dried (Na_2SO_4), was evaporated to an oily product. This oil, on chromatography over silica with hexane–acetone (7:3), gave **3**: 2.1 g (68%); mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 2.81 (s, 3 H, NCH_3), 4.95 (s, 2 H, CH_2Ph), 7.38 (s, 5 H, phenyl), 10.05 (br s, 1 H, NH).

Acknowledgment. We express appreciation to the National Institutes of Health (General Medical Sciences, Grant GM 26711) for support of this research and to the Colorado State University Regional NMR Center, funded by National Science Foundation Grant No. CHE 78-18581, for 360-MHz NMR spectra.

Registry No. 1a, 79722-09-1; **1b**, 27786-77-2; **1c**, 79722-10-4; **1d**, 79722-11-5; **1e**, 79722-12-6; **1f**, 79722-13-7; **2a**, 79722-14-8; **2b**, 79722-15-9; **2c**, 79722-16-0; **2d**, 79722-17-1; **2e**, 79722-18-2; **2f**, 79722-19-3; **3**, 79735-23-2; **4**, 79722-20-6; **5**, 22513-22-0; **7**, 16948-16-6; *O*-benzylhydroxylamine, 622-33-3; *N*-(*tert*-butoxycarbonyl)-*O*-benzylhydroxylamine, 79722-21-7; di-*tert*-butyl carbonate, 34619-03-9; *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*O*-benzylhydroxylamine, 79722-22-8; *N*-Boc-L-alanine, 15761-38-3; *N*-Cbz-L-alanine, 1142-20-7; *N*-Boc-L-valine, 13734-41-3; *N*-Boc-*O*-bzl-L-serine, 23680-31-1; *N*-Boc-β-bzl-L-aspartic acid, 7536-58-5; *N*-Boc-γ-bzl-L-glutamic acid, 13574-13-5.

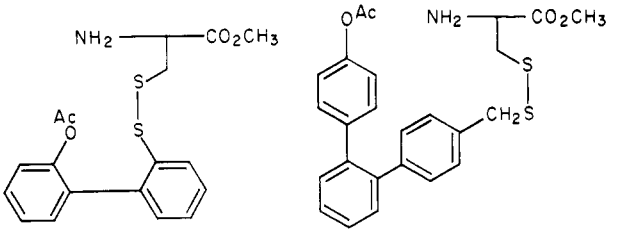
Convenient Routes to 4,4″-Functionalized *o*-Terphenyls and 2,2′-Functionalized Biphenyls

G. Hanson and D. S. Kemp*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received September 16, 1981

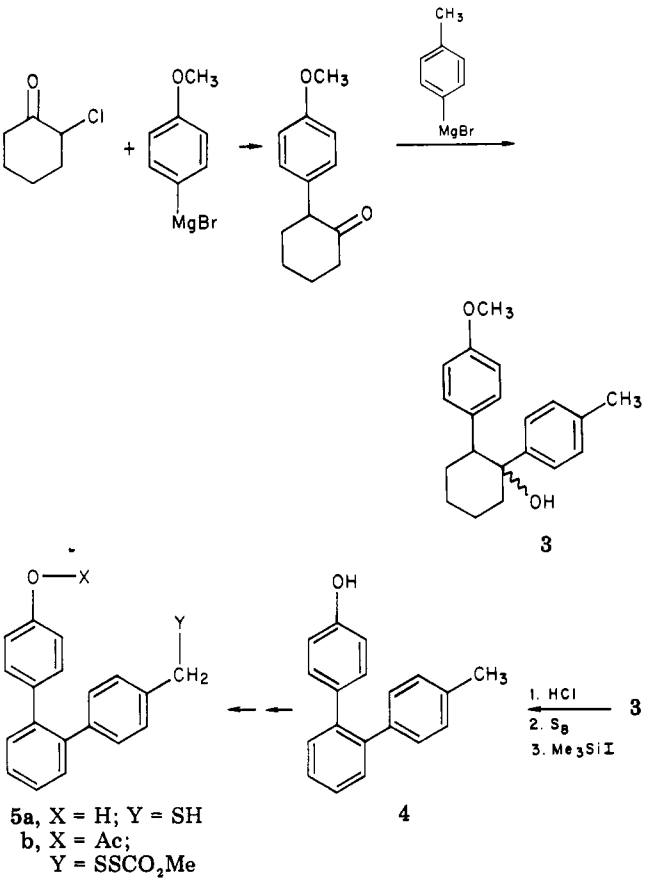
Elsewhere[1,2] we have described a thiol capture strategy for the amide bond-forming step of peptide synthesis and have reported a successful first test of the strategy in the form of a synthesis of a protected derivative of the peptide hormone somatostatin.[3] A key step in the thiol capture process involves an intramolecular acyl transfer involving a medium-sized ring containing a disulfide or a sulfur–mercury bond. Efficient transfer has been shown[2] to require precise geometries, and we here report synthesis of two molecular frameworks, **1** and **2**, which fail to undergo detectable intramolecular acyl transfer and therefore do not meet the geometrical requirements. The syntheses of these species required new routes to functionalized 2,2′-substituted biphenyls and 4,4″-substituted *o*-terphenyls, and these are here reported.



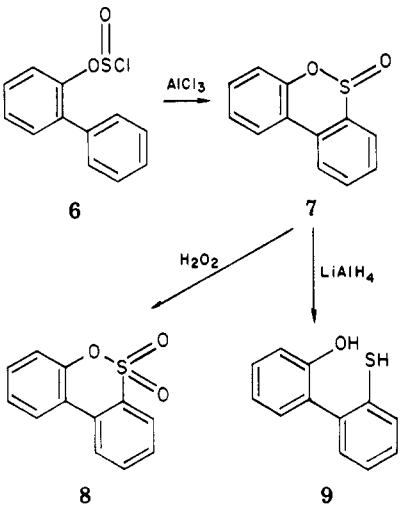
1 2

Although various derivatives of the *o*-terphenyl ring system have been reported, few are known in which both terminal rings are functionalized. Useful synthetic entries

Scheme I



Scheme II



are 2-arylcyclohexanones, reported by Bachmann[4] to result conveniently from the reactions of aryl Grignard reagents with 2-chlorocyclohexanone. Our reaction sequence is outlined in Scheme I.

The dehydrogenation step proceeded satisfactorily only with sulfur fusion; palladium catalysts in our hands resulted in erratic and scale-dependent yields, and also formed the hydrogenolysis product of **3** as a byproduct that was difficult to remove. Subsequent functionalization of the dehydrogenation product followed routine paths. Demethylation with trimethylsilyl iodide gave **4**; acetylation followed by bromination (NBS), and treatment with

(1) Kemp, D. S.; Kerkman, D. J.; Hanson, G.; Leung, S.-L. *J. Org. Chem.* **1981**, *46*, 490. Kemp, D. S.; Kerkman, D. J.; Leung, S.-L. *Tetrahedron Lett.* **1981**, *22*, 181.
(2) Kemp, D. S. *Biopolymers* **1981**, *20*, 1793.
(3) Kemp, D. S.; Galakatos, N.; Bolin, D. "Proceedings of the 7th American Peptide Symposium", Pierce Chemical Co., in press.
(4) Bachmann, W. F.; Fujimoto, G. I.; Nick, L. B. *J. Am. Chem. Soc.* **1950**, *72*, 1995.

0022-3263/81/1946-5441$01.25/0

NaSH gave **5a**. Reaction with methoxyoxomethanesulfenyl chloride (ScmCl)[5] and acetic anhydride gave **5b**. Treatment of this species with Boc-L-Cys-OMe followed by HCl produced disulfide **2** as a hydrochloride salt.

Our route to **1** proceeds from the chlorosulfite ester **6** of *o*-hydroxybiphenyl, which is commercially available. Treatment of **6** with aluminum chloride results in a novel cyclization to the biphenosultine **7**, which was characterized by oxidation to **8** with hydrogen peroxide in acetic acid. This reaction, reduction to the desired *o*-mercapto-*o'*-hydroxybiphenyl (**9**), and direct spectroscopic comparison distinguish **7** from its isomer, dibenzothiophene sulfone. The conversion of **6** to **7** is to our knowledge the first example of remote functionalization by aromatic sulfinylation, although an aliphatic case can be cited as a precedent.[6] More obvious routes to **9** involving *o*-alkoxy-*o'*-diazoniumbiphenyls result primarily in cyclization to dibenzofurans.[7]

Conversion of **9** to **1** was effected by a route similar to that used for converting **5a** to **2**. Allowing either **1** or **2** to remain for periods of days at 25 °C in DMF solution resulted only in a slow disulfide interchange with no trace of the desired amide. Since the unsymmetrical disulfide is an important constituent of the mixture at equilibrium, failure to observe intramolecular acyl transfer in structures **1** and **2**, which meet many of the required structural features[1] for transfer, can probably be attributed to their flexibility. Rigidity appears to be a requirement for efficient transfer.[1,2]

Experimental Section

Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared (IR) spectra, reported in centimeters^{-1}, were recorded on a Perkin-Elmer 567 or 283B grating infrared spectrophotometer. The NMR (^{1}H) spectra were taken on either a Varian T-60 or an Hitachi Perkin-Elmer R24B and are reported (δ) in parts per million downfield from internal tetramethylsilane unless otherwise noted. The following abbreviations for NMR spin multiplicity are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Coupling constants, J values, are expressed in hertz. Low-resolution mass spectra were determined on a Varian MAT-44. For these spectra, the m/e value is given followed in parentheses by the intensity expressed as a percentage of the base peak. High-resolution mass spectra were obtained courtesy of Dr. C. E. Costello (M.I.T.). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

4-Hydroxy-4″-methyl-*o*-terphenyl (4). *p*-Bromotoluene (2 g, 11 mmol) in ether (10 mL) was added dropwise to a mixture of magnesium (0.38 g, 15 mmol) and ether (10 mL) under argon at room temperature. After the mixture was stirred for 2 h, a solution of 2-(4-methoxyphenyl)cyclohexanone[4] (2.3 g, 11 mmol) in ether/THF (1:1, 20 mL) was added dropwise to the Grignard reagent, and the exothermic reaction was allowed to stir for 12 h. The mixture was acidified with aqueous HCl and then extracted with ether (50 mL). The organic layer was separated and washed with water and dried (Na_2SO_4), and the solvent was evaporated under aspirator vacuum. The crude oil so obtained was purified to some extent by distillation (Kugelrohr, 170 °C, 0.1 mm) to give **3** (2.2 g, 67%), mixed with starting ketone, as a colorless, viscous oil: IR (film) 3500, 3000, 2950, 1710 (ketone), 1610, 1510, 1440, 1250 cm^{-1}; mass spectrum, m/e 296 (M$^+$, 32), 160 (39), 121 (100); NMR ($CDCl_3$) δ 1.5–2.2 (m, 9 H), 2.3 (s, 3 H), 3.0 (s, 1 H), 3.75 (s, 3 H), 3.80 (s, 1 H, ketone OCH_3), 6.5–7.2 (m, 8 H).

The crude alcohol **3** (3 g, 10 mmol) was dissolved in methylene chloride (20 mL) and subjected to a stream of dry HCl gas for 2 min. The mixture turned orange and deposited droplets of water. The solution was dried (Na_2SO_4) and the solvent evaporated at reduced pressure to give an oil, whose IR spectrum showed no hydroxyl band at 3300 cm^{-1}. This material was quickly distilled (Kugelrohr, 200 °C, 0.1 mm) to give a colorless oil (3 g), which was heated with elemental sulfur (0.87 g) under argon at 220 °C for 35 min. The crude mass was chromatographed on silica (248 g; petroleum ether/ether, 7:1), to yield, as a pale yellow oil, 4-methoxy-4″-methyl-*o*-terphenyl: 1.67 g, 60%; IR ($CHCl_3$) 3050, 3000, 2920, 2840, 1609, 1575, 1505, 1474, 1242; mass spectrum, m/e 274 (M$^+$, 100), 215 (57), 107 (34); NMR ($CDCl_3$) δ 2.40 (s, 3 H), 3.92 (s, 3 H), 6.95–7.70 (m, 12 H).

The above oil (1.6 g, 5.8 mmol) was mixed with chloroform (20 mL) and to this was added in portions trimethylsilyl iodide (2 mL). This mixture was refluxed for 48 h and then quenched with MeOH (2 mL). The volatile organics were evaporated at reduced pressure, and the resulting residue chromatographed on silica (130 g; petroleum ether/ether, 7:1). The starting methoxy compound was recovered (126 mg), and when ether was used as eluant, crystalline **4** (1.10 g, 72%) was obtained. Recrystallization from cyclohexane gave colorless needles: mp 120–121 °C; IR ($CHCl_3$) 3580, 3000, 2920, 1611, 1510, 1474, 1250, 1170; mass spectrum m/e 260 (M$^+$, 98), 245 (38), 215 (30), 197 (67); NMR ($CDCl_3$) δ 2.32 (s, 3 H), 4.90 (s, 1 H, slowly exchangeable with D_2O), 6.59–7.40 (m, 12 H); UV λ_{max} (CH_3OH) 242 nm (ϵ 26 000).

Anal. Calcd for $C_{19}H_{16}O$: C, 87.6; H, 6.2. Found: C, 87.3; H, 6.5.

4-Acetoxy-4″-[[(methoxycarbonyl)dithio]methyl]-*o*-terphenyl (5b). A solution of **4** (32 mg, 0.12 mmol) in acetic anhydride (1 mL) was treated briefly with HCl gas. The solution was stirred at room temperature for 3 h and then the solvent was evaporated under high vacuum. The residue was taken up in ether, washed with saturated $NaHCO_3$ and water, and dried (Na_2SO_4). The ether was removed with a rotary evaporator to give the acetate (27 mg, 72%) as an oil: IR ($CHCl_3$) 3000, 1750, 1479, 1374, 1192, 1169, 1010 cm^{-1}; NMR ($CDCl_3$) δ 2.34 (s, 3 H), 2.36 (s, 3 H), 6.81–7.40 (m, 12 H); UV λ_{max} (CH_3OH) (ϵ 26 000).

The above acetate (0.5 g, 1.65 mmol) was mixed with *N*-bromosuccinimide (0.32 g, 1.8 mmol), azobis(isobutyronitrile) (3 mg), and carbon tetrachloride (15 mL), and this mixture was illuminated with a 250-W incandescent bulb. The mixture was allowed to reflux for 25 min, at which point the NBS had been fully converted to succinimide. The resulting filtrate was evaporated to give crude benzylic bromide as a brown oil, suitable for use in the next step: NMR ($CDCl_3$) δ 2.25 (s, 3 H), 4.45 (s, 2 H), 6.9–7.5 (m, 12 H); mass spectrum m/e 383 (M$^+$, 1), 380 (M$^+$, 1), 259 (38).

To a solution of NaSH, prepared by adding NaH (0.4 g) to ethanol (5 mL) and bubbling in H_2S for 15 min, was added the above benzylic bromide dropwise in ether/ethanol (3 mL, 1:2). A precipitate formed as the mixture was heated to reflux under an atmosphere of H_2S. After 20 min, ethanol (10 mL) was added to bring about homogeneity, heating was continued for 3 h, the mixture was cooled, and aqueous HCl (1 N, 20 mL) was added cautiously. The mixture was then extracted with ethyl acetate (20 mL), washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated to give a dark oil, containing ca. 60% 4-hydroxy-4″-(mercaptomethyl)-*o*-terphenyl (**5a**): NMR ($CDCl_3$) δ 1.70 (t, J = 7 Hz, 1 H), 3.74 (d, J = 7 Hz), 6.6–7.4 (m, 19 H).

The crude thiol **5a** was dissolved in methanol (5 mL) and treated under argon with methoxyoxomethanesulfenyl chloride[5] (ScmCl, 150 μL); after 10 h at 25 °C, the methanol was evaporated, and a dark oil (568 mg) was obtained. Careful chromatography on silica (40 g; ether/petroleum ether, 1:1) gave a pure Scm phenol (408 mg, 65% from acetylated **4**): IR ($CHCl_3$) 3600, 3450, 3030, 1730, 1611, 1511, 1475, 1435, 1150 cm^{-1}; NMR ($CDCl_3$) δ 3.80 (s, 3 H), 3.95 (s, 2 H), 6.60–7.4 (m, 13 H); mass spectrum, m/e 382 (M$^+$, 0.5), 259 (100).

The above Scm phenol (295 mg, 0.77 mmol) was dissolved in dry pyridine (2 mL) containing acetic anhydride (0.315 mL) and the solution was stirred under argon for 5 h. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate, washed with citric acid (0.5 M, 2 × 10 mL), water and brine, and dried (Na_2SO_4). After solvent removal, a pale yellow oil, **5b** 283 mg, 87%, was obtained, which was pure by TLC analysis: IR ($CDCl_3$) 1740, 1200, 1146 cm^{-1}; NMR ($CDCl_3$) δ 2.21 (s, 3 H), 3.78 (s, 3 H), 3.90 (s, 2 H), 6.90–7.4 (m, 12 H); high-

(5) Brois, S. J.; Pilot, J. F.; Barnum, H. W. *J. Am. Chem. Soc.* **1970**, 7629.
(6) Dhami, K. S. *Chem. Ind. (London)* **1968**, 1004.
(7) Mascarelli, L.; Pirona, M. *Chem. Abstr.* **1938**, *32*, 6238.

resolution mass spectrum calcd for $C_{23}H_{20}O_4S_2$ 424.080, found 424.079.

2-Hydroxybiphenyl-2'-sulfinic Acid δ-Sultine (7). *o*-Hydroxybiphenyl (1 g, 5.9 mmol) in methylene chloride (5 mL) was added to thionyl chloride (0.47 mL, 6.4 mmol) in methylene chloride (5 mL) at 0 °C under dry argon. Triethylamine (0.82 mL, 5.8 mmol) was added dropwise over a period of 5 min. This mixture was stirred at 0 °C for 15 min and at 25 °C for an additional 15 min before being filtered by suction and subsequent dropwise addition over a 15-min period to a vigorously stirred suspension of aluminum chloride (1.6 g, 12 mmol) in methylene chloride (50 mL at 0 °C under dry argon). The dark green solution was stirred at 0 °C for 1 h and at 25 °C for 12 h. Addition of water (50 mL), filtration, acid wash (30 mL, 3 N), drying (Na_2SO_4), and solvent evaporation led to a red-orange oil (0.85 g) which readily crystallized: mp 92–96 °C. Distillation (Kugelrohr, 180 °C, high vacuum) gave a yellowish oil (0.65 g, 51%), crystallizing as thin prisms: mp 94–97 °C. An analytical sample was prepared by first heating (50–60 °C) under vacuum to drive off a yellow impurity and then recrystallizing the residue from MeOH several times to yield colorless prisms of **7**, mp 95.5–97 °C, indefinitely stable in air: NMR ($CDCl_3$) δ 7.1–8.1 (m); IR ($CHCl_3$) 3070, 3010, 1590, 1474, 1181, 1140, 1125, 1110 cm^{-1}; mass spectrum, *m/e* 216 (M^+, 100), 188 (71), 187 (73), 168 (68), 160 (57), 152 (1.5), 139 (82); high resolution mass spectrum calcd for $C_{12}H_8O_2S$ 216.024, found 216.023.

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.6; H, 3.7; S, 14.8. Found: C, 66.7; H, 3.9; S, 14.7.

Dibenzo-1,2-oxathiin 2,2-Dioxide (8). A mixture of **7** (46 mg, 0.2 mmol), acetic acid (2 mL), and 30% hydrogen peroxide (0.2 mL) was refluxed for 2 h. Cooling and addition of ice caused deposition of small crystals of **8**: 41 mg, 83%; mp 108–110 °C; IR ($CHCl_3$) 1475, 1380, 1180, 870 cm^{-1}; mass spectrum, *m/e* 232 (M^+, 46), 163 (43), 139 (100). Sublimation (90 °C, 0.1 mm) gave an analytical sample: mp 109–111 °C.

Anal. Calcd for $C_{12}H_8O_3S$: C, 62.1; H, 3.5; S, 13.8. Found: C, 62.2; H, 3.5; S, 14.1.

2-Mercapto-2'-hydroxybiphenyl (9). Biphenosultine **7** (200 mg, 0.93 mmol) in anhydrous ether (10 mL) was added dropwise to a slurry of $LiAlH_4$ (100 mg) in ether (10 mL), and this mixture was stirred at 25 °C for 3 h. Aqueous HCl (3 N, 10 mL) was cautiously added, and the ether layer was separated, dried (Na_2SO_4), and evaporated to give crude thiol **9** as a pale yellow oil. Distillation (Kugelrohr, 140 °C, high vacuum) of the crude material gave pure **9** as a colorless oil: 175 mg, 94%; IR ($CHCl_3$) 3542, 3000, 2578, 1582, 1491, 1465, 1330, 1284, 1176 cm^{-1}; NMR ($CDCl_3$) δ 3.0–5.2 (brs, 2 H), 6.90–7.40 (m, 8 H); high-resolution mass spectrum calcd for $C_{12}H_{10}OS$ 202.045, found 202.043.

Anal. Calcd for $C_{12}H_{10}OS$: C, 71.3; H, 5.0; S, 15.8. Found: C, 71.4; H, 5.1; S, 15.7.

Preparation of Unsymmetrical Disulfide Hydrochlorides 1 and 2. The Scm acetate was mixed with methyl *N-tert*-butyloxycarbonyl-L-cysteinate (1 equiv) in methanol/chloroform (1:1) under nitrogen. To this solution was added triethylamine (1 equiv), and the mixture was stirred for 2 h at 25 °C. The solvent was evaporated and the residue was taken up in ethyl acetate, which was then washed with cold citric acid (0.5 M), water, and brine, and dried (Na_2SO_4). After solvent evaporation, the crude oil obtained was purified by preparative layer chromatography on silica (ether). The purified material was then treated with saturated HCl in dioxane at room temperature for 20 min. Freezing and lyophilization gave the hydrochlorides **1** or **2** as white powders.

Compound 1: mp 79–90 °C dec; NMR (DMF-d_7) δ 2.30 (s, 3 H), 3.40 (brd, 2 H), 3.80 (s, 3 H), 4.15 (s, 2 H), 4.40 (m, 1 H), 7.0–7.6 (m, 12 H); IR ($CHCl_3$) 3200–2400, 1746 cm^{-1}.

Compound 2: NMR (DMF-d_7) δ 2.00 (s, 3 H), 3.6 (m, 2 H), 3.7 (s, 3 H), 4.40 (m, 1 H), 7.1–8.2 (m, 10 H); mass spectrum, *m/e* 377 (M^+ – HCl, 0.9), 378 (0.3), 379 (0.2).

Acyl-Transfer Experiments. NMR Method. Hydrochloride **1** or **2** was dissolved in DMF-d_7 and treated with triethylamine (1 equiv) to liberate the free base. The reaction was monitored by NMR spectroscopy (regions δ 1.9–2.5 and 6.8–7.1). Observation was carried out for 5 days at room temperature. Concentrations of amine were typically 0.1 M. At the conclusion of the NMR runs, the solvent was evaporated and the crude mixture was purified by preparative layer chromatography, giving predominantly symmetrical disulfide bearing an intact ester residue. Detection of 5% of amide is possible by this method.

IR Method. Hydrochloride **1** or **2** was deprotonated with aqueous potassium carbonate, and the free amine was extracted and dissolved in acetonitrile, and the solution (0.1 M) was placed in an IR cell. The IR region from ca. 1750 to 1660 cm^{-1} was observed for a period of ca. 5 days.

Acknowledgment. Financial support from the National Institutes of Health (GM 13453-15) is gratefully acknowledged.

Registry No. 1, 79664-38-3; **1**·HCl, 79664-39-4; **2**, 79664-40-7; **2**·HCl, 79664-41-8; **3**, 79664-42-9; **4**, 79664-43-0; **4** acetate, 79664-44-1; **5a**, 79664-45-2; **5b**, 79664-46-3; **5** (X = Ac, Y = Br), 79664-47-4; **5** (X = H, Y = $SSCO_2Me$), 79664-48-5; **6**, 79664-49-6; **7**, 77123-91-2; **8**, 4371-25-9; **9**, 79664-50-9; *p*-bromotoluene, 106-38-7; 2-(4-methoxyphenyl)cyclohexanone, 37087-68-6; 4-methoxy-4''-methyl-*O*-terphenyl, 79664-51-0; methoxyoxomethanesulfenyl chloride, 26555-40-8; *O*-hydroxybiphenyl, 90-43-7; methyl *N-tert*-butyloxycarbonyl-L-cysteinate, 55757-46-5.

Reaction of a Selenosulfonate with Diazomethane. Unexpected Photochemical Formation of a β-Selenosulfone[1]

Thomas G. Back

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4

Received September 2, 1981

Insertions of diazo compounds into the Se–Se, Se–CH_2, or Se–X linkage of diselenides,[2] allyl phenyl selenide (with arrangement),[3] or selenenyl halides[3,4] (X = Cl or Br), respectively, have recently been reported. However, similar reactions with other organoselenium compounds have yet to be investigated. In this laboratory, current interest in the chemistry of selenosulfonates[5] (RSO_2SeR) prompted the present study of the reaction of *Se*-phenyl *p*-toluene-selenosulfonate (**1**) with diazomethane.

When a dichloromethane solution of **1** was treated with excess ethereal diazomethane at room temperature in the presence of normal fluorescent laboratory lighting, gradual evolution of nitrogen was observed. The reaction proceeded vigorously when performed near a 100-W incandescent light bulb and the selenosulfonate was consumed within 30 min. Surprisingly, the major product was not one of monoinsertion of methylene into **1** but rather the β-(phenylseleno)ethyl sulfone **2** (Scheme I), isolated in 60% yield. Selenosulfonate **1** also reacted with excess diazomethane at room temperature in the dark, although a longer reaction time was required. Under these conditions, however, none of the previous product **2** was formed. Instead, a mixture of sulfone **3** and sulfinate esters **4** and **5**

(1) Financial assistance from the Natural Sciences and Engineering Research Council and from the Research Corporation is gratefully acknowledged.

(2) (a) Petragnani, N.; Schill, G. *Chem. Ber.* **1970**, *103*, 2271. (b) Pellicciari, R.; Curini, M.; Ceccherelli, P.; Fringuelli, R. *J. Chem. Soc., Chem. Commun.* **1979**, 440.

(3) Giddings, P. J.; John, D. I.; Thomas, E. J. *Tetrahedron Lett.* **1980**, 395, 399.

(4) (a) Buckley, D. J.; Kulkowit, S.; McKervey, A. *J. Chem. Soc., Chem. Commun.* **1980**, 506. (b) Petragnani, N.; Rodrigues, R.; Comasseto, J. V. *J. Organomet. Chem.* **1976**, *114*, 281.

(5) (a) Back, T. G.; Collins, S. *Tetrahedron Lett.* **1980**, 2213. (b) *Ibid.* **1980**, 2215. (c) Back, T. G.; Collins, S. *J. Org. Chem.* **1981**, *46*, 3249.

0022-3263/81/1946-5443$01.25/0