AN UNUSUAL BASE-INDUCED DEBROMINATION REACTION OF 3,4-DIBROMO-3-METHOXYCARBONYLSULFOLANE

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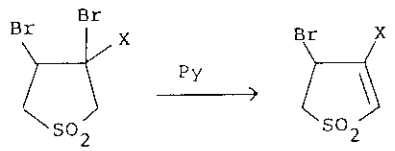
Abstract-*Treatment of the title compound with several bases gives neither dehydrobromination nor substitution reaction. An unusual debromination reaction takes place to give 3-methoxycarbonyl-3-sulfolene.*

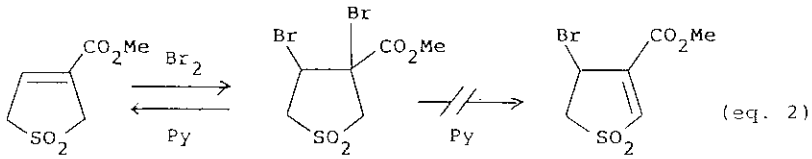
4-Bromo-2-sulfolenes have recently been employed as synthons for butadienyl cations.[1] A general route for their preparation involves a base-induced partial dehydrobromination reaction of the corresponding 3,4-dibromosulfolanes (eq. 1, X = H, Me, Cl, TMS) which in turn are prepared by bromine addition of proper 3-sulfolenes.[2]



(eq. 1)

For further exploration of the synthetic utilization of this strategy, we needed to prepare an ester-substituted 4-bromo-2-sulfolene **3**. Its precursor, 3,4-dibromo-3-methoxycarbonylsulfolane **2**, has been prepared from **1**.[3] When **2** was subjected to the standard reaction conditions[4] for partial dehydrobromination (1.9 equiv. of pyridine in acetone at room temperature), a trace of the anticipated 2-sulfolene **3** was not detected. Instead, the 3-sulfolene **1** was formed in a very high yield. Although the form of the eliminated bromine was not detected, it is believed that the debromination reaction invoves the attack of pyridine at the 4-bromine (eq. 2). By using 1.0 equivalent of pyridine at room temperature or at

reflux, this reaction gave a similar result.



1 2 3

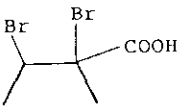
Debromination reactions of vicinal dibromides have been reported.[5] These reactions are commonly achieved with reducing agents such as zinc or with soft nucleophiles such as sulfur- or phosphorus-containing compounds. However, being basic, pyridine is rarely used as a debrominating agent.[6] In the reaction shown in eq. 2, there should be a competition between the pyridine-induced abstraction of the proton on the 2- or 5-position and the attack by pyridine on the bromine of the 3-position. Of course, direct substitution may also occur as a side reaction. The debromination process is apparently more favored. The direction of the competition was expected to be shifted in favor of the proton abstraction giving the dehydrobrominated product if a harder base is used in place of pyridine.[7] Based on this thought, **2** was treated with a number of bases and the results are listed in **Table I**.

Table I. Reactions of **2** with different bases

entry	base	solvent	temp	time	product (yield)
1	pyridine(1.9 eq.)	acetone	RT	24 h	**1** (90%)
2	pyridine(1 eq.)	acetone	RT	24 h	**1** (92%)
3	pyridine(1 eq.)	acetone	50°C	24 h	**1** (90%)
4	DBN (1 eq.)	THF	RT	7 h	**1** (89%)
5	K_2CO_3 (1 eq.)	CH_2Cl_2	RT	24 h	**1** (93%)
6	NaOMe (1 eq.)	MeOH/THF (1:3)	RT	24 h	**1** (22%) + **2** (65%)
7	NaOH (1 eq.)	H_2O/THF (1:6)	RT	24 h	**1** (47%) + **2** (47%)
8	NaOAc (1 eq.)	MeOH/THF (2:3)	RT	24 h	**1** (81%)
9	NaH (1 eq.)	THF	0°C	4 h	no reaction
10	NaH (1 eq.)	THF	RT	24 h	**1** (76%)
11	LiHMDS (1 eq.)	THF	-78°C	2 h	**1** (19%) + **6** (34%)
12	*n*-Bu_4NF (1 eq.)	THF	RT	24 h	**1** (29%) + **2** (34%)

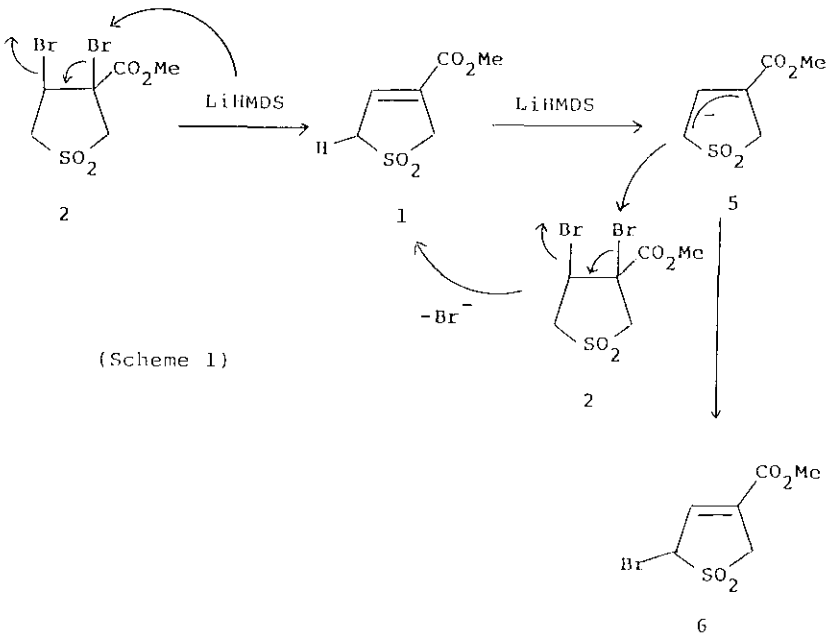
Surprisingly, in all cases only the debromination reaction took place. Neither dehydrobromination nor substitution reactions were observed. The bromine on the 3-position of **2** must be highly susceptible to nucleophilic attack so that debromination occurs even when a very hard base is used.

The elimination of HBr from 3-(trimethylsilyl)-3,4-dibromosulfolane is known to take place easily (eq. 1).[8] On the other hand, treatment of 2,3-dibromo-2-methylbutanoic acid **4** with KOH also gives the dehydrobromination product.[9] The unexpected difference in the mode of reaction of **2** from that of **4** or other dibromosulfolanes obviously can not be explained simply by the steric or electronic effects exerted by the methoxycarbonyl or the sulfone group. Nevertheless, an unusual debromination reaction of a dibromoamide system by treatment with hard bases has been reported previously.[10]



4

The reaction rate of debromination reaction using a strong base such as hydroxide or methoxide (entries 6 and 7) is much slower than the rate using a weak base such as pyridine (entry 2) at room temperature for 24 hours. This result is not too surprising because a soft base should have a stronger affinity for bromine than a hard base.

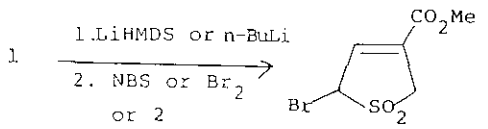


2 1 5 2 6

(Scheme 1)

It should be noted that in entry 11, the major product **6** is a secondary product. A proposed mechanism for its formation is described in Scheme 1. The deprotonation of the primary product **1** produces the carbanion **5** which attacks the bromine of another molecule of **2** to form **6** along with another molecule of carbanion **5** and a bromide.

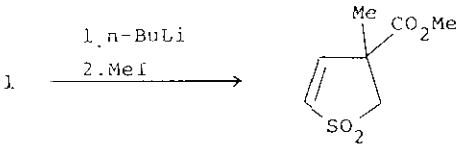
Generation of the sulfolenyl anion **5** from **1** and lithium hexamethyl disilazide (LiHMDS) or n-BuLi followed by treatment with NBS or Br_2 gives **6** (eq. 3). The results of these reactions support the reaction mechanism as shown in Scheme 1 since the carbanion **5** must be involved as an intermediate to lead to the formation of **6**. In addition, using **2** in place of NBS or Br_2 in this reaction also causes the formation of **6**. This result not only further confirms the reaction mechanism that the sulfolenyl anion **5** attacks the bromine on **2** (as shown in Scheme 1), but also again illustrates the ease of debromination of **2** in the presence of a nucleophile.



(eq. 3)

6

Although the substitution reactions of a sulfolenyl anion with electrophiles generally take place only at the 2- or 5-position of the 3-sulfolene,[11] the direct deprotonation of **1** with n-BuLi followed by alkylation with MeI gives exclusively the C-3 methylated product **7** in 72% yield (eq. 4). The difference in regioselectivity suggests that a methyl ester is a stronger electron-withdrawing group than a sulfone so that the negative charge density of the anion **5** is higher at the 3-position than at the 5-position, whereas that of other sulfolenyl anions is higher at the 2- or 5-position than at the 3- or 4-position. In the case where a large electrophile such as a positive bromine is reacted with **5**, the steric bulk around C-3 may become the dominating factor for the control of the regioselectivity of substitution.

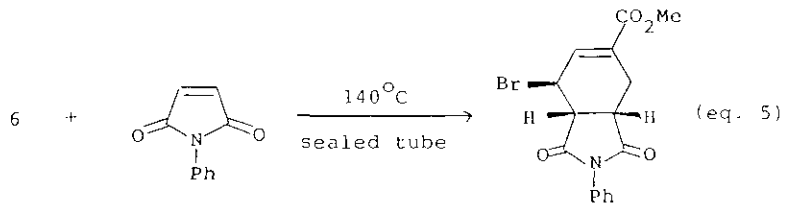


(eq. 4)

7

With a good leaving group bromide present, compound **6** was anticipated to undergo

substitution reactions to afford various 5-substituted 3-methoxycarbonyl-3-sulfolenes. Unfortunately, several attempts toward this direction failed. For example, treatment of **6** with phenylthiolate resulted in only debromination reaction giving **1**, whereas treatment of **6** with methyl cuprate gave a complex mixture with no indication of the formation of any methylated products. Nevertheless, **6** can be directly used as a diene source in the Diels-Alder reaction with N-phenylmaleimide to give **8** (eq. 5). This cycloadduct **8** containing many different functionalities, should be readily transformed into other useful compounds for organic synthesis.



(eq. 5)

8

EXPERIMENTAL

General methods. ^{1}H Nmr spectra were determined on a Bruker AW-80 MSL-200 NMR spectrometer with $CDCl_3$ as solvent. Ir spectra were taken on a Perkin-Elmer 882 infrared spectrophotometer. Mass spectra were recorded on a Hewlett-Packard 5995B gas chromatograpg/mass spectrometer. Elemental analyses were performed on a Perkin-Elmer PE-2400 elemental analyzer. A LiChrosorb hplc column (Merck, cat. 50935) was used in hplc purification throughout the experimental procedures.

Debromination Reaction of 3,4-Dibromo-3-methoxycarbonylsulfolane 2 with Bases. A solution of **2** with a base in a proper solvent is stirred for a certain period of time (the conditions are indicated in Table I). The mixture was then subjected to aqueous workup and $CHCl_3$ extraction. The products and yields are listed in Table I.

In the case where LiHMDS was used: The addition of LiHMDS to **2** in THF was carried out at -78°C. The reaction mixture was stirred at -78°C for 2 h and then was warmed up to room temperature gradually. Saturated brine was added and the layers separated. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was

purified by hplc (hexane/EtOAc, 1:1) to give 3-methoxycarbonyl-3-sulfolene **1**[3] (19%) and 2-bromo-4-methoxycarbonyl-3-sulfolene **6** (34%). Compound **6**: colorless oil; ir (neat) 2880, 1720, 1440, 1330, 1260, 1230, 1120 cm^{-1}; ^1H nmr (80 MHz) δ 3.81 (s, 3 H), 4.06 (s, 2 H), 5.53 (s, 1 H), 7.09 (s, 1H); ms m/z 256 (M^+ + 2), 254 (M^+), 225, 223, 192, 190, 133, 131, 111 (100%), 103. Anal. Calcd for $C_6H_7BrO_4S$: C, 28.25; H, 2.77. Found: C, 28.64; H, 2.53.

Bromine Substitution Reaction of 3-Methoxycarbonyl-3-sulfolene 1. To a solution of **1** (117 mg, 0.67 mmol) in THF (3 ml) at -78°C was added LiHMDS or n-BuLi (0.75 mmol) dropwise. After the dark-yellow solution was stirred for 15 min, a solution of NBS (214 mg, 1.2 mmol) in THF (1 ml) was added slowly. The stirring was continued at -78°C for another 2 h and then at room temperature for 12 h. Saturated brine (2 ml) was added and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 X 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was purified by hplc (hexane/EtOAc, 1:1) to give **1** (14.2 mg, 12%) and **6** (150 mg, 88%).

Methylation Reaction of 3-Methoxycarbonyl-3-sulfolene 1. To a solution of **1** (117 mg, 0.67 mmol) in THF (3 ml) with or without the presence of HMPA (2.7 mmol) at -78°C was added dropwise n-BuLi (0.75 mmol). After the dark-yellow solution was stirred at this temperature for 15 min, MeI (0.08 ml, 1.34 mmol) was added slowly. The stirring was continued at -78°C for 2 h and then at room temperature for 12 h. Saturated brine was added and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 X 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was purified by hplc (hexane/EtOAc, 1:1) to give 4-methoxycarbonyl-4-methyl-2-sulfolene **7** (91.7 mg, 72%): colorless oil; ir (neat) 2880, 1736, 1604, 1458, 1300, 1146, 1100 cm^{-1}; ^1H nmr (80 MHz) δ 1.59 (s, 3 H), 3.10 (d, 1 H, J = 13.2 Hz), 3.77 (s, 3 H), 3.84 (d, 1 H, J = 13.2 Hz), 6.57 (d, 1 H, J = 6.4 Hz), 6.75 (d, 1 H, J = 6.4 Hz); ms m/z 157 (M^+), 139, 126, 125, 107, 99, 97, 83, 81, 55, 43 (100%).

Cycloaddition Reaction of 2-Bromo-4-methoxycarbonyl-3-sulfolene 6 with N-Phenylmaleimide. A mixture of **6** (295 mg, 1.15 mmol), N-phenylmaleimide (1.73 g, 10 mmol), and hydroquinone (trace) in anhydrous benzene (6 ml) in a sealed tube was heated at 140°C for 2.5 h. After the solution was cooled to room temperature,

the solvent was removed under reduced pressure. The crude oil was eluted through a silica gel column (hexane/EtOAc, 1:1) to give, in addition to a dimeric product of the parent diene of **6** (153 mg, 52%), the cycloadduct **8** in 48% (201 mg) yield. The stereochemistry of **8** can be assigned on the basis of nmr spectral data. The small coupling constant (1.8 Hz) between the proton on the bromine-bearing carbon and that on the ring junction indicates the stereochemistry to be the same as the one which is drawn in the text.[12] An analytical sample was obtained by hplc purification (hexane/EtOAc, 1:1): white solid, mp 133-134°C; ir (KBr) 2960, 1700, 1500, 1430, 1380, 1280, 1180 cm^{-1}; ^1H nmr (200 MHz) δ 2.79 (ddd, 1 H, J = 3.3, 8.8, 16.9 Hz), 3.37 (dd, 1 H, J = 1.67, 16.9 Hz), 3.58 (ddd, 1 H, J = 1.67, 8.8, 9.0 Hz), 3.78 (s, 3 H), 3.80 (dd, 1 H, J = 1.8, 9.0 Hz), 5.29 (dd, 1 H, J = 1.8, 6.75 Hz), 7.17-7.48 (m, 6 H); ms m/z 365 (M^+ + 2), 363 (M^+), 284, 164, 137, 136, 119, 105, 93, 91, 79, 78, 77 (100%), 59. Anal. Calcd for $C_{16}H_{15}BrNO_4$: C, 52.76; H, 3.87; N, 3.85. Found: C, 52.66; H, 3.57; N, 3.57.

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12. The cycloaddition reaction initially produces compound **8** and its epimer (1:2.4, total yield 48%) which are formed from the *exo*- and *endo*-addition modes, respectively. However, the epimer [^{1}H nmr (200 MHz) δ 2.67 (ddd, 1 H, J = 3.3, 8.7, 12.0 Hz), 3.30-3.39 (m, 3 H), 3.82 (s, 3 H), 5.23-5.27 (m, 1 H), 7.30-7.50 (m, 6 H)] isomerizes to **8** quantitatively at room temperature upon being exposed to toluenesulfonic acid. Even the acidity of silica gel can induce such an epimerization so that upon elution through a silica gel column, the ratio of **8** to the epimer in the product mixture changes from 1:2.4 to 2:1. Compound **8** and its epimer can be separated by silica gel column or hplc (hexane/ EtOAc, 1:1). An analytically pure sample of **8** can be collected, whereas the sample of the epimer is unavoidably contaminated with **8** because of the rapid epimerization process. Thus, spectral data (ir, ms, elemental analysis) of the *endo*-adduct were not obtainable.

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