First Examples of Oxidizing Secondary Alcohols to Ketones in the Presence of the Disulfide Functional Group: Synthesis of Novel Diketone Disulfides

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The disulfide functionality is present in a number of organic compounds of interest in the fields of both chemistry and biology. Because the disulfide group is known to be highly susceptible to further oxidation by a wide range of agents, performing a chemoselective oxidation without further oxidizing the disulfide moiety poses a synthetic challenge. Reported herein are the first examples of such a chemoselective oxidation in which a series of novel secondary alcohol disulfides **2a**−**f** have been converted to the corresponding symmetrical diketones **3a**−**f** utilizing a modified Swern oxidation.

Introduction

Organic disulfides are a class of compounds of widespread occurrence in biological systems. The disulfide functional group (−SS−) exists not only in proteins but also in numerous natural products. Notable examples of natural disulfides of pharmacological interest include thiocoraline,[1a] BE-22179,[1b] triostin A,[1c] echinomycin,[1d] the thiarubrines,[1e,1f] and related 1,2-dithiin-type antibiotic pigments.[1g] In the synthetic transformations of organic disulfides, it may be desirable to perform an oxidation reaction on a particular functional group without disturbing the disulfide moiety. However, the realization of this type of chemoselective oxidation may present a challenge because organic disulfides are highly susceptible toward further oxidation. Indeed, it has been well documented that organic disulfides can be readily oxidized by a broad range of agents to produce thiosulfinates, thiosulfonates, sulfonic acids, and a variety of other products.[2a−j] We have recently investigated the feasibility of oxidizing secondary alcohols into the corresponding ketones in the presence of the disulfide functional group, and we wish to report our results herein.

Results and Discussion

During the course of our drug-discovery research, diketone disulfides **3a**−**f** (see Table 1) were desired as versatile synthetic intermediates. Our general approach to these compounds is outlined in Scheme 1. The first step was the preparation of dialdehyde disulfides (**1a**−**d**) from their monoaldehyde precursors. Disulfides **1a**−**c** were prepared by using the published procedures,[3a−c] and the new compound **1d** was obtained by treatment of diphenylacetaldehyde with S_2Cl_2 in CCl_4. The second step was the conversion of dialdehyde disulfides **1a**−**d** into diols **2a**−**f** via a Grignard reaction with methylmagnesium bromide, vinylmagnesium bromide, or phenylmagnesium chloride. It is noteworthy that Grignard reagents are known to cleave the S−S bond in organic disulfides to give the corresponding thioethers and thiols.[4] To minimize this side reaction and to maximize the yields of diol disulfides **2a**−**f**, we have taken the following measures: (1) nearly a stoichiometric quantity of the Grignard reagent was used and added dropwise to the stirred solution of the dialdehyde disulfide **1**; (2) RMgCl or RMgBr was the choice of reagents, because they consistently gave higher yields of **2** than did RMgI; (3) *tert*-butyl methyl ether was found to be a more appropriate reaction solvent relative to tetrahydrofuran in some cases in terms of the yield of the desired product (see the Supporting Information). Gratifyingly, moderate to good yields (61−89%) of diols **2a**−**f** were produced under those

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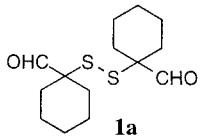
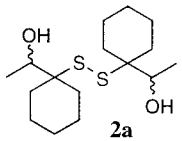
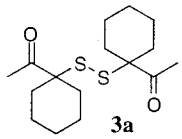
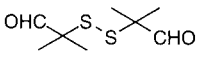
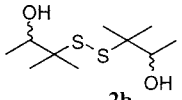
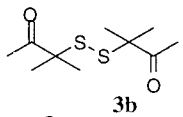
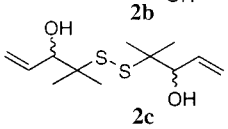
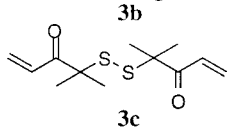
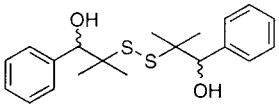
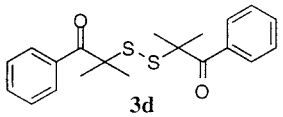
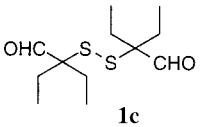
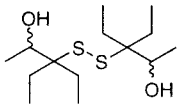
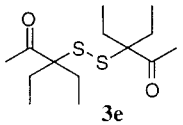
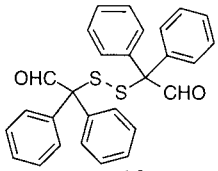
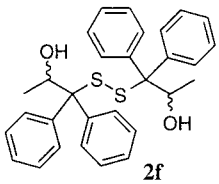
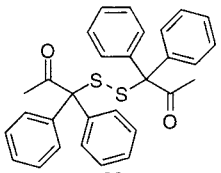
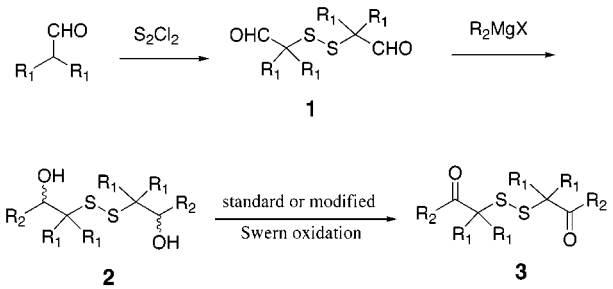
Table 1. Starting Material, Intermediates, and Products

Entry	Dialdehyde-disulfide	Diol-disulfide	Yield	Diketone-disulfide	Yield
1	 **1a**	 **2a**	88%	 **3a**	96%
2	 **1b**	 **2b**	61%	 **3b**	92%
3	**1b**	 **2c**	89%	 **3c**	98%
4	**1b**	 **2d**	82%	 **3d**	97%
5	 **1c**	 **2e**	63%	 **3e**	81%
6	 **1d**	 **2f**	68%	 **3f**	91%

Scheme 1[a]



[a] See Table 1 for the identities of R_1 and R_2.

carefully controlled conditions despite the reported vulnerability of the S−S bond to attack by Grignard reagents. Diols **2a**−**f** thus obtained existed as an inseparable mixture of two diastereomers. However, the formation of diastereomeric diols was inconsequential since the two diastereomers would be converted to the same diketone-disulfide after the ensuing oxidation step.

For the conversion of **2a**−**f** to **3a**−**f**, we needed a method that would be capable of oxidizing secondary alcohols to ketones while leaving the disulfide function intact. To the best of our knowledge, there have been no such literature examples reported to date. We felt that this lack of precedent would thus require a judicious choice of appropriate oxidant as well as reaction conditions. We first examined some mild transition metal oxidizing agents, such as pyridinium chlorochromate,[5a,b] pyridinium dichromate,[5a,b] and tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide,[5c,5d] using **2a** as the test substrate. However, treatment of **2a** with these oxidants under standard conditions[5] resulted in a complex mixture, which was not synthetically useful. Next, we focused on the use of activated dimethyl sulfoxide-based methods,[6] such as the Swern oxidation. Since it was known that DMSO was capable of oxidizing thiols to disulfides without overoxidation,[7] we anticipated that the disulfide function would tolerate activated DMSO.

In the first runs of Swern oxidation with substrate **2a**, we initially adopted the standard protocol,[8] which recommends that once the addition of triethylamine is complete, the reaction mixture is allowed to warm from −78 to 0 °C or room temperature, prior to quenching with water. Although this procedure led to complete conversion of the substrate and did furnish the desired product **3a** (ca. 60% yield), it also generated a significant amount

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of cyclohexyl methyl ketone. After some experimentation, we discovered that the yield of **3a** could be greatly enhanced if the reaction was quenched with water at low temperature. Thus, after addition of NEt_3, the reaction was maintained at −78 °C for 2 h to ensure complete consumption of the substrate, and then a mixture of water and THF was added dropwise while maintaining the temperature of the reaction below −60 °C. This simple yet important modification provided the desired product **3a** in excellent yield (96%). This modified procedure of Swern oxidation has also been utilized in the conversion of diols **2b**, **2c**, and **2e** into diketone disulfides **3b**, **3c**, and **3e** in 81−98% yields. On the other hand, the conventional Swern oxidation protocol was also found to be appropriate for the conversion of diols **2d** and **2f** to the corresponding diketones **3d** and **3f**.

In conclusion, diketone disulfides (**3a**−**f**) have been synthesized from dialdehyde disulfides (**1a**−**d**) through a carefully controlled Grignard reaction, followed by a Swern oxidation. This work has established the first examples of oxidizing secondary alcohols into the corresponding ketones without detriment to the disulfide functional group. This information should be useful in the synthetic transformations of organic disulfides, which constitute an important class of compounds in both chemistry and biology.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra, taken in $CDCl_3$, were recorded at 300 and 75 MHz, respectively. Low-resolution mass spectra were obtained using atmospheric pressure-turbo ion spray ionization. High-resolution mass spectra were obtained from the Auburn Mass Spectra Center, Auburn, AL. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Triethylamine was purified by distillation over CaH_2 prior to use. All other commercial reagents and anhydrous solvents were used as received. Dialdehyde-disulfides **1a**−**c** were synthesized according to the literature procedures.[3a−c]

2-[(2-Oxo-1,1-diphenylethyl)disulfanyl]-2,2-diphenylethanal (1d). A stirred solution of diphenylacetaldehyde (25.0 g, 127 mmol) and S_2Cl_2 (5.10 mL, 64 mmol) in CCl_4 (30 mL) was heated to 40 °C. After 5 min, the formation of HCl gas started. The reaction mixture was stirred at the same temperature for 2 h, and TLC indicated the complete conversion of the substrate. The solvent was evaporated; the residue was dissolved in EtOAc and washed with 1 M aqueous K_2CO_3 and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a solid. Recrystallization from CH_2Cl_2/hexanes (1:4) afforded the title compound as a white crystalline solid (23.9 g, 83%): mp 95−96 °C; ^1H NMR δ 9.20 (s, 2 H), 7.4−7.2 (m, 20 H); ^{13}C NMR δ 190.8, 136.1, 129.8, 128.7, 128.6, 72.8; LRMS (APTIS) *m*/*z* 472 $[(M + NH_4)^+]$. Anal. Calcd for $C_{28}H_{22}O_2S_2$: C, 73.98; H, 4.88; S, 14.11. Found: C, 73.77; H, 5.02; S, 14.18.

1-[[[(Hydroxyethyl)cyclohexyl]disulfanyl]cyclohexyl]-ethan-1-ol (2a). To a stirred solution of dialdehyde disulfide **1a** (12.5 g, 43.7 mmol) in THF (200 mL) at 0 °C under a nitrogen atmosphere was added methylmagnesium bromide (1.4 M in THF/toluene, 63 mL, 88 mmol) dropwise over a period of 30 min. After the addition, the mixture was stirred at 0 °C for an additional 15 min, quenched by 2 M aqueous HCl (80 mL), and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, concentrated on a rotary evaporator. The resulting oil was purified by flash chromatography (silica gel, 2:1 CH_2Cl_2/EtOAc) to afford the desired diol disulfide (a mixture of two diastereomers, 12.3 g, 88%) as a white foam: ^1H NMR δ 3.9−3.7 (m, 2 H), 2.18 (br, 2 H), 1.9−1.5 (m, 20 H), 1.3−1.2 (2 doublets, J = 6.3 Hz for both, 6H); ^{13}C NMR δ 72.4, 72.2, 60.5, 60.3, 31.2, 30.8, 30.1, 29.6, 25.9, 25.8, 21.95, 21.92, 21.82, 21.76, 17.1, 17.0; LRMS (APTIS) *m*/*z* 319.2 $[(M + H)^+]$. Anal. Calcd for $C_{16}H_{30}O_2S_2$: C, 66.33; H, 9.49; S, 20.13. Found: C, 66.48; H, 9.55; S, 20.11.

1-[[(Acetylcyclohexyl)disulfanyl]cyclohexyl]ethan-1-one (3a). The Modified Swern Oxidation Procedure. To a stirred solution of oxalyl chloride (12.6 mL, 144 mmol) in CH_2Cl_2 (150 mL) at −78 °C under a nitrogen atmosphere was added dimethyl sulfoxide (20.5 mL, 289 mmol, in 20 mL of CH_2Cl_2) dropwise over a period of 20 min. After 15 min, the diol disulfide **2a** (15.3 g, 48.0 mmol) in CH_2Cl_2 (60 mL) was added dropwise over 30 min, and the dropping funnel was rinsed with 5 mL of CH_2Cl_2. The mixture was stirred at −78 °C for 90 min. Triethylamine (50 mL, 360 mmol) was added dropwise over 15 min, and the stirred mixture was maintained at −78 °C for 2 h. Aqueous THF (100 mL, 1:1 H_2O/THF) was added at such a rate that the internal temperature was kept below −60 °C while the reaction mixture was agitated vigorously. Upon complete addition, the dry ice−acetone bath was removed, and the stirred mixture was allowed to warm to 0 °C. The mixture was then taken up with additional CH_2Cl_2, washed with 2 M aqueous HCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a foam. Crystallization from CH_2Cl_2/hexanes (1:1) afforded the desired diketone disulfide **3a** (14.5 g, 96%) as a white crystalline solid: mp 80−81 °C; ^1H NMR δ 2.25 (s, 6 H), 2.1−2.0 (m, 4 H), 1.7−1.3 (m, 16 H); ^{13}C NMR δ 204.6, 61.7, 32.4, 25.0, 24.5, 23.0; LRMS (APTIS) *m*/*z* 315 $[(M + H)^+]$. Anal. Calcd for $C_{16}H_{26}O_2S_2$: C, 61.10; H, 8.33; S, 20.39. Found: C, 61.22; H, 8.18; S, 20.42.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **1d**, **2a**−**f**, and **3a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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