Ultrasonically Dispersed Potassium in Organic Synthesis. Reactions with Unsaturated Cyclic Sulfones†

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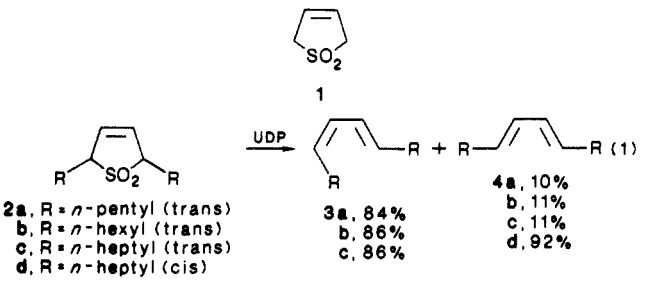
Received August 14, 1986

Ultrasonically dispersed potassium was found to promote the extrusion of sulfur dioxide from di- and trisubstituted 3-sulfolenes to give the corresponding dienes stereoselectively. This reagent was also found to be regioselective in the cleavage of the C–S bond between sulfur and the sp^2 carbon of substituted 2-sulfolenes to produce stereoselectively homoallylic sulfones bearing a trans double bond.

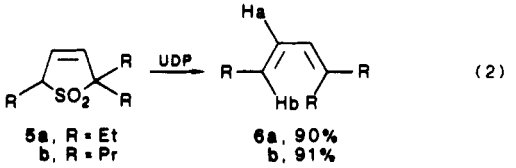
Ultrasonically dispersed potassium (UDP), generated by the irradiation of metallic potassium in toluene, has been found to be an effective reagent for the promotion of Dieckmann cyclization of diesters[1] and the selective reductive cleavage of C–S bond of cyclic sulfones.[2] We now report that this new reagent can be used to promote the stereoselective SO_2 extrusion from di- and trisubstituted 3-sulfolenes and to cleave a carbon–sulfur bond of a substituted 2-sulfolene regio- and stereoselectively.

When 2,5-dialkyl-3-sulfolene **2**, prepared easily by one-pot dialkylation of 3-sulfolene (**1**),[3] was treated with UDP (2.5 equiv), reaction took place instantaneously and was complete within 1 min (eq 1). The corresponding conjugated diene **3** or **4** was produced in very high yield. The cis-dialkylated sulfolene **2d** gave only the (*E,F*)-diene **4c** while the trans-dialkylated sulfolenes **2a–c** gave mixtures of (*E,Z*)-dienes **3a–c** and (*E,E*)-dienes **4a–c** in about a 8:1 ratio in all cases. The purities of the dienes were examined by GC analysis (Apiezon column, 3M) and their configurations were determined by ^1H NMR spectra (400 MHz). The *E,E* isomers showed two sets of vinyl protons and the *E,Z* isomers showed four sets of vinyl protons.



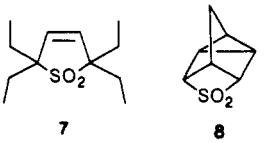
When the reaction of UDP (2.5 equiv) with **2a–c** was performed with nitrogen bubbled through it, the ratio of (*E,Z*)-/(*E,E*)-dienyl products was raised to 20:1, indicating a much better stereoselectivity. This result is comparable to that of the thermolysis of a similar system.[4] However, the overall yield was lower (<80%) and it required more than 30 min before the reaction was complete probably because of the unfavorable effect of nitrogen bubbling on sonication. It is believed that a cheletropic SO_2 extrusion[5] from **2a–d** is involved in the UDP reactions of **2a–d**. The slightly inferior selectivity in UDP reactions to that in thermolysis might be attributed to the *E/Z* isomerization of the dienes under the reaction conditions. In a control experiment, a mixture of (*E,Z*)-2,4-hexadiene (1 equiv) and **2c** (1 equiv) in toluene-d_8 was treated with UDP (2 equiv). The reaction proceeded very slowly and was not complete after 90 min. The ^{13}C NMR analysis of this reaction mixture revealed the existence of both (*E,Z*)- and (*E,E*)-2,4-hexadiene in about 1:1 ratio. This experiment indicates that a gradual isomerization of (*E,Z*)-dienes to the thermodynamically more stable *E,E* isomers indeed takes place under the reaction conditions. Therefore, **4a–c** might be simply secondary products from the UDP reactions of **2a–c**. The possibility of another mechanism which involves the reductive C–S bond scission by sequential electron transfer is unlikely. It was found that stoichiometric amount of K is not necessary since 0.9 equiv of K was sufficient to bring the reaction of UDP with **2c** to completion, although at a much slower rate (80 min in this case vs. the typical 1 min). Had the reaction taken place via reductive cleavage process, 2 equiv of K would be required for the complete consumption of the 2-sulfolene **2c**.

Trisubstituted sulfolenes **5a,b** reacted similarly with UDP and gave only (>98% pure by NMR) the trans trisubstituted dienes in high yields (eq 2). The assignment



of the configuration of **6a,b** was based upon the large coupling constant (15 Hz) between H_a and H_b. A detailed mechanism of the UDP-promoted cheletropic extrusion is not clear. Earlier, LAH has been found to promote the cheletropic reactions as well.[6] In this way, dienes are generated from sulfolenes under moderate conditions so that high-temperature thermolysis may be avoided.

For tetrasubstituted sulfolenes such as **7** and norbornadienyl sulfone **8**, UDP was found to be ineffective even at higher temperature (up to 60 °C) or for a longer reaction time (up to 4 h). All attempts resulted in no reaction and the complete recovery of starting materials. Thus, it appears that UDP can be used to extrude selec-



† Partial contribution from the Department of Chemistry, Providence College, Taichung, Taiwan, Republic of China.

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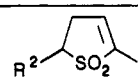
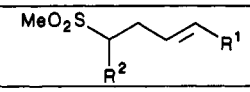
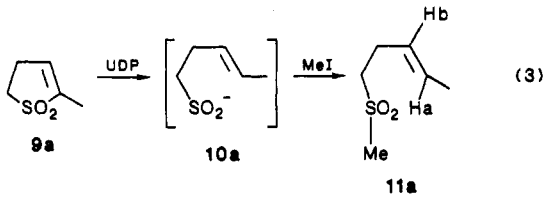
Table I. Reductive Cleavage of 2-Sulfolenes with UDP

		yield, %
9a, R^1 = Me, R^2 = H	**11a**	40
9b, R^1 = Et, R^2 = H	**11b**	43
9c, R^1 = R^2 = Me	**11c**	45
9d, R^1 = R^2 = Et	**11d**	72
9e, R^1 = R^2 = *n*-Bu	**11e**	40
9f, R^1 = R^2 = *n*-heptyl	**11f**	48

tively SO_2 from 2,5-disubstituted and 2,2,5-trisubstituted 3-sulfolenes in the presence of 2,2,5,5-tetrasubstituted ones. In fact, mixtures of trialkylated and tetraalkylated 3-sulfolenes are normally separated only by careful HPLC technique. However, when a mixture of **7** and 2,2,5-triethyl-3-sulfolene (**5a**) was subjected to UDP treatment for 5 min, compound **7** remained unchanged while compound **5a** gave its corresponding diene **6a**, which could be separated from **7** easily by normal column chromatography.

The reactions of UDP with substituted 2-sulfolenes were also studied. When **9a** was treated with an excess of UDP (2.5 equiv), the starting material was consumed in 15 min as indicated by TLC analysis. This reaction mixture was immediately treated with MeI (4 equiv) to give **11a** as the only major product (eq 3). Some other minor products



(3)

were formed in insignificant amounts and were not characterized. The sulfinate **10a** must have been the intermediate before treatment with MeI; however, no efforts were made to isolate this water-soluble intermediate. When only 1 equiv of K was used in the reaction, approximately 50% of the unreacted starting material was recovered. A ^{13}C NMR spectrum of **11a** showed only six peaks (δ 17.8, 25.7, 40.8, 54.7, 126.2, 128.6) indicating the presence of only one isomer. ^1H NMR analysis showed a coupling constant of 15 Hz between the two vinyl protons [H_a δ 5.61 (dq) and H_b δ 5.42 (dt)] indicating the double bond to be trans. These data illustrate reductive cleavage of the carbon–sulfur bond of **9a** with UDP to be highly regio- and stereoselective.

UDP treatment of 2-alkyl- and 2,5-dialkyl-2-sulfolenes **9b–f**, easily prepared from the alkylated 3-sulfolenes by base-induced double bond isomerization,[7] gave similar results to produce the corresponding sulfones **11b–f** in useful yields. (see Table I). Such reaction conditions should also be effective for the desulfonylation of other endocyclic vinyl sulfone systems. It is important that the reactions be quenched with MeI immediately after the completion of the reductive cleavage step to avoid unknown side products possibly from overreduction. The reaction of 2-sulfolene (**12**) with excess of UDP at room temperature took place much more slowly, and the starting material was consumed only after 40 min. Standard

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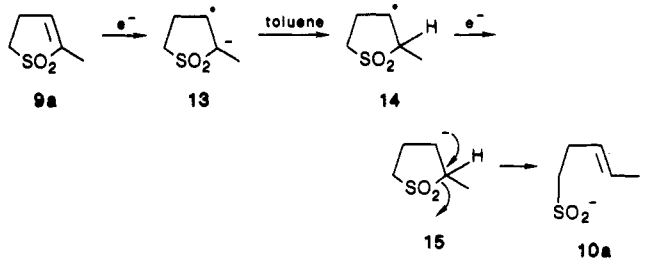
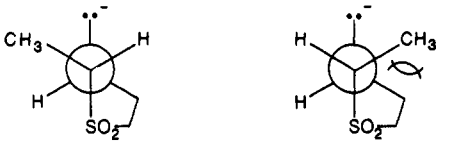
workup of the reaction revealed poor mass balance and only 3 mg of unidentifiable mixture was obtainable from 100 mg of **12**. Continuous extraction of the aqueous layer with $CHCl_3$ did not improve the material recovery; the main product(s) is presumably volatile.

Scheme I



A mechanism for the regio- and stereoselective C–S bond cleavage of compounds **9** giving the sulfinates **10** is proposed as shwon in Scheme I. The intermediate **15**, which determines the stereochemical outcome of the final product, prefers to take the configuration as in **15A** rather than the less stable one as in **15B**. Compound **15A** then undertakes an elimination process to produce **10a** with the double bond in trans configuration.



15A **15B**

Ultrasound irradiation is essential to all these reactions. For example, when **9a** was stirred with an excess of finely cut potassium for 20 h in the absence of ultrasound irradiation, the reaction resulted in the recovery of more than 90% of starting material and only less than 5% of the desired product. It was also found that ultrasound alone did not induce any degree of sulfur dioxide extrusion from 3-sulfolenes.

Experimental Section

General Methods. ^1H NMR spectra were determined on a JEOL FX-100 NMR spectrometer or a Bruker AM-400 NMR spectrometer as solutions in $CDCl_3$. IR spectra were determined on a Perkin-Elmer 290 IR spectrophotometer. Mass spectra were recorded on a JEOL JMS-D-100 mass spectrometer. Elemental analyses were performed at National Taiwan University, Taipei, on a Perkin-Elmer 240 instrument. All reactions were carried out under an atmosphere of dry nitrogen. Toluene was freshly distilled over sodium before use.

Extrusion of Sulfur Dioxide from Substituted 3-Sulfolenes with UDP. Substituted 3-sulfolene **2** or **5** (1 mmol) in toluene was added dropwise to a suspension of UDP (2.5 mmol)[1,2] in toluene at room temperature. After the mixture was irradiated with ultrasound for 1 min, the excess of potassium was filtered off, and the solvent was removed under reduced pressure. The dienyl product so obtained was spectroscopically pure. The *E,Z* and *E,E* isomers were separated by GC (Apiezon, 3M; injection temperature, 200 °C; column temperature, 70 °C).

6,8-Tetradecadiene (**3a** and **4a**): IR (neat) 3050, 3000, 2970, 2900, 1485, 1390, 1000, 940 cm^{-1}; NMR (*E,Z* isomer, **3a**) δ 0.88 (t, 6H, J = 6.5 Hz), 1.20–1.45 (m, 12 H), 2.09 (dt, 2 H, J = 7.3, 7.2 Hz), 2.15 (dt, 2 H, J = 7.4, 7.1 Hz), 5.31 (dt, 1 H, J = 11.0, 7.4 Hz), 5.65 (dt, 1 H, J = 15.0, 7.3 Hz), 5.94 (dd, 1 H, J = 15.0, 11.0 Hz), 6.30 (dd, 1 H, J = 11.0, 11.0 Hz), (*E,E* isomer, **4a**) δ 0.88 (t, 6 H, J = 6.5 Hz), 1.20–1.50 (m, 12 H), 2.04 (dt, 4 H, J = 7.3, 6.9 Hz), 5.51–5.65 (m, 2 H), 6.01 (dd, 2 H, J = 12.8, 7.3 Hz); MS, m/z 194 (M^+), 114, 110, 96 (100%), 82, 68, 54. Anal. Calcd for $C_{14}H_{26}$: C, 86.5; H, 13.5. Found: C, 86.1; H, 13.6.

7,9-Hexadecadiene (**3b** and **4b**): IR (neat) 3025, 2960, 2930, 2860, 1470, 1380, 980, 940 cm^{-1}; NMR (*E,Z* isomer, **3b**) δ 0.88 (t, 6 H, J = 6.5 Hz), 1.20–1.42 (m, 16 H), 2.08 (dt, 2 H, J = 7.2, 7.2

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Hz), 2.15 (dt, 2 H, J = 7.3, 7.1 Hz), 5.29 (dt, 1 H, J = 10.8, 7.3 Hz), 5.65 (dt, 1 H, J = 15.0, 7.2 Hz), 5.94 (dd, 1 H, J = 10.8, 10.9 Hz), 6.30 (dd, 1 H, J = 15.0, 10.9 Hz), (*E,E* isomer, **4b**) δ 0.98 (t, 6 H, J = 6.5 Hz), 1.20–1.48 (m, 16 H), 2.04 (dt, 4 H, J = 7.2, 6.7 Hz), 5.52–5.60 (m, 2 H), 6.00 (dd, 2 H, J = 14.3, 7.2 Hz); MS, m/z 222 (M^+), 138, 100, 96, 82, 68, 54 (100%). Anal. Calcd for $C_{16}H_{30}$: C, 86.4; H, 13.6. Found: C, 86.1; H, 13.8.

8,10-Octadecadiene (**3c** and **4c**): IR (neat) 3090, 3000, 2900, 1490, 1400, 1000, 960 cm^{-1}; NMR (*E,Z* isomer, **3c**) δ 0.90 (t, 6 H, J = 6.5 Hz), 1.25–1.45 (m, 20 H), 2.08 (dt, 2 H, J = 7.6, 7.2 Hz), 2.16 (dt, 2 H, J = 7.6, 7.2 Hz), 5.30 (dt, 1 H, J = 10.8, 7.6 Hz), 5.65 (dt, 1 H, J = 15.1, 7.6 Hz), 5.93 (dd, 1 H, J = 11.0, 10.8 Hz), 6.32 (dd, 1 H, J = 15.1, 11.0 Hz), (*E,E* isomer, **4c**) δ 0.87 (t, 6 H, J = 6.5 Hz), 1.20–1.44 (m, 20 H), 2.04 (dt, 4 H, J = 7.1, 6.1 Hz), 5.50–5.64 (m, 2 H), 5.99 (dd, 2 H, J = 14.3, 7.2 Hz); MS, m/z 250 (M^+, 100%), 124, 110, 96, 82. Anal. Calcd for $C_{18}H_{34}$: C, 86.3; H, 13.7. Found: C, 86.2; H, 13.8.

(*E*)-3-Ethyl-3,5-octadiene (**6a**): IR 3020, 2950, 2870, 1620, 1460, 1380, 970 cm^{-1}; NMR δ 0.95–1.10 (m, 9 H), 2.00–2.35 (m, 6 H), 5.55 (dt, 1 H, J = 15.0, 7.2 Hz), 5.76 (d, 1 H, J = 7.6 Hz), 6.30 (dd, 1 H, J = 15.0, 7.6 Hz); MS, m/z 138 (M^+), 109 (100%), 95, 81, 79, 67, 55. Anal. Calcd for $C_{10}H_{18}$: C, 86.9; H, 13.1. Found: C, 86.7; H, 13.0.

(*E*)-4-Propyl-4,6-decadiene (**6b**): IR 3020, 2950, 2850, 1620, 1460, 1380, 960 cm^{-1}; NMR δ 0.90–1.05 (m, 9 H), 1.31–1.52 (m, 6 H), 1.98–2.12 (m, 6 H), 5.57 (dt, 1 H, J = 15.0, 7.3 Hz), 5.79 (d, 1 H, J = 7.8 Hz), 6.25 (dd, 1 H, J = 15.0, 7.8 Hz); MS, m/z 180 (M^+), 141, 137, 123, 109, 95 (100%), 81, 67. Anal. Calcd for $C_{13}H_{24}$: C, 86.7; H, 13.3. Found: C, 86.4; H, 13.2.

Reductive Cleavage of the C–S Bond of Substituted 2-Sulfolenes. Substituted 2-sulfolene **9** (1 mmol) in toluene was added dropwise to a suspension of ultrasonically dispersed potassium (2.5 mmol) in toluene at room temperature. The irradiation was continued for 15 min, upon which time MeI (4 mmol) was added, and the reaction mixture was stirred for another 20 min. With the precipitate in the solution, saturated NH_4Cl was added, and the layers were separated. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried and concentrated under reduced pressure. The crude oil was purified with HPLC (LiChrosorb; hexane/ethyl acetate, 1:1) to give the pure product.

Methyl 3-pentenyl sulfone (**11a**): IR (neat) 3020, 3000, 2960, 2930, 2860, 1460, 1300, 1130, 1120, 960, 750 cm^{-1}; ^{1}H NMR δ 1.68 (d, 3 H, J = 6.8 Hz), 2.51–2.56 (m, 2 H), 2.89 (s, 3 H), 3.02–3.06 (m, 2 H), 5.42 (dq, 1 H, J = 15.0, 6.8 Hz), 5.60 (dt, 1 H, J = 15.0, 6.5 Hz); ^{13}C NMR δ 17.84, 25.72, 40.85, 54.67, 126.21, 128.64; MS, m/z 150 (M^+), 149, 81, 69, 68 (100%), 67, 53, 41. Anal. Calcd for $C_6H_{12}O_2S$: C, 48.6; H, 8.2. Found: C, 48.3, H, 8.2.

3-Hexenyl methyl sulfone (**11b**): IR (neat) 3010, 2960, 2875, 1460, 1300, 1140, 970 cm^{-1}; NMR δ 0.95 (t, 3 H, J = 6.5 Hz), 1.80–2.20 (m, 2 H), 2.32–2.70 (m, 2 H), 2.88 (s, 3 H), 2.82–3.18 (m, 2 H), 5.25–5.80 (m, 2 H); MS, m/z 162 (M^+), 147, 121, 94, 82 (100%), 69, 68, 55, 41. Anal. Calcd for $C_7H_{14}O_2S$: C, 51.8; H, 8.7. Found: C, 51.7; H, 8.8.

Methyl 1-methyl-3-pentenyl Sulfone (**11c**): IR (neat) 3060, 3020, 2880, 1650, 470, 1300, 1130, 1110, 1020, 970 cm^{-1}; NMR δ 1.21–1.32 (d, 3 H, J = 7.5 Hz), 1.68 (d, 3 H, J = 6.0 Hz), 2.00–2.38 (m, 2 H), 2.50–2.78 (m, 1 H), 2.86 (s, 3 H), 5.25–5.70 (m, 2 H); MS, m/z 162 (M^+), 108, 82 (100%), 68. Anal. Calcd for $C_7H_{14}O_2S$: C, 51.8; H, 8.7. Found: C, 51.9; H, 8.6.

1-Ethyl-3-hexenyl methyl sulfone (**11d**): IR (neat) 3000, 2960, 2860, 1470, 1300, 1140, 970 cm^{-1}; NMR δ 0.98 (t, 3 H, J = 7.0 Hz), 1.08 (t, 3 H, J = 7.0 Hz), 1.40–2.20 (m, 4 H), 2.25–2.62 (m, 2 H), 2.65–2.85 (m, 1 H), 2.81 (s, 3 H), 5.17–5.82 (m, 2 H); MS, m/z 190 (M^+), 131, 110 (100%), 95, 81. Anal. Calcd for $C_9H_{18}O_2S$: C, 56.8; H, 9.5. Found: C, 56.4, H, 9.4.

1-Butyl-3-octenyl methyl sulfone (**11e**): IR (neat) 3000, 2950, 2900, 1480, 1130, 970 cm^{-1}; NMR δ 0.89 (t, 6 H, J = 6.5 Hz), 1.15–1.50 (m, 10 H), 1.75–2.10 (m, 2 H), 2.30–2.80 (m, 3 H), 2.80 (s, 3 H), 5.35–5.55 (m, 2 H); MS, m/z 246 (M^+), 242, 166 (100%), 100, 96. Anal. Calcd for $C_{13}H_{26}O_2S$: C, 63.4; H, 10.6. Found: C, 63.4; H, 10.7.

1-Heptyl-3-undecenyl methyl sulfone (**11f**): IR (neat) 2970, 2950, 2860, 1470, 1300, 1100, 970 cm^{-1}; NMR δ 0.85 (t, 6 H, J = 6.0 Hz), 1.12–1.48 (m, 22 H), 1.70–2.10 (m, 2 H), 2.36–2.80 (m, 3 H), 2.80 (s, 3 H), 5.35–5.60 (m, 2 H); MS, m/z 330 (M^+), 306, 250 (100%), 222, 194, 165, 152, 138, 124, 110, 96, 82. Anal. Calcd for $C_{19}H_{38}O_2S$: C, 69.0; H, 11.6. Found: 68.9; H, 11.8.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support (NSC75-0201-M001C-05 and NSC-76-0208-M001-22).

Synthesis of a Sterically Impeded Analogue of the Carcinogenic Anti Diol Epoxide Metabolite of Benzo[*a*]pyrene

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Received November 13, 1986

Synthesis is described of *trans*-7,8-dihydroxy-7,8-dihydro-1-isopropylbenzo[*a*]pyrene and the corresponding bay region diol epoxide derivative, *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydro-1-isopropylbenzo[*a*]pyrene. These compounds are analogues of the proximate and ultimate carcinogenic metabolites of benzo[*a*]pyrene that differ from the latter in their possession of an isopropyl group in the 1-position remote from the ring that undergoes metabolic activation. These compounds were utilized in separate metabolism and DNA binding studies to test the hypothesis that intercalation of active diol epoxide metabolites into DNA is an essential step in the mechanism of PAH carcinogenesis.

Carcinogenic polycyclic aromatic hydrocarbons (PAH), such as benzo[*a*]pyrene, require activation by the P-450 microsomal enzymes to exhibit their mutagenic and carcinogenic potential.[1-3] Benzo[*a*]pyrene (BP) (**1a**) has been most intensively investigated, and its principal biologically active metabolite has been identified as (+)-*trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**3a**), commonly referred to as (+)-*anti*-BPDE.[4] Considerable evidence has implicated DNA as the critical target,[1,3] and covalent binding of *anti*-BPDE to DNA and RNA in mammalian cells has been shown to take place principally on guanosine to form a 2-aminodeoxyguanosine adduct.[5,6] Kinetic studies are consistent with a mechanism

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