sulfenic acid **8** were made on $CDCl_3$ solutions at concentration ranged from 6.6×10^{-3} to 6.6×10^{-2} mol dm^{-3}. In these measurements, although concentration effects on the chemical shift of the SOH proton were negligible, the half width of the peak was influenced by the initial concentration of **8**, the elapse time, and the existence of contaminating water. Thus, the SOH hydrogen resonated at δ 3.79 with the half width of 2 Hz at the concentration of 6.6×10^{-3} mol dm^{-3} and the hydrogen was readily exchangeable with deuterium by shaking with D_2O.[27] When the sample was again measured after 2 days, the peak was observed at δ 3.78 with the half width of 19 Hz. On the other hand, in a 10-fold more concentrated solution (6.6×10^{-2} mol dm^{-3}), it appeared at δ 3.83 with the half width of 13 Hz and peak broadening was again observed depending on the elapse of time (32 Hz after 2 days). Interestingly, addition of a few grains of Zeolite 3-A (Wako Pure Chemical Industries, Ltd.) to each solution provided high-field shift and narrowing of the peak; the peak at the concentration of 6.6×10^{-3} mol dm^{-3} shifted to δ 3.68 with the half width of 5.7 Hz (17 h after the addition of Zeolite) and that at the concentration of 6.6×10^{-2} mol dm^{-3} δ 3.69 with the half width of 7.8 Hz (after 28 h). These observations can be explained in terms of hydrogen bonding among sulfenic acid **8** and a trace amount of water in $CDCl_3$ which comes to equilibrium fairly slowly.

In the ^{1}H and ^{13}C NMR spectra of **8**, three thiophene parts are equivalent to each other, indicating the SOH group in **8** freely rotates on the NMR time scale. In the infrared spectrum, the absorption due to the OH stretching appears as a broad band centered at 3456 cm^{-1}. Absorptions due to another possible form of sulfenic acids, RS(═O)H,[4a,c,11] were not observed in the expected regions.

An ORTEP drawing of the sulfenic acid **8**[26] is depicted in Figure 1 with selected bond lengths and angles. The C(1)−S(1) and S(1)−O(1) bond lengths are 1.833(9) and 1.622(9) Å, respectively, and the bond angle of C(1)−S(1)−O(1) is 102.3(5)°. These values are comparable to those of methanesulfenic acid (microwave),[4b] ((2-phenyl-4-acetylphenoxy-2,6-dimethylphenyl)imino)methanesulfenic acid (X-ray),[8] and 4,6-dimethyl-1,3,5-triazine-2-sulfenic acid (X-ray)[14] except for the corresponding C(sp^2)−S bond lengths. The results of the X-ray analysis as well as the IR spectrum indicate undoubtedly that sulfenic acid **8** exists as RS−OH form and not the RS(═O)H one.[4a,c,11]

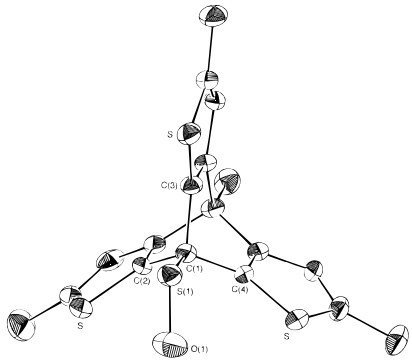

Figure 1. ORTEP drawing of sulfenic acid **8** with 20% of ellipsoid (hydrogen atoms are omitted). Selected bond lengths (Å) and angles (deg): S(1)−O(1), 1.622(9); S(1)−C(1), 1.833(9); C(1)−C(2), 1.520(11); C(1)−C(3), 1.553(11); C(1)−C(4), 1.526(10); O(1)−S(1)−C(1), 102.3(5); S(1)−C(1)−C(2), 120.8(6); S(1)−C(1)−C(3), 108.4(5); S(1)−C(1)−C(4), 116.6(6).

Sulfenic acid **8** is a pale yellow, crystalline compound. The acid is stable for a long time in the dark but is light-sensitive and isomerizes gradually to the sulfine **9** in solution or even in the solid state when exposured to light. The isomerization also occurred by heating a solution of **8** or stirring it in the presence of an acid. Sulfenic acid **8** underwent a typical reaction as a sulfenic acid to give sulfoxide **10** (72%) by treatment with methyl propiolate in dichloromethane at room temperature.[4a,e]

In conclusion, we have succeeded in the synthesis of thiophenetriptycene-8-sulfenic acid (**8**) from the corresponding thiol **2** by MCPBA oxidation. This study shows a possibility that isolable sulfenic acids can be prepared by oxidation, even by peroxy acid oxidation, of the corresponding thiol carrying adequately sterically demanding substituents.

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Supporting Information Available: Characterization data (^{1}H and ^{13}C NMR, IR, and MS) for **2**, **4**−**6**, and **8**−**10**; structure determination summaries and tables of X-ray structure data for **8** (13 pages). See any current masthead page for ordering and Internet access instructions.

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(25) Sulfenic acid **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H, bridgehead-Me), 2.33 (s, 9H, arom-Me), 3.79 (s, 1H, SOH), 6.65 (s, 3H, arom-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.8 (CH_3), 15.3 (CH_3), 50.2 (2C), 119.6 (CH), 135.0 (C), 148.5 (C), 158.2 (C); MS *m*/*z* 376 (M^+, 25), 360 (100), 345 (68), 3219 (50), 301 (27); IR (KBr) 3456 (OH), 766 (SO)[4a] cm^{-1}.

(26) Crystal data for **8**: trigonal, $P\bar{3}$, $a = 20.340(3)$ Å, $b = 20.340(3)$ Å, $c = 10.028(2)$ Å, $V = 3593$ Å^3, $Z = 8$, $R = 0.0709$, $R_w = 0.0861$, GOF = 4.61. The least-squares refinement was done on one whole molecule and a third part of the molecule of **8**. In Figure 1, only the whole molecule refined is shown.