Efficient Selenation of Quinones: Synthesis of Novel Benzo[*b*]naphtho[2,3-*e*]selenintrione and Dibenzo[*b*,*e*]seleninone

Makoto SAKAKIBARA, Takeshi TORU, Takahiro IMAI, Yoshihiko WATANABE, and Yoshio UENO*
Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466
(Received January 23, 1992)

Selenation of 2-bromonaphthoquinone with an areneselenolate ion generated from bis(2-methoxycarbonylphenyl) diselenide, chlorodiphenylphosphine, and LiOH afforded 2-[(2-methoxycarbonylphenyl)seleno]-1,4-naphthoquinone from which 12*H*-benzo[*b*]naphtho[2,3-*e*]selenin-6,11,12-trione was synthesized. 1,4-Dimethoxy-2,3-dimethyl-10*H*-dibenzo[*b*,*e*]selenin-10-one was prepared starting from 6-bromo-2,3-dimethylbenzoquione through the selenation and cyclization steps.

Previously we reported a new, efficient method for generation of benzeneselenolate ion by treatment of diphenyl diselenide with tributylphosphine and aqueous NaOH.[1] This procedure is extremely efficient especially for the synthesis of 2-arylseleno-1,4-naphthoquinones compared with other selenation methods.[2] We also demonstrated that bis(2-amino-3-pyridyl) diselenide could be used as a selenating reagent in the synthesis of naphtho[2,1-*b*]pyrido[3,2-*e*][1,4]selenazines.[3] We herein describe the selenation of 2-bromo-1,4-naphthoquinone (**1**) with bis(2-methoxycarbonylphenyl) diselenide (**2**), and the transformation of the 2-arylseleno-1,4-naphthoquinone into 12*H*-benzo[*b*]naphtho[2,3-*e*]-selenin-6,11,12-trione (**4**) which is a new selenium analog of the biologically active xanthocycline nucleus.[4] We also describe the synthesis of 1,4-dimethoxy-2,3-dimethyl-10*H*-dibenzo[*b*,*e*]selenin-10-one (**10**).

Results and Discussion

Selenation of 2-Bromo-1,4-naphthoquinone (1). We initially tried the selenation of 2-bromo-1,4-naphthoquinone[5] **1** by treatment with bis(2-methoxycarbonylphenyl) diselenide[6] **2**, tributyl- or triphenylphosphine, and aqueous NaOH or $LiOH \cdot H_2O$ under conditions similar to those used in the case of diphenyl diselenide,[1] but found that it was difficult to generate selenolate ions from the diaryl diselenide **2**, which bears electron-withdrawing ester groups at the ortho positions (Entries 1—4 in Table 1). Selenolate ions would be liberated from the initially formed selenophosphonium ion **I** or pentavalent phosphorus species **II** and from subsequently formed phosphonium ion **III**.[7] We therefore examined several other phosphorus reagents being able to reduce the Se–Se bond and to form the species **I** or **II** and probably **III**.

Triphenyl phosphite and chlorodiphenylphosphine are good reducing agents for the reduction of pyridine N-oxide.[8] Treatment of bromonaphthoquinone **1** with triphenyl phosphite or chlorodiphenylphosphine and the diselenide **2** resulted in the formation of the desired 2-arylseleno-1,4-naphthoquinone **3**, though in low yields (Entries 5 and 6). The yield of **3** was improved by use of an excess amount of the diselenide **2**. Thus, a tetrahydrofuran (THF)–methanol solution of the diselenide **2** (1.10 molar amount) and chlorodiphenylphosphine (1.20 molar amount) was stirred at room temperature for 5 min. To this solution was added $LiOH \cdot H_2O$ (2.20 molar amount) and then the mixture was stirred for additional 15 min to give a solution containing the areneselenolate ion, which was added to a THF solution of the bromoquinone **1** to give 2-[(2-methoxycarbonylphenyl)seleno]-1,4-naphthoquinone **3** in 81% yield (Entry 8).

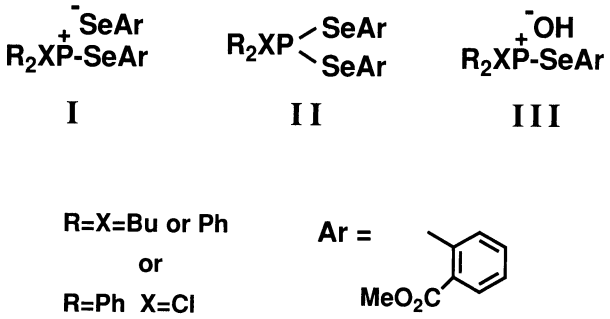
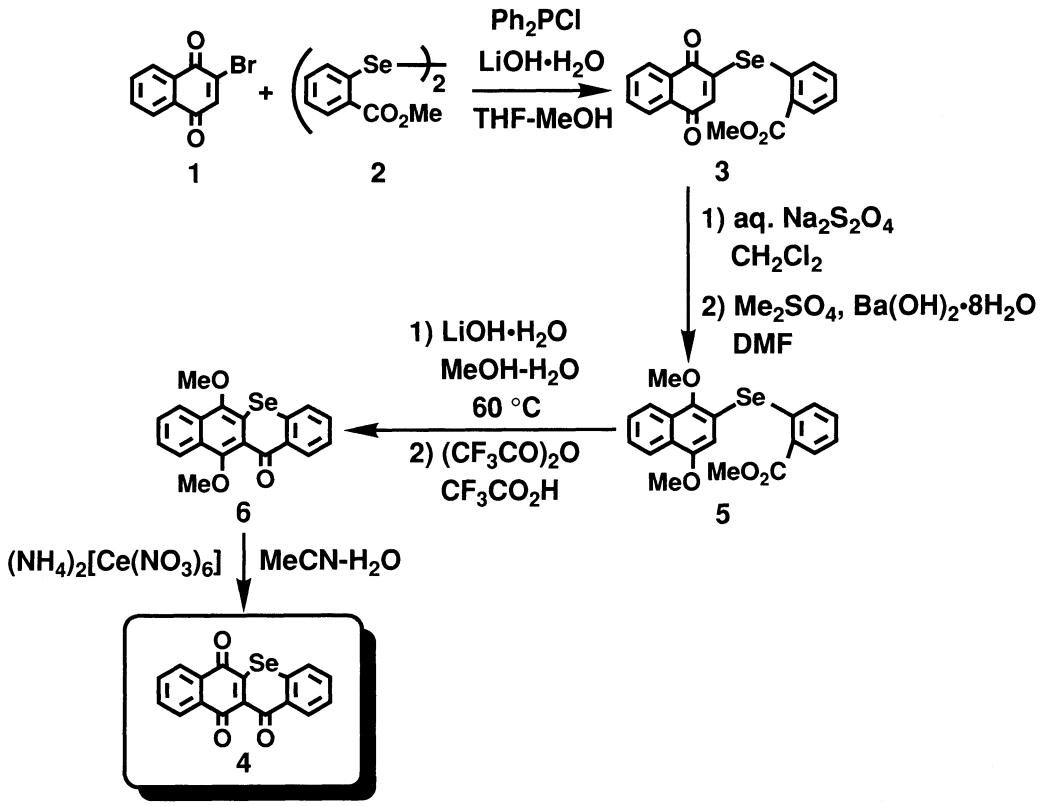


Fig. 1.

Preparation of 12*H*-Benzo[*b*]naphtho[2,3-*e*]selenin-6,11,12-trione (4). Direct cyclization of the 2-arylseleno-1,4-naphthoquinone **3** to the benzonaphthoseleninone **4** was not successful in the presence of acid catalysts such as concd H_2SO_4 and polyphosphoric acid (PPA), because **3** underwent the cleavage of the Se–C bond under the acidic conditions employed for the cyclization. The 2-arylseleno-1,4-naphthoquinone **3** was reduced by treatment with aqueous $Na_2S_2O_4$ to give the 2-arylselenohydroquinone, which was then treated with dimethyl sulfate in the presence of $Ba(OH)_2 \cdot 8H_2O$[9] to afford the dimethoxynaphthalene **5** in 78% yield. Treatment of **5** with PPA[10] at 90 °C for 4 h gave the dimethoxybenzonaphthoseleninone **6** in 29% yield.

Table 1. Synthesis of Arylseleno-1,4-naphthoquinone **3**

Entry	Diselenide (molar amount)	Phosphine (molar amount)	Alkaline (molar amount)	Solvent	Reaction conditions	Yield/%
1	**2** (0.55)	Bu_3P (0.60)	aq NaOH (1.10)	THF	Ar, rt, 3 h	0
2	**2** (0.55)	Ph_3P (0.60)	aq NaOH (1.10)	THF	Ar, rt, 2 h	0
3	**2** (1.10)	Bu_3P (1.20)	$LiOH·H_2O$ (2.20)	THF–MeOH	Ar, rt, 2 h	0
4	**2** (1.10)	Ph_3P (1.20)	$LiOH·H_2O$ (2.20)	THF–MeOH	Ar, rt, 2 h	0
5	**2** (0.55)	$(PhO)_3P$ (0.60)	aq NaOH (1.10)	THF	Ar, rt, 2 h	28
6	**2** (0.55)	Ph_2PCl (0.60)	aq NaOH (1.10)	THF	Ar, rt, 2 h	28
7	**2** (0.55)	Ph_2PCl (0.60)	$LiOH·H_2O$ (1.10)	THF–MeOH	Ar, rt, 30 min	50
8	**2** (1.10)	Ph_2PCl (1.20)	$LiOH·H_2O$ (2.20)	THF–MeOH	Ar, rt, 30 min	81

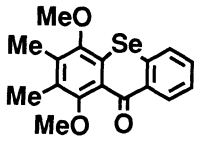


Scheme 1.

The demethylated benzonaphthoselenintrione **4** was also formed in this reaction (18% yield). The cleavage of the Se–C bond of **5** was again observed under these conditions and lowered the yield of **6**. Reactions of **5** with other acids such as concd H_2SO_4, CF_3SO_3H, or CF_3CO_2H did not improve the yield of cyclization. We then examined the cyclization of the carboxylic acid which would be cyclized under moderate conditions. Hydrolysis of the ester **5** with $LiOH·H_2O$ in aqueous MeOH afforded the carboxylic acid which was treated with $(CF_3CO)_2O$–CF_3CO_2H[11] at room temperature for 15 min to give the dimethoxybenzonaphthoseleninone **6** in 88% yield. A small amount (2%) of the benzonaphthoselenintrione **4** was also formed in this step. Finally, the benzonaphthoselenintrione **4** was obtained in 77% yield by oxidative demethylation of **6** with ammonium hexanitratocerate (IV)[12] in aqueous acetonitrile.

Preparation of 1,4-Dimethoxyl-2,3-dimethyl-10*H*-dibenzo[*b*,*e*]selenin-10-one (10). We extended this efficient selenation and cyclization reactions for the preparation of the dibenzo[*b*,*e*]seleninone framework whose derivatives, selenoxanthenes, show antithistamine and antireserpine activities.[13] Selenation of 6-bromo-2,3-dimethyl-1,4-benzoquinone[14] **7** with the diselenide **2** (1.50 molar amount), chlorodiphenylphosphine (1.50 molar amount), and $LiOH \cdot H_2O$ (3.00 molar amount) as described in the preparation of **3** afforded methyl 2-[(4,5-dimethyl-3,6-dioxo-1,4,-cyclohexadienyl)seleno]benzoate **8** in 91% yield. The selenobenzoate **8** was reduced into 2-arylselenohydrobenzoquinone with aqueous $Na_2S_2O_4$. Dimethylation of the hydroquinone with Me_2SO_4 in the presence of $Ba(OH)_2 \cdot H_2O$ gave methyl 2-[(2,5-dimethoxy-3,4-dimethylphenyl)seleno]benzoate **9** in 71% yield. Hydrolysis of the ester **9** followed by cyclization with $(CF_3CO)_2O$–CF_3CO_2H afforded 1,4-dimethoxy-2,3-dimethyl-10*H*-dibenzo[*b*,*e*]selenin-10-one **10** in 83% yield. Unfortunately, attempts to demethylate **10** were not successful.

In summary, novel selenium-containing heterocycles were synthesized through the elaborated selenation method followed by cyclization of the resulting arylselenoquinones. Derivatization of these seleninones is currently under way in this laboratory.



10

Fig. 2.

Experimental

General. Melting points were determined on a Yanagimoto micromelting point apparatus and were uncorrected. UV spectra were obtained with a JASCO Ubest-30 spectrometer using 1 cm quartz cells. IR spectra were measured on a JASCO A-102 spectrometer. ^1H NMR spectra were recorded on a JEOL JNM-PMX 60 SI NMR spectrometer in deuteriochloroform, using Me_4Si as an internal standard. Mass spectra were obtained with a Hitachi M-2000 spectrometer. Elemental analyses were performed by the Microanalytical Laboratory of Kyoto University.

2-[(2-Methoxycarbonylphenyl)seleno]-1,4-naphthoquinone (3). A solution of **2** (1.230 g, 2.87 mmol) and freshly distilled chlorodiphenylphosphine (0.560 ml, 3.12 mmol) in a mixture of THF (5 ml) and methanol (2 ml) was stirred at room temperature under argon for 5 min. To this mixture was added $LiOH \cdot H_2O$ (0.241 g, 5.74 mmol). After stirring for 15 min, the mixture was added dropwise to a solution of 2-bromo-1,4-naphthoquinone **1** (0.619 g, 2.60 mmol) in THF (2 ml) under argon and stirred for further 30 min. The reaction mixture was then poured into a mixture of brine (20 ml) and ether (15 ml), and the aqueous layer was extracted with ether (2×15 ml). The combined extract was washed successively with H_2O (2×5 ml) and brine (2×5 ml), dried over $MgSO_4$, and evaporated. Column chromatography on silica gel with hexane–ethyl acetate (97 : 3) as an eluent yielded **3** (0.787 g, 81%). Mp 108.4—109.0 °C (from hexane–CH_2Cl_2); UV ($CHCl_3$) λ_{max} 262 (ε 15900), 319 (5800), and 446 nm (2300); IR (KBr) 1713, 1653, 1633, 1578, 1550, 1295, and 1248 cm^{-1}; ^1H NMR δ=3.86 (s, 3H), 6.51 (s, 1H), and 7.34—8.18 (m, 8H); MS *m*/*z* (rel intensity, %) 372 (M^+, 100), 370 (M^+, 51), 313 (30), 295 (16), 215 (26), 184 (34), 157 (29), 156 (21), and 129 (49). Found: C, 58.30; H, 3.13%. Calcd for $C_{18}H_{12}O_4Se$: C, 58.24; H, 3.26%.

Methyl 2-(1,4-Dimethoxy-2-naphthylseleno)benzoate (5). A red solution of **3** (0.150 g, 0.404 mmol) in dichloromethane (10 ml) and an aqueous solution (20 ml) of 85% $Na_2S_2O_4$ (1.240 g, 6.05 mmol) were placed in a separatory funnel and then the mixture was shaken until the organic layer became colorless. The aqueous layer was extracted with dichloromethane (2×5 ml). The combined extracts were dried over $MgSO_4$ and evaporated to give a crude mixture containing the hydroquinone. This crude solid was dissolved in *N*,*N*-dimethylformamide (DMF) (2 ml). To a resulting solution $Ba(OH)_2 \cdot 8H_2O$ (0.139 g, 0.440 mmol) was added and the mixture was stirred at room temperature under argon for 5 min. Then, dimethyl sulfate (0.115 ml, 1.22 mmol) was added. After stirring for 1 h, the mixture was poured into a mixture of brine (20 ml) and ether (10 ml). The aqueous layer was extracted with ether (2×5 ml). The combined extract was washed successively with H_2O (2×5 ml) and brine (2×5 ml), dried over $MgSO_4$, and evaporated. Column chromatography on silica gel with hexane–ethyl acetate (98 : 2) as an eluent yielded **5** (0.127 g, 78%). Mp 110.7—111.5 °C (from hexane–CH_2Cl_2); UV ($CHCl_3$) λ_{max} 294 (ε 8000), 322 (10500), and 335 nm (10500); IR (KBr) 1698, 1580, 1272, and 1253 cm^{-1}; ^1H NMR δ=3.90 (s, 6H), 3.98 (s, 3H), 6.90—7.18 (m, 4H), 7.42—7.70 (m, 2H), and 7.93—8.38 (m, 3H); MS *m*/*z* (rel intensity, %) 402 (M^+, 45), 400 (M^+, 25), 387 (23), 203 (73), and 175 (100). Found: C, 59.81; H, 4.55%. Calcd for $C_{20}H_{18}O_4Se$: C, 59.85; H, 4.27%.

6,11-Dimethoxy-12*H*-benzo[*b*]naphtho[2,3-*e*]selenin-12-one (6). A solution of **5** (54 mg, 0.13 mmol) and $LiOH \cdot H_2O$ (28 mg, 0.67 mmol) in a mixture of methanol (2 ml) and H_2O (2 ml) was heated at 60 °C for 2 h. After cooling, the mixture was acidified with 1 M HCl (1 M=1 mol dm^{-3}) and extracted with ether (3×10 ml). The combined extract was washed successively with H_2O (2×5 ml) and brine (2×5 ml), dried over $MgSO_4$, and evaporated to give the carboxylic acid which was used for the cyclization without further purification. $(CF_3CO)_2O$ (0.5 ml) and CF_3CO_2H (1.0 ml) was added and the resulting mixture was left to stand without stirring for 15 min. The mixture was then poured into ice-cooled H_2O (10 ml), neutralized with 5% $NaHCO_3$, and extracted with ether (3×10 ml). The combined extract was washed successively with H_2O (2×5 ml) and brine (2×5 ml), dried over $MgSO_4$, and evaporated. Column chromatography on silica gel with hexane–ethyl acetate (95 : 5) as an eluent yielded **6** (42 mg, 88%) and **4** (1 mg, 2%).

6: Mp 139.0—141.0 °C (from hexane–CH_2Cl_2); UV ($CHCl_3$) λ_{max} 279 (ε 34400), 330 (7200), and 434 nm (2800); IR (KBr) 1640, 1613, 1587, 1544, 1352, and 1283 cm^{-1}; ^1H NMR δ=4.06 (s, 3H), 4.13 (s, 3H), 7.38—7.75 (m, 5H), 7.92—8.11 (m, 1H), and 8.28—8.51 (m, 2H); MS *m*/*z* (rel intensity, %) 370 (M^+,78), 368 (M^+, 43), 355 (100), 312 (18), and 104 (20). Found: C,

61.77; H, 3.83%. Calcd for $C_{19}H_{14}O_3Se$: C, 61.80; H, 3.82%.

12*H*-Benzo[*b*]naphtho[2,3-*e*]selenin-6,11,12-trione (4). To a suspension of **6** (23 mg, 0.057 mmol) in acetonitrile (2 ml) was added dropwise a solution of ammonium hexanitratocerate(IV) (125 mg, 0.228 mmol) in H_2O (1 ml). After stirring for 30 min at room temperature, the mixture was poured into a mixture of brine (20 ml) and dichloromethane (10 ml), and the aqueous layer was extracted with dichloromethane (2×10 ml). The combined extract was washed successively with H_2O (2×5 ml) and brine (2×5 ml), dried over $MgSO_4$, and evaporated. Column chromatography on silica gel with hexane–ethyl acetate (9 : 1) as an eluent yielded **4** (15 mg, 77%). Mp 281.0—281.4°C (from hexane–CH_2Cl_2); UV ($CHCl_3$) λ_{max} 286 (ε 12200), 322 (11600), and 466 nm (5300); IR (KBr) 1663, 1650, 1647, 1580, 1277, and 1260 cm^{-1}; ^1H NMR δ=7.30—7.91 (m, 5H), 7.91—8.37 (m, 2H), and 8.37—8.58 (m, 1H); MS *m/z* (rel intensity, %) 340 (M^+, 100), 338 (M^+, 43), 312 (46), 284 (39), 256 (31), and 104 (36). Found: C, 60.11; H, 2.32%. Calcd for $C_{17}H_8O_3Se$: C, 60.20; H, 2.38%.

Methyl 2-[(4,5-Dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-seleno]benzoate (8). A mixture containing areneselenolate ion which was generated from **2** (191 mg, 0.446 mmol), chlorodiphenylphosphine (0.080 ml, 0.45 mmol), and LiOH·H_2O (38 mg, 0.91 mmol) as described in the preparation of **3** was added to a solution of **7** (64 mg, 0.30 mmol) in THF (0.5 ml) under argon and stirred at room temperature for 1 h. The workup and purification gave **8** (95 mg, 91%). UV ($CHCl_3$) λ_{max} 315 (ε 5200) and 466 nm (1600); IR (film) 1720, 1710, 1640, 1630, 1575, 1290, 1255, and 1235 cm^{-1}; ^1H NMR δ=2.00 (br s, 6H), 3.87 (s, 3H), 6.29 (s, 1H), and 7.18—8.13 (m, 4H); MS *m/z* (rel intensity, %) 350 (M^+, 100) and 348 (M^+, 52). Found: C, 55.30; H, 4.19%. Calcd for $C_{16}H_{14}O_4Se$: C, 55.02; H, 4.05%.

Methyl 2-[(2,5-Dimethoxy-3,4-dimethylphenyl)seleno]-benzoate (9). Reduction of **8** (93 mg, 0.27 mmol) with 85% $Na_2S_2O_4$ (823 mg, 4.02 mmol) to the hydroquinone followed by treatment with $Ba(OH)_2 \cdot 8H_2O$ (93 mg, 0.29 mmol) and dimethyl sulfate (0.076 ml, 0.80 mmol) in DMF as described in the preparation of **5** gave **9** (73 mg, 71%). Mp 115.4—115.7°C (from hexane–CH_2Cl_2); UV ($CHCl_3$) λ_{max} 264 (ε 9200), 289 (6900), and 332 nm (5800); IR (KBr) 1660, 1580, and 1255 cm^{-1}; ^1H NMR δ=2.25 (s, 3H), 2.33 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 3.97 (s, 3H), 6.88—7.30 (m, 4H), and 7.89—8.16 (m, 1H); MS *m/z* (rel intensity, %) 380 (M^+, 100), 378 (M^+, 55), 365 (17), 306 (21), and 215 (23). Found: C, 56.87; H, 5.28%. Calcd for $C_{18}H_{20}O_4Se$: C, 56.99; H, 5.33%.

1,4-Dimethoxy-2,3-dimethyl-10*H*-dibenzo[*b*,*e*]selenin-10-one (10). Hydrolysis of **9** (86 mg, 0.23 mmol) with LiOH·H_2O (48 mg, 1.14 mmol) under the same conditions as in the preparation of **6** and subsequent cyclization with $CF_3(CO)_2O$ (0.9 ml)–CF_3CO_2H (1.8 ml) gave **10** (67 mg, 83%). Mp 101.2—102.0°C (from hexane–CH_2Cl_2); UV ($CHCl_3$) λ_{max} 269 (ε 25600), 308 (5900), and 392 nm (4200); IR (KBr) 1630, 1580, 1570, and 1300 cm^{-1}; ^1H NMR δ=2.33 (s, 3H), 2.36 (s, 3H), 3.87 (s, 6H), 7.23—7.73 (m, 3H), and 8.28—8.60 (m, 1H); MS *m/z* (rel intensity, %) 348 (M^+, 100), 346 (M^+, 51), 333 (66), and 305 (38). Found: C, 58.57; H, 4.55%. Calcd for $C_{17}H_{16}O_3Se$: C, 58.79; H, 4.65%.

References

1) M. Sakakibara, Y. Watanabe, T. Toru, and Y. Ueno, *J. Chem. Soc., Perkin Trans. 1,* **1991**, 1231 and M. Sakakibara, K. Katsumata, Y. Watanabe, T. Toru, and Y. Ueno, *Synthesis,* in press.

2) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.,* **95**, 2697 (1973); K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.,* **95**, 6137 (1973); D. Liotta, W. Markiewicz, and H. Santiesteban, *Tetrahedron Lett.,* **1977**, 4365 and D. Liotta and H. Santiesteban, *Tetrahedron Lett.,* **1977**, 4369.

3) M. Sakakibara, T. Ishida, Y. Watanabe, T. Toru, and Y. Ueno, *Bull. Chem. Soc. Jpn.,* **64**, 2242 (1991).

4) B. Simoneau and P. Brassard, *J. Chem. Soc., Perkin Trans. 1,* **1984**, 1507, and references cited therein.

5) S. M. McElvain and E. L. Engelhardt, *J. Am. Chem. Soc.,* **66**, 1077 (1944).

6) A. Ruwet and M. Renson, *Bull. Soc. Chim. Belg.,* **75**, 157 (1966).

7) See Ref. 1. For the reaction of triphenylphosphine and diphenyl disulfide, see also L. E. Overman, D. Matzinger, E. M. O'Connor, and J. D. Overman, *J. Am. Chem. Soc.,* **96**, 6081 (1974).

8) J. I. G. Cadogan and R. K. Mackie, *Chem. Soc. Rev.,* **3**, 87 (1974).

9) G. G. Kublak and P. N. Confalone, *Tetrahedron Lett.,* **31**, 3845 (1990).

10) P. Müller, T. Venakis, and C. H. Eugster, *Helv. Chim. Acta,* **62**, 2350 (1979) and N.-Y. Shih, P. Mangiaracina, M. J. Green, and A. K. Ganguly, *Tetrahedron Lett.,* **30**, 5563 (1989).

11) H. Gerlach, *Helv. Chim. Acta,* **60**, 3039 (1977).

12) P. Jacob, III, P. S. Callery, A. T. Shulgin, and N. Castagnoli, Jr, *J. Org. Chem.,* **41**, 3627 (1976).

13) K. Šindelář, E. Svátek, J. Metyšová, J. Metyš, and M. Protiva, *Collect. Czech. Chem. Commun.,* **34**, 3792 (1969).

14) K. J. M. Andrews, D. H. Marrian, and D. R. Maxwell, *J. Chem. Soc.,* **1956**, 1844.