Preparation and Diels-Alder Reactions of 3-Substituted 3-Sulfolenes

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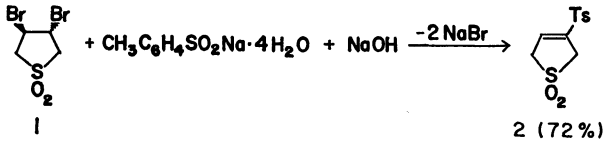
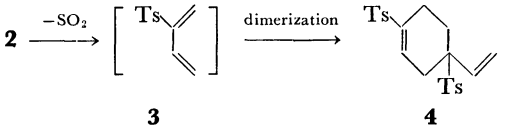
It was found that 3-(*p*-tolylsulfonyl)- and 3-(*p*-tolylsulfinyl)-3-sulfolenes prepared from 3-sulfolene react with various dienophiles to give the corresponding Diels-Alder cycloadducts in good yields, and that only the "para" substituted cycloadducts are obtained with monofunctionalized (CHO, $COCH_3$, CO_2CH_3, CN, and C_6H_5) ethylenes and methyl 2-methylpropenoate, respectively.

Readily available 3-sulfolene (2,5-dihydrothiophene 1,1-dioxide) loses SO_2, giving pure butadiene on heating at 110—130 °C.[1] However, only a few reports have been given on the preparation of substituted dienes starting from 3-sulfolene.[2] In this paper we wish to report on the preparation and the reactions of 3-(*p*-tolylsulfonyl)- and 3-(*p*-tolylsulfinyl)-3-sulfolenes (**2** and **9**) which produce the electron-deficient dienes, 2-(*p*-tolylsulfonyl)- and 2-(*p*-tolylsulfinyl)-1,3-butadienes, respectively.

*Preparation and Reaction of 3-(*p*-Tolylsulfonyl)-3-sulfolene.* 3-(*p*-Tolylsulfonyl)-3-sulfolene (**2**) was readily prepared by the reaction of *trans*-3,4-dibromosulfolane (**1**) obtained by the bromination of 3-sulfolene[3] with sodium *p*-toluenesulfinate tetrahydrate and sodium hydroxide in methanol, in a one-pot substitution-elimination reaction as shown in the following scheme.



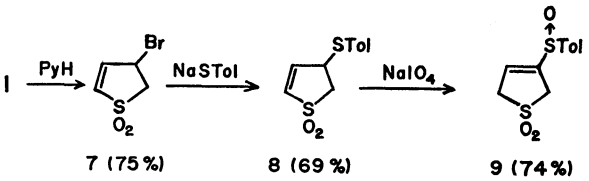
In order to confirm the reaction in which **2** thus obtained produces 2-(*p*-tolylsulfonyl)-1,3-butadiene (**3**) on heating, a solution of **2** in xylene was refluxed for 3 h. Evolution of SO_2 was confirmed by the color change in the universal indicator. However, the final product was not the expected **3** but its dimer **4** (97% yield). The structure of **4** was confirmed by elemental analysis and spectral data including ^{13}C-NMR spectrum of its reduction product. The fact that the dimer **4** was obtained in such an excellent yield indicates that the intermediate **3** is reactive to a dienophile. It was found that the reaction is accelerated by the addition of pyridine to capture SO_2.



Hence the Diels-Alder reaction of **2** with various dienophiles **5a**—**i** was attempted. Since the monofunctionalized ethylenes **5e**—**i** and methyl 2-methylpropenoate (**5d**) are liable to polymerize, the reactions were carried out in the presence of a catalytic amount of hydroquinone and pyridine (as a scavenger of SO_2, equimolar with **2**) in a sealed tube. It was found that the Diels-Alder reaction of **2** with dienophiles **5a**—**i** gives the corresponding cycloadducts **6a**—**i** in excellent yields in all cases except **5b,g** (Table 1).

All the products **6d**—**i** and dimer **4** are "para" substituted cycloadducts. Their structures were confirmed by elemental analyses and spectral data including ^{13}C-NMR spectra of their reduction products, which indicate four peaks assigned to the "para" substituted cyclohexanes. It is evident that the Diels-Alder reaction of **2** with the dienophiles **5d**—**i** proceeds regioselectively. The reaction of **2** with dienophiles **5a**—**c** is stereospecific.

*Preparation and Reaction of 3-(*p*-Tolylsulfinyl)-3-sulfolene.* 3-(*p*-Tolylsulfinyl)-3-sulfolene (**9**) was prepared in three steps from **1** as follows: 4-bromo-2-sulfolene (**7**), prepared from **1** by the procedure of Bailey and Cummins,[3] was reacted with sodium *p*-toluenethiolate to give 4-(*p*-tolylthio)-2-sulfolene (**8**). Oxidation of **8** by sodium periodate gave the desired **9** accompanied by the isomerization of the double bond.



The Diels-Alder reaction of **9** with various dienophiles **5b**—**g** was attempted in a similar manner. It was found that the reaction also proceeds regioselectively to give the corresponding "para" substituted cycloadducts **10d**—**g** (Table 2).

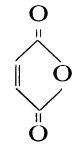
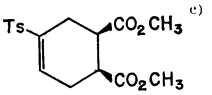
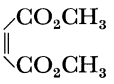
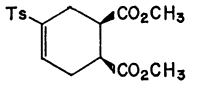
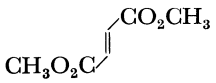
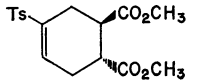
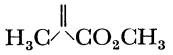
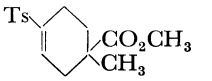
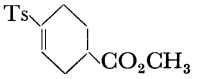
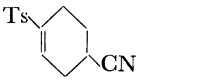
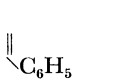
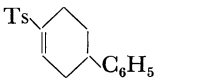
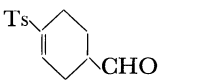
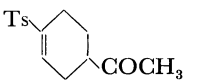
It is apparent that both the Diels-Alder reactions of 3-(*p*-tolylsulfonyl)- and 3-(*p*-tolylsulfinyl)-3-sulfolenes (**2** and **9**) give the corresponding "para" regioisomers in good yields *via* 2-substituted butadienes. These results are in line with those predicted by means of Houk's generalization.[4]

Experimental

All the melting points are uncorrected. The ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL JNM/MH-60 and JEOL PFT/PS-100 NMR spectrometers, respectively. The chemical shifts are reported in the δ scale relative to TMS as an internal standard. The IR spectra were taken with JASCO IRA-1 diffraction grating infrared spectrometer.

Materials. All the solvents were distilled according to the usual methods and stored over a drying agent. Thin-layer chromatography (TLC) was performed on Merck's Kieselgel 60 PF_{254} (Art. 7749) using a mixture of benzene and ethyl acetate as an eluent, unless otherwise stated.

Table 1. Cycloadducts of 3-(*p*-tolylsulfonyl)-3-sulfolene (**2**) with various dienophiles

	Dienophile	Molar ratio **5/2**	Condition[a]	Isolated yield (%)[b] **6a—i**
5a		10	A	 [c] 99
5b		10	A	 50[d]
5c		10	A	 98
5d		20	B	 93
5e		20	B	 quant.
5f		20	B	 89[e]
5g		10	C	 64[f]
5h		20	B	 84
5i		20	B	 quant.

a) A: Refluxed in xylene for 3 h. B: Heated in a sealed tube at 140—150 °C in xylene for 2 h in the presence of catalytic amount of hydroquinone and pyridine (1 equiv). C: Toluene was used in the place of xylene in B at 110—120 °C. b) Based on **2**. c) Initial product subjected to hydrolysis followed by esterification with diazomethane in THF-ether. d) Dimer **4** isolated in 42% yield. e) Dimer **4** isolated in 11% yield. f) Dimer **4** isolated in 32% yield.

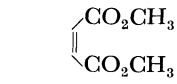
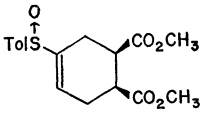
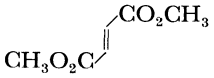
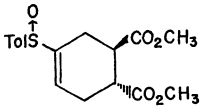
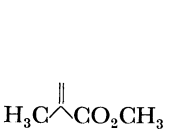
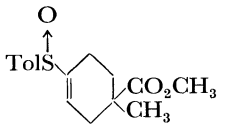
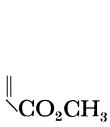
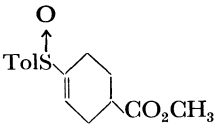
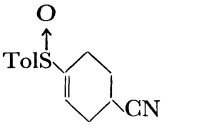
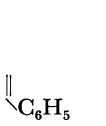
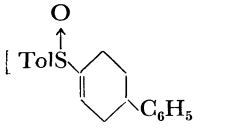
*3-(*p*-Tolylsulfonyl)-3-sulfolene (**2**).* To a methanol solution (300 ml) of sodium hydroxide (1.760 g, 44 mmol) were added sodium *p*-toluenesulfinate tetrahydrate (50 g, 200 mmol) and 3,4-dibromosulfolane (**1**, 11.118 g, 40 mmol).[3] After being refluxed for 5 h, the reaction mixture was poured over ice to give the crude **2** (8.596 g, mp 108—110 °C), which was recrystallized from ethanol (7.848 g, 72%): mp 125—126 °C; IR 1315, 1307, 1298, 1142, 1125 cm^{-1}; NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.84 (m, 2H), 4.02 (m, 2H), 6.98 (m, 1H), 7.34 (d, 2H, J=9 Hz), 7.73 (d, 2H, J=9 Hz). Found: C, 48.63; H, 4.51; S, 23.24%. Calcd for $C_{11}H_{12}O_4S_2$: C, 48.53; H, 4.44; S, 23.51%.

*1,4-Bis(*p*-tolylsulfonyl)-4-vinylcyclohexene (**4**).* To a xylene solution (6 ml) of **2** (273 mg, 1 mmol) were added pyridine (79 mg, 1 mmol) and a catalytic amount of hydroquinone (*ca.* 5 mg). The mixed solution was heated at 140—150 °C in a sealed tube for 2 h. After addition of ethyl acetate and 1 M HCl, the organic layer was washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The crystalline residue was separated by preparative TLC to afford **4** (417 mg, mp 166—170 °C) in a nearly quantitative yield. Recrystallization from ethanol gave pure **4** (404 mg, 97%): mp 198—199 °C; IR 1280, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.7—3.0 (m, 6H), 2.40 (s, 6H), 4.87 (d, 1H, J=17 Hz), 5.23 (d, 1H, J=11 Hz), 5.63 (dd, 1H, J=11 and 17 Hz), 6.90 (m, 1H), 7.25 (m, 4H), 7.59 (d, 4H, J=8 Hz). Found: C, 63.52; H, 5.79; S, 15.35%. Calcd for $C_{22}H_{24}O_4S_2$: C, 63.45; H, 5.81; S, 15.37%.

Dimethyl cis-*4-(*p*-Tolylsulfonyl)-4-cyclohexene-1,2-dicarboxylate (**6a**).* A suspension of **2** (91 mg, 1/3 mmol) and maleic anhydride (**5a**, 10/3 mmol) in xylene (2 ml), which became a clear solution on heating, was refluxed for 3 h. After evaporation of the solvent, excess **5a** was removed by sublimation. The residue was treated with 6 M HCl and tetrahydrofuran (THF) to hydrolyze the product followed by concentration. The residue was redissolved in THF and dried over Na_2SO_4 followed by addition of an ethereal solution of diazomethane. After evaporation of the solvent, the residue was separated by preparative TLC to afford **6a** (116 mg) in a 99% yield. Recrystallization from ethanol gave pure **6a**: mp 144—146 °C; IR 1720, 1295, 1285, 1240, 1205, 1145 cm^{-1}; NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.4—3.3 (m, 6H), 3.44 (s, 3H), 3.66 (s, 3H), 6.93 (m, 1H), 7.24 (d, 2H, J=9 Hz), 7.64 (d, 2H, J=9 Hz). Found: C, 57.86; H, 5.61; S, 9.24%. Calcd for $C_{17}H_{20}O_6S$: C, 57.95; H, 5.72; S, 9.08%.

In a similar manner except for esterification with diazomethane, other cycloadducts **6b** (=**6a**) and **6c** were obtained from **2** and the corresponding dienophiles **5b** and **5c**.

Table 2. Cycloadducts of 3-(*p*-tolylsulfinyl)-3-sulfolene (**9**) with various dienophiles

	Dienophile	Molar ratio **5**/**9**	Condition[a]	Isolated yield (%)[b] **10b—g**
5b		10	A	 66
5c		10	A	 89
5d		20	B	 74
5e		20	B	 97
5f		20	B	 63[c]
5g		10	C	 56

a) As in Table 1. b) Based on **9**. c) Consists of two diastereoisomers isolated in 29 and 34% yields, respectively.

6c: Mp 110—112 °C; IR 1720, 1300, 1200, 1140 cm^{-1}; NMR ($CDCl_3$) δ 1.6—3.2 (m, 6H), 2.43 (s, 3H), 3.61 (s, 3H), 3.66 (s, 3H), 6.97 (m, 1H), 7.30 (d, 2H, J=9 Hz), 7.69 (d, 2H, J=9 Hz). Found: C, 58.11; H, 5.62; S, 9.11%. Calcd for $C_{17}H_{20}O_6S$: C, 57.95; H, 5.72; S, 9.08%.

*Methyl 1-Methyl-4-(*p*-tolylsulfonyl)-3-cyclohexene-1-carboxylate (**6d**).* A mixture of **2** (273 mg, 1 mmol), methyl 2-methylpropenoate (**5d**, 2.002 g, 20 mmol), pyridine (79 mg, 1 mmol), and a catalytic amount of hydroquinone in xylene (5 ml) was heated at 140—150 °C in a sealed tube for 2 h. After addition of ethyl acetate, the solution was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was separated by preparative TLC to afford **6d** (287 mg) in 93% yield. Recrystallization from hexane gave pure **6d**: mp 72.5—73 °C; IR 1720, 1300, 1155, 1125 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.5—3.1 (m, 6H), 2.39 (s, 3H), 3.53 (s, 3H), 6.95 (m, 1H), 7.27 (d, 2H, J=9 Hz), 7.68 (d, 2H, J=9 Hz). Found: C, 62.38; H, 6.56%. Calcd for $C_{16}H_{20}O_4S$: C, 62.32; H, 6.54%.

In a similar manner, cycloadducts **6e—i** were obtained from **2** and the corresponding dienophiles **5e—i** in good yields (Table 1).

6e: Mp 58—60 °C; IR 1728, 1300, 1290, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.2—2.7 (m, 7H), 2.42 (s, 3H), 3.62 (s, 3H), 6.96 (m, 1H), 7.27 (d, 2H, J=9 Hz), 7.69 (d, 2H, J=9 Hz). Found: C, 61.14; H, 6.14%. Calcd for $C_{15}H_{18}O_4S$: C, 61.21; H, 6.17%.

6f: Mp 110—111 °C; IR 2230, 1285, 1140 cm^{-1}; NMR ($CDCl_3$) δ 1.6—3.2 (m, 7H), 2.39 (s, 3H), 6.90 (m, 1H), 7.30 (d, 2H, J=9 Hz), 7.69 (d, 2H, J=9 Hz). Found: C, 64.37; H, 5.70; N, 5.34%. Calcd for $C_{14}H_{15}NO_2S$: C, 64.36; H, 5.79; N, 5.36%.

6g: Mp 126—127 °C; IR 1295, 1280, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.5—3.2 (m, 7H), 2.45 (s, 3H), 7.16 (m, 1H), 7.32 (m, 5H), 7.43 (d, 2H, J=9 Hz), 7.91 (d, 2H, J=9 Hz). Found: C, 72.98; H, 6.47%. Calcd for $C_{19}H_{20}O_2S$: C, 73.06; H, 6.45%.

6h: Oil; IR 1725, 1290, 1150 cm^{-1}; NMR ($CDCl_3$) δ 1.5—2.7 (m, 7H), 2.38 (s, 3H), 6.95 (m, 1H), 7.24 (d, 2H, J=9 Hz), 7.64 (d, 2H, J=9 Hz), 9.55 (s, 1H). *Semicarbazone of **6h***: mp 217—218 °C (dec). Found: C, 55.95; H, 6.15; N, 13.03%. Calcd for $C_{15}H_{20}N_3O_3S$: C, 55.89; H, 6.25; N, 13.04%.

6i: Oil; IR 1700, 1310, 1295, 1280, 1140 cm^{-1}; NMR ($CDCl_3$) δ 1.2—2.7 (m, 7H), 2.12 (s, 3H), 2.38 (s, 3H), 6.94 (m, 1H), 7.23 (d, 2H, J=8 Hz), 7.63 (d, 2H, J=8 Hz). *Semicarbazone of **6i***: mp 218—219 °C. Found: C, 57.39; H, 6.35; N, 12.39%. Calcd for $C_{16}H_{21}N_3O_3S$: C, 57.30; H, 6.31; N, 12.53%.

*Reduction of **6d**.* A methanol solution of **6d** (155 mg, 0.5 mmol) and boron trifluoride etherate (142 mg, 1 mmol) was shaken vigorously under hydrogen atmosphere in the presence of Pd–C as a catalyst. After the usual treatment, the reduction product, methyl 1-methyl-4-(*p*-tolylsulfonyl)-1-cyclohexanecarboxylate, was separated by preparative TLC in a 71% (111 mg) yield. Recrystallization from hexane gave the pure compound: mp 122—123 °C; IR 1735, 1300, 1145 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 21.6 (q, 1C), 23.1 (t, 2C), 27.7 (q, 1C), 34.3 (t, 2C), 42.8 (s, 1C), 51.9 (q, 1C), 62.7 (d, 1C), 128.9 (d, 2C), 129.6 (d, 2C), 134.2 (s, 1C), 144.5 (s, 1C), 176.3 (s, 1C). Found: C, 62.06; H, 7.04%. Calcd for $C_{16}H_{22}O_4S$: C, 61.92; H, 7.15%.

Similarly, the reduction product of **6e**, methyl 4-(*p*-tolyl-

sulfonyl)-1-cyclohexanecarboxylate, was obtained: mp 102—104 °C; IR 1728, 1285, 1150 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 21.6 (q, 1C), 22.3 (t, 2C), 25.8 (t, 2C), 38.3 (d, 1C), 51.8 (q, 1C), 62.6 (d, 1C), 128.9 (d, 2C), 129.7 (d, 2C), 134.3 (s, 1C), 144.5 (s, 1C), 174.2 (s, 1C). Found: C, 61.04; H, 6.95%. Calcd for $C_{15}H_{20}O_4S$: C, 60.80; H, 6.80%.

The structures of **6f** and **6h** were confirmed by transformation into **6e**. They were hydrolyzed or oxidized to 4-(*p*-tolylsulfonyl)-3-cyclohexene-1-carboxylic acid giving **6e** by subsequent esterification with diazomethane. Their melting points and spectral data were identical with those of **6e**.

*Reduction of **6g**.* To a solution of **6g** (56 mg, 0.18 mmol) in THF–methanol (1:1) was added excess sodium borohydride at room temperature until **6g** disappeared on TLC. After the usual treatment, the reduction product, 1-phenyl-4-(*p*-tolylsulfonyl)cyclohexane, was separated by preparative TLC in a nearly quantitative yield (56 mg). Recrystallization from ethanol gave the pure compound: mp 153—154 °C; IR 1305, 1270, 1140 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 21.6 (q, 1C), 25.9 (t, 2C), 32.6 (t, 2C), 43.1 (d, 1C), 63.0 (d, 1C), 126.3 (d, 1C), 126.5 (d, 2C), 128.4 (d, 2C), 129.0 (d, 2C), 129.7 (d, 2C), 134.3 (s, 1C), 144.5 (s, 1C), 145.7 (s, 1C). Found: C, 72.27; H, 7.02%. Calcd for $C_{19}H_{22}O_2S$: C, 72.59; H, 7.05%.

Similarly, the dimer **4** was reduced to 1,4-bis(*p*-tolylsulfonyl)-4-vinylcyclohexane: mp 226—228 °C; IR 1280, 1140 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 20.9 (t, 2C), 21.6 (q, 2C), 27.2 (t, 2C), 62.0 (d, 1C), 67.0 (s, 1C), 123.8 (t, 1C), 128.8 (d, 2C), 129.1 (d, 2C), 129.8 (d, 2C), 130.9 (d, 2C), 131.5 (s, 1C), 132.6 (d, 1C), 134.1 (s, 1C), 144.8 (s, 1C). Found: C, 62.97; H, 6.02%. Calcd for $C_{22}H_{26}O_4S_2$: C, 63.15; H, 6.26%.

1-Acetyl-4-(p-tolylsulfonyl)cyclohexane. To a methanol solution of ***6i*** (278 mg, 1 mmol) was added excess sodium borohydride at room temperature. After evaporation, water and then ethyl acetate were added to the residue. The organic layer was separated, dried over Na_2SO_4, and concentrated to give crude 1-[4-(*p*-tolylsulfonyl)cyclohexyl]ethanol, which was further oxidized with Jones reagent. After the usual treatment, 1-acetyl-4-(*p*-tolylsulfonyl)cyclohexane was separated by preparative TLC in a 96% (268 mg) yield. Recrystallization from aqueous ethanol gave the pure compound: mp 110—112 °C; IR 1705, 1280, 1140 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 21.6 (q, 1C), 24.8 (t, 2C), 26.9 (t, 2C), 28.2 (q, 1C), 49.7 (d, 1C), 62.5 (d, 1C), 128.9 (d, 2C), 129.7 (d, 2C), 134.0 (s, 1C), 144.7 (s, 1C), 210.2 (s, 1C). Found: C, 64.18; H, 7.26%. Calcd for $C_{15}H_{20}O_3S$: C, 64.27; H, 7.19%.

*4-(p-Tolylthio)-2-sulfolene (**8**).* To a methanol solution (4 ml) of **7** (394 mg, 2 mmol) prepared according to the procedure of Bailey and Cummins[3] was added dropwise a mixture of *p*-toluenethiol (248 mg, 2 mmol) and 1 M NaOH (2 ml, 2 mmol) with stirring at room temperature. After being stirred for 3 h, the reaction mixture was concentrated. Dichloromethane was added to the concentrate which was then washed with water, and dried over Na_2SO_4. The residue obtained by evaporation was separated by preparative TLC to afford **8** in a 69% (331 mg) yield: oil; IR 1305, 1145 cm^{-1}; NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.09 (dd, 1H, J=5 and 14 Hz), 3.55 (dd, 1H, J=8 and 14 Hz), 4.30 (m, 1H), 6.55 (m, 2H), 7.05 (d, 2H, J=8 Hz), 7.27 (d, 2H, J=8 Hz).

*3-(p-Tolylsulfinyl)-3-sulfolene (**9**).* To a methanol solution (4 ml) of **8** (440 mg, 1.8 mmol) was added dropwise an aqueous solution (2 ml) of sodium periodate (385 mg, 1.8 mmol) with stirring at room temperature. After being stirred for 3 days, the resulting precipitate was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was redissolved in dichloromethane, and the solution was dried over Na_2SO_4. After concentration, the residue was separated by preparative TLC to afford **9** in a 75% (354 mg) yield. Recrystallization from ethanol gave the pure compound: mp 146—147 °C; IR 1300, 1130, 1050 cm^{-1}; NMR (DMSO-d_6) δ 2.36 (s, 3H), 3.63 (m, 2H), 4.08 (m, 2H), 6.81 (m, 1H), 7.31 (d, 2H, J=9 Hz), 7.50 (d, 2H, J=9 Hz). Found: C, 51.54; H, 4.43%. Calcd for $C_{11}H_{12}O_3S_2$: C, 51.56; H, 4.72%.

*Diels-Alder Reaction of **9**.* The Diels-Alder reaction of **9** with dienophiles **5b**—**g** was carried out in a similar manner to that for **2**. The structure of cycloadducts **10b**—**g**, all of which were oil, containing diastereoisomers based on the chiral center of sulfoxide group, were confirmed by transformation into the corresponding sulfones **6b**—**g** by oxidation with a mixture of acetic acid and hydrogen peroxide. The melting points and spectral data of the oxidation products were the same as those of the authentic **6b**—**g** prepared by Diels-Alder reaction of **2**.

Particularly in the case of 4-(*p*-tolylsulfinyl)-3-cyclohexene-1-carbonitrile (**10f**), two diastereoisomers were isolated by TLC in 29% and 34% yields, respectively. They were converted into 4-(*p*-tolylsulfonyl)-3-cyclohexene-1-carbonitrile (**6f**) by the oxidation in nearly 95% yields.

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