Base-Catalyzed Rearrangement of Some 1,3-Oxathiolane Sulfoxides: Mechanistic Viewpoint of the Sigmatropic and Elimination Reactions

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Received April 14, 2004

Rearrangements of 1,3-oxathiolane sulfoxides 8 and 9 in the presence of base are described from a mechanistic viewpoint of sigmatropic and elimination reactions. In the presence of triethylamine the (Z)-sulfoxide 8 gave the corresponding thioisulfinate 10 by way of dimerization of the sulfenic acid intermediate 2 at room temperature while the (E)-sulfoxide 9 was recovered even after refluxing in ethyl acetate by the reversal of the [2,3]-sigmatropic rearrangement of the sulfenic acid 4. Triethylamine promoted the developing charge separation in the transition state of the sigmatropic rearrangement of the (Z)-sulfoxide 8 to facilitate the ring opening to the sulfenic acid 2. The reason for more facile ring opening of the (Z)-sulfoxide 8 in comparison with the corresponding (E)-sulfoxide 9 is attributable to the differences in the reactivity of the hydrogen adjacent to the carbonyl group. Triethylamine was not strong base to deprotonate the carbonyl-activated methylene hydrogen of the (E)-sulfoxide 9 but enough to catalyze the sigmatropic process of the sulfoxides. The sulfenic acid 2 dimerized to the thioisulfinate 10 while the sulfenic acid 4 proceeded the sigmatropic ring closure. In the presence of strong base such as potassium hydroxide, the elimination reaction was predominant over the sigmatropic rearrangement. In this reaction condition, both sulfoxides 8a and 9a gave a mixture of the disulfide 12, the isomeric disulfide 14, and the sulfenic acid 13. Under the strong alkaline condition an elimination of activated hydrogen from the carbon adjacent to the carbonyl group to furnish the sulfenic acid 2a and the isomeric sulfenic acid 18. The formation of the transient intermediate in the reaction was proven by isolation of the isomeric disulfide 14. The reactive entity was regarded as the sulfenic acid rather than sulfenate anion under these reaction conditions.

Key Words: Sigmatropic rearrangement, Sulfoxide, Sulfenic acid, Thioisulfinate, Sulfinic acid

Introduction

In our previous paper,1 we reported ring expansion of 1,3-oxathiolane sulfoxide 1 to dihydro-1,4-oxathiin 3 or 5 via sulfenic acid 2 or 4, respectively under the acidic or neutral conditions. Under neutral condition, the ring opening reaction proceeded by a [2,3]-sigmatropic process depending on the stereochemistry of the sulfoxide. However, in the presence of acid catalyst the sulfoxide 1 gave 3 exclusively through the sulfenic acid 2. As an extension of these studies on the sigmatropic rearrangement of these sulfoxides and on the reactivity of the sulfenic acids, we now report base catalyzed rearrangement of the 1,3-oxathiolane sulfoxide 1. An important feature of the 1,3-oxathiolane sulfoxide 1 is the presence of both carbonyl-activated methylene and unactivated methyl hydrogens β to the sulfoxide and the S-C bond being ruptured to give the corresponding sulfenic acids 2, and 4. It is interesting to investigate whether the ring opening reaction of 1 takes place or not in the presence of base catalyst and it is also interesting to find out that the reactivity of the feasible intermediates of sulfenic acids (e.g. 2, 4) under these reaction conditions.

Results and Discussion

The starting 1,3-oxathiolane sulfoxides were prepared by the previously reported method (Scheme 1).2 Hemithioketalization of β-keto acid derivatives 6 with 2-mercaptoethanol gave 1,3-oxathiolanes 7. Oxidation of 7 using 30% aqueous hydrogen peroxide in the presence of benzeneseleninic acid catalyst or m-chloroperbenzoic acid gave a mixture of the (Z)-sulfoxide 8 (2SR, 3RS) as a major and the (E)-sulfoxide
These (Z)-sulfoxide anilide 8a and (E)-sulfoxide anilide 9a were separated by either fractional crystallization or chromatography. The sulfoxide ester was synthesized from the oxidation of the corresponding sulfide 7b by the similar method. Actually, the (Z)-sulfoxide ester 8b could not be isolated due to its instability while the (E)-sulfoxide 9b was fairly stable at room temperature.

**Rearrangement of (Z)-8 and (E)-9 Sulfoxides in the Presence of Triethylamine.** In general, a sulfenic acid is unstable and dimerizes to a thiosulfinate with a loss of water due to the dual characteristics of a sulfenic acid as S-nucleophile/S-electrophile. As shown in Scheme 2 when the (Z)-sulfoxide anilide 8a was treated with triethylamine or potassium acetate in either ethyl acetate or methylene chloride at room temperature gave the thiosulfinate 10a (83% yields). In the absence of triethylamine, the (Z)-sulfoxide anilide 8a decomposed slowly to a complex mixture containing acetoacetanilide at room temperature, presumably by the action of trace amount of water and acid in the medium. In case of methyl ester, we could not isolate the (Z)-sulfoxide ester 8b due to its instability (vide supra). Instead, immediate treatment of the freshly prepared mixture of 8b and 9b with triethylamine at room temperature afforded a mixture of the corresponding thiosulfinate 10b and 9b. Apparently, the (Z)-sulfoxide ester 8b transformed smoothly to the thiosulfinate 10b while the (E)-sulfoxide ester 9b was fairly stable in this reaction condition. The probable reaction pathway leading to the thiosulfinate 10 from the (Z)-sulfoxides 8 begins with ring opening of the (Z)-sulfoxide 8 through the [2,3]-sigmatropic rearrangement involving carbonyl-activated methylene hydrogen followed by dimerization of the sulfenic acid intermediate 2. Possibly, the reason for more facile ring opening of the (Z)-sulfoxide ester 8b (below room temperature) in comparison with the corresponding 8a is attributable to the differences in the reactivity of the hydrogen adjacent to the carbonyl group. Presumably, triethylamine or potassium acetate promoted the developing charge separation in the transition-state (TS) to facilitate the ring opening of the (Z)-sulfoxide 8 to the sulfenic acid 2. Similar results were obtained by using of either inorganic salts such as sodium bicarbonate, sodium carbonate and potassium carbonate or weak organic base such as pyridine instead of triethylamine.

In contrast, the (E)-sulfoxide anilide 9a and ester 9b were fairly stable at room temperature under the same condition and recovered completely even after heating at reflux in ethyl acetate or benzene in the presence of triethylamine.

The deuterium incorporation reaction of the (E)-sulfoxide 9 suggests that this sulfoxide is converted to the sulfenic acid 4 by the ring opening at this temperature but the sulfenic acid 4 cyclized back to the (E)-sulfoxide 9 without formation of the corresponding thiosulfinate 11. Probably, the higher pi-electron density of the isolated double bond in the sulfenic acid 4, in comparison with the carbonyl deactivated double bond in the sulfenic acid 2, facilitates the [2,3]-sigmatropic ring closure to the (E)-sulfoxide 9. It seems likely that triethylamine was not strong base to deprotonate the carbonyl-activated methylene hydrogen of the (E)-sulfoxide 9 but enough to catalyze the sigmatropic process of the sulfoxides.

**Rearrangement in the Presence of Potassium Hydroxide.** Either the (Z)-sulfoxide 8a or the (E)-sulfoxide 9a was subjected to an aqueous solution of potassium hydroxide in
dioxane to afford a 3:2 mixture of a disulfide 12 and sulfinic acid 13 in addition to a small amount (less than 10%) of isomeric disulfide 14 (Scheme 3).

Probably, in the presence of potassium hydroxide the elimination reactions were predominant over the sigmatropic rearrangement of both sulfoxides. Thus, hydroxide ion attacked the carbonyl-activated methylene hydrogen initially regardless of the stereochemistry of the sulfoxides. The elimination reactions may proceed via TS involving the anti arrangement between departing proton (carbonyl-activated methylene hydrogen) and leaving of C-S bond. As shown in Scheme 4, two TS are possible for each sulfoxide. For the (Z)-sulfoxide 8a, conformation 15 is more preferable than 17 due to the unfavorable steric repulsions between the bulky carboxanilide group and the oxathiolane ring. Similarly, 16 is more favorable than 19 in case of the (E)-sulfoxide 9a. The predominant conformations 15 and 16 result the sulfenic acid 2a, and the less favorable conformations 17 and 19 give the isomeric sulfenic acid 18. Apparently, the disulfide 12 and sulfinic acid 13 were derived from the sulfenic acid 2a (vide infra) from a viewpoint of configuration of double bond of these molecules and the isolation of a minor product, isomeric disulfide 14 was clear evidence for generation of the isomeric sulfenic acid 18 from the reactions.

The reaction mechanism can be explained briefly as follows. Both sulfoxides can be initially transformed into the sulfenic acid 2a as a major and the isomeric sulfenic acid 18, major and minor respectively in the presence of potassium hydroxide in aqueous dioxane. These sulfenic acids would initially dimerize by themselves or react with each other with loss of water, or sulfenic acid-thiolsulfinate exchange to give the four different thiol sulfurates as transient intermediates in this reaction condition, which were easily hydrolyzed to give the corresponding disulfides and sulfinic acids. Actually, we isolated the disulfide 12, the sulfenic acid 13, and the isomeric disulfide 14 from the reaction of both sulfoxides as depicted in Scheme 3. Undoubtedly, 12 and 13 are derived from the sulfenic acid 2a, and 14 is formed by condensation reaction of 2a and isomeric sulfenic acid 18 from a viewpoint of configuration of double bond of the products. However, neither likely disulfide nor the sulfinic acid (not shown) derived from dimerization of 18 could be found, probably due to the relatively unfavorable formation of 18 from the reaction. The disulfide 12 and the isomeric disulfide 14 were separated by preparative TLC.

The disulfide 12 had an identical 1H NMR spectrum and mp with those obtained previously and the structure of new...
isomeric disulfide 14 was confirmed by 1H and 13C NMR, IR, MS spectra, elemental analysis data, and finally by the X-ray crystallographic analysis (Figure 1). Comparing their 1H NMR spectra, four triplets at 2.93, 3.07, 3.94, 4.39 ppm for methylene protons and two singlets at 4.91, 5.13 ppm for vinyl protons were shown for 14 while two triplets at δ 3.04, 4.07 ppm for methylene protons and one singlet at δ 5.12 ppm for vinyl proton for 12 due to the symmetry of the compound.

The sulfenic acid 13 was obtained as a white amorphous solid by the acidification of the aqueous layer of the reaction mixture. Although its 1H NMR and IR spectra agreed with the structure, it was too unstable to purify at room temperature. Therefore, its structure was confirmed by its 1H and 13C NMR, IR, MS spectra, elemental analysis data, and finally by the X-ray crystallographic analysis (Figure 1).

Conclusion

Sigmatropic rearrangement of the 1,3-oxathiolane sulfoxide was catalyzed by weak base such as triethylamine or potassium acetate, presumably by the promotion of developing charge separation in the transition-state to facilitate the ring opening of the sulfoxide to the corresponding sulfenic acid. The sulfenic acid either dimerize to the corresponding thiosulfinate or proceed the sigmatropic ring closure depending on the electronic character of the internal double bond in the sulfenic acid. Triethylamine was not strong base to deprotonate the carbonyl-activated methylene hydrogen of the sulfoxide but enough to catalyze the sigmatropic process of the sulfoxides. In the presence of strong base such as potassium hydroxide the elimination was predominant over the sigmatropic process to afford the sulfenic acid as a major and the less favorable conformational isomeric sulfenic acid. The sulfenic acid was regarded as a reactive entity under basic as well as neutral or acidic conditions, and converted to dimerize with loss of water into the corresponding thiosulfinate. While the thiosulfinates were fairly stable in the presence of triethylamine, it easily hydrolyzed in the presence of potassium hydroxide to give the corresponding disulfide and the sulfenic acid.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. All 1H and 13C NMR spectra were recorded on a Varian Gemini 300 NMR (300 MHz for 1H, 78.5 MHz for 13C) or Bruker AM-200 (200 MHz for 1H, 50.3 MHz for 13C) spectrometer. Chemical shift (δ) are given in ppm and the coupling constants (J) in Hz. IR spectra were obtained on a Perkin-Elmer 16F-PC FT-IR and are reported in cm⁻¹. MS spectra were recorded on a Hewlett Packard 5890 series GC/MSD. HRMS were obtained on a Finnigan MAT95SS. Elemental analysis was performed using a Fisons EA1108 analyzer. All chromatographic isolation was accomplished on silica gel GF254 (230-400 mesh).

Synthesis of thiosulfinate 10a by treatment of (Z)-sulfoxy anilide 8a with potassium acetate. To a stirred solution of (Z)-sulfoxy 8a (5.07 g, 0.02 mol) in ethyl acetate (300 mL) was added potassium acetate (0.20 g) and allowed to stir at room temperature for 9 days. The white precipitate was filtered to give thiosulfinate 10a (4.04 g, 83%). This product had identical melting point, 1H NMR and IR spectra with those of the compound obtained from the preceding experiment.1

Synthesis of thiosulfinate 10a by treatment of (Z)-sulfoxy anilide 8a with triethylamine. To a stirred solution of (Z)-sulfoxide 8a (12.65 g, 0.05 mol) in ethyl acetate (600 mL) was added triethylamine (6.97 mL) and allowed to stir at room temperature for 3 days. The white precipitate was filtered to afford thiosulfinate 10a (9.07 g, 74%). This product had identical 1H NMR and IR spectra with those of the compound obtained from the preceding experiment.

Synthesis of thiosulfinate 10b by treatment of a mixture of (Z)-sulfoxy methyl ester 8b and (E)-sulfoxy methyl ester 9b (7:3) with triethylamine. A freshly

Figure 1. ORTEP plots of isomeric disulfide 14 with heteroatoms labeled.
prepared a mixture of (Z)-sulfoxide 8b and (E)-sulfoxide 9b (7 : 3) (1.20 g, 6.24 mmol) was dissolved in ethyl acetate (10 mL) and added triethylamine (1.74 mL). The reaction mixture was stirred at room temperature for 3 days. Evaporation of the solvent gave a colorless oily residue. The products were separated by preparative TLC using benzene/ethyl acetate (7 : 3) as an eluent. The first and the second bands were extracted with chloroform to give the (E) and sulfoxide 9b (Rf 0.2, 80 mg) as colorless oil respectively. These products had identical 1H NMR and IR spectra with those of the compound obtained from the preceding paper.1

10b: colorless oil: 1H NMR (300 MHz, CDCl3) 2.31 (s, 6H, 2CH3), 3.40-3.58 (m, 4H, CH2S), 3.68 (s, 6H, OCH3), 4.20-4.12 and 4.18-4.30 (m, 4H, OCH2), 5.03 and 5.08 (2s, 2H, 2 × vinyl CH); IR (NaCl) 1712 (C=O), 1054 (S–O – S) and 985 (C–O–C). The solvent was removed to give a light yellow oily residue, which was stirred at room temperature for 3 days. The solvent was evaporated to give a light yellow gummy residue. This residue was dissolved in methylene chloride (200 mL), washed twice with water, and dried over Na2SO4. The organic layer was evaporated to give a yellow foamy solid, as a mixture of disulfide 12, isomeric disulfide 14, and (Z)-sulfoxide 8a by TLC. These compounds were separated by preparative TLC using ethyl acetate and n-hexane (1 : 1) as eluent. The first band (Rf 0.7), the second band (Rf 0.3), and the third band (Rf 0.1) were respectively extracted with chloroform to give 12 (715 mg), 14 (124 mg), and 8a (290 mg). The water layer was combined and neutralized with 1 N hydrochloric acid (about 16 mL) under ice bath. The white precipitates were collected by filtration and dried at -20 °C to obtain sulfonic acid 13 (1.76 g, 35%).

The disulfide 12 had identical m.p. 1H NMR and IR spectra with those of the compound obtained from the preceding paper.1

Disulfide 12: mp 167-168 °C (crystallized from ethyl acetate/petroleum ether); 1H NMR (300 MHz, CDCl3) 2.40 (3H, 2 × CH3), 3.04 (t, 4H, J = 6.5, 2 × SCH2), 4.07 (t, 4H, J = 6.5, 2 × OCH2), 5.12 (s, 2H, vinyl CH), 7.07-7.55 (m, 10H, ArH), 7.21 (br s, 2H, NH); IR (KBr) 1662 (C=O), 1613 (C=C).

Sulfonic acid 13: mp 64-66 °C (crude product); 1H NMR (300 MHz, DMSO-d6) 2.20 (s, 3H, CH3), 2.62 (t, 1H, J = 6.8, SCH), 2.73 (t, 1H, J = 5.9, SCH), 3.63 (t, 1H, J = 6.8, OCH), 3.69 (t, 1H, J = 5.9, OCH), 4.29 (br s, 1H, SO2H), 7.30-7.58 (m, 5H, ArH), 10.1 (br s, 1H, NH); IR (KBr) 3328 (OH and NH), 1669 (C=O), 1603 (C=C), 1161 (C=O-C). Isomeric disulfide 14: mp 115-116 °C (crystallized from ethyl acetate/petroleum ether); 1H NMR (300 MHz, CDCl3) 2.12 and 2.35 (2s, 6H, 2 × CH3), 2.93 (t, J = 6.0, 2H, SCH), 3.07 (t, J = 5.5, 2H, SCH), 3.94 (t, J = 6.0, 2H, OCH), 4.39 (t, J = 5.5, 2H, OCH), 4.91 and 5.13 (2s, 2H, 2 × vinyl CH), 7.06-7.68 (m, 10H, ArH), 7.58 and 9.17 (2 × br s, 2H, 2 × NH); 13C NMR (50.3 MHz, CDCl3) 18.55, 18.91, 37.01, 37.98, 65.06, 65.57, 94.87, 104.38, 119.68, 120.12, 123.37, 123.85, 128.75, 128.86, 138.35, 139.04, 160.14, 164.18, 165.47, 168.92; IR (KBr) 1685 (C=O), 1646 (C=O); MS (Fast Atom Bombardment Method, Matrix, nitrobenzyl alcohol, ion multiplier voltage, 1.2KV) m/z (relative intensity) 473 (20, M++1), 236, 92, 135 (CH2OC2H5), 133, 105 (O), 76, 52, 44, 29, 21, 19, 17, 15, 13, 11, 9, 7, 5, 3.

Data of X-Ray analysis: The data was collected on an Enraf-Nonius CAD4 automated diffractometer equipped with a Mo X-Ray tube and a graphite monochromator. Triclinic space group PI with a = 9.248(2) Å, b = 11.485(3) Å, c = 13.707(3) Å, V = 1350.1(5) Å3, Z = 2, dcalc = 1.163 gcm−3, μ = 0.226 mm−1. A total of 2323 independent absorption-corrected reflections were collected. The structure was solved using SHELXS86 and SHELXL97 programs. The resulting structural parameters were refined to convergence of R1 = 0.0962 using full-matrix least-squares techniques and a structural model which incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms.

Preparation of (E)-sulfoxide anilide 9a with potassium hydroxide. Similar results were obtained from the treatment of the (E)-sulfoxide 9a with potassium hydroxide under same reaction condition described above. From the reaction of the (E)-sulfoxide 9a (1.01 g, 4 mmol), 12 (137 mg), 14 (26 mg), 9a (25 mg), and 13 (260 mg) were obtained. These compounds had identical m.p. 1H NMR and IR spectra with those of the compounds obtained from the above reaction.

Preparation of thiosulfone 20. To a stirred solution of the sulfinic acid 13 (288 mg, 1.07 mmol) in dioxane (200 mL) and water (9 mL) was added methyl iodide (6 mL) and allowed to stir at room temperature for 1 h. The solvent was evaporated to give an oily residue. This was dissolved in chloroform, washed with water twice, and dried (Na2SO4). The solvent was removed to give a light yellow oily residue, crystallized form chloroform/n-hexane to obtain 20 as white needles (29 mg, 10%), mp 164-166 °C (crystallized from chloroform/n-hexane); 1H NMR (200 MHz, CDCl3) 2.37 (s, 3H, CH3), 3.03 (s, 3H, SO2CH3), 3.40 (t, J = 5.4, 2H, SCH2), 4.23 (t, J = 5.4, 2H, OCH2), 5.11 (s, 1H, vinyl CH), 7.09-7.54 (m, 6H, ArH and NH); 13C NMR (50.3 MHz, CDCl3) 18.53, 42.89, 54.17, 61.59, 95.41, 120.03, 124.11, 129.02, 138.35, 164.76, 165.14, 168.62; IR (KBr) 3364 (NH), 1678 (C=O), 1620 (C=C), 1284 and 1129 (SO3); MS (70 eV) m/z (relative intensity) 283 (4.2, M+), 191 (29.9 (M−C6H5NH), 107 (37.5, CH3SO2CH2CH2), 83 (100, O=CCH=C(CH3)O); Analysis Calcd for C13H17N4S2O4: C, 61.0, H, 5.97, N, 5.93, Found, C 60.8, H, 5.92, N, 5.82.

Preparation of methyl sulfinate 21. To a suspended solution of the sulfinic acid 13 (1.35 g, 5 mmol) in ice-cooled chloroform (10 mL) was added excess amount of a solution of diazomethane dissolved in ether and allowed to
stir for 15 min. The solvents were evaporated to give a light yellow solid residue. Crystallization from benzene/petroleum ether gave 21 as colorless plates (1.15 g, 81%). mp 105-107°C (crystallized from benzene/petroleum ether); 1H NMR (300 MHz, CDCl3) 2.35 (3, 3H, CH3), 3.00-3.08 and 3.17-3.26 (m, 2H, CH2S), 3.84 (s, 3H, OCH3), 4.05-4.22 (m, 2H, OCH2), 5.09 (s, 1H, vinyl CH), 7.06-7.55 (m, 5H, ArH), 7.37 (br s, 1H, NH); IR (KBr) 3310 (NH), 1684 (C=O), 1619 (C=C), 1154 (C-O-C), 1103 (SO2); Analysis Calcd for C13H17NO4S: C, 55.1, H, 6.05, N, 4.94. Found, C, 55.2, H, 6.03, N, 4.94.

Preparation of thiolsulfonate 22. To a stirred solution of thiolsulfinate 10 (244 mg, 0.5 mmol) in acetone (20 mL) was added a solution of sodium periodate (128 mg, 0.5 mmol) in water (2 mL). The reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated to give a white solid. This was dissolved in chloroform, washed with water, and dried (Na2SO4). Evaporation of the solvent gave a white solid (90 mg). Crystallization from acetone/petroleum ether gave 22 as a white amorphous solid (75 mg, 30%). mp 147-149°C (crystallized from acetone/petroleum ether); 1H NMR (200 MHz, CDCl3 + DMSO-d6) 2.35 and 2.36 (2s, 6H, 2 × CH3), 3.52 (t, J = 6.05, 2H, SCH2), 3.90 (t, J = 6.11, 2H, SO2CH3), 4.12 (t, J = 6.05, 2H, OCH2), 4.20 (t, J = 6.11, 2H, OCH2), 5.33 and 5.40 (2s, 2H, 2 × vinyl CH), 6.98-7.61 (m, 10H, ArH), 8.95 and 9.05 (2 × br s, 2H, 2 × NH); IR (KBr) 3298 (NH), 1669 (C=O), 1319 and 1126 (SO2); MS (70 eV) m/z (relative intensity) 504.6 (M+, not observed), 269 (3.6, M+ - CHCH2OC(CH3) = CHCONHCH5, 253 (50.8, S' = CHCH2OC(CH3) = CHCONHCH5), 177 (22.9, CH3COCHCONHCH5), 93 (100, CH3NH+); Analysis Calcd for C24H28N2O6S2: C, 57.1, H, 5.59, N, 5.55. Found C, 57.1, H, 5.61, N, 5.67.

References and Notes

9. It was reported that hydrolysis of a thiolsulfinate in the presence of hydroxide ion affords a thiolsulfonate via -disulfoxide. Similarly, the hydrolysis of a thiolsulfinate 10a in the presence of hydroxide ion would afford the corresponding thiolsulfonate 22.