CH_3), 1.374, 1.389, 1.465, 1.507 (each: 3, s, Me from acetonide), 3.66 (1, t, J = 8.0 Hz, 35-Ha), 4.03 (3, m), 4.16 (1, dd, J = 12 Hz, 6 Hz).

27b: mp 196–197 °C; ^{1}H NMR (400 MHz) δ 0.706 (3, s, 18α-CH_3), 0.794 (3, s, 4β-CH_3), 0.817 (3, s, 4α-CH_3), 0.849 (3, s, 10β-CH_3), 0.939 (3, d, J = 6.3 Hz, 22-CH_3), 0.951 (6, s, 8β- and 14α-CH_3), 1.397, 1.410, 1.418, 1.437 (each: 3, s, Me from acetonide), 3.68 (1, dd, J = 4.5 Hz, 8.0 Hz, 35-Ha), 3.82 (1, t, J = 7.5 Hz, 33-H), 3.89 (1, dt, J = 3.0 Hz, 7.5 Hz, 32-H), 4.03 (1, dd, J = 6.0 Hz, 8.0 Hz, 35-Hb).

Acknowledgment. We thank E. Krempp for all NMR measurements, Dr. G. Teller for the mass spectra, Rhône-Poulenc for the generous gift of aminobacteriohopanetriol, and the Ministère de l'Education Nationale (Réseau Européen de Laboratoires) and the Centre National de la Recherche Scientifique (Unité de Recherche Associée 135) for financial support.

Registry No. **2a**, 51024-98-7; **4**, 38706-33-1; **4** (iodide), 120446-11-9; **5**, 120446-13-1; **6**, 120522-08-9; **7**, 23568-31-2; **8**, 120522-09-0; **9**, 120522-10-3; **10**, 62139-14-4; **10** (iodide), 120446-12-0; **11**, 120446-14-2; **12**, 1707-77-3; (*S,S*)-**13**, 91274-05-4; (*S,R*)-**13**, 114185-09-0; (*S,S*,)-**13** (diacetate), 120446-17-5; (*S,R*)-**13** (diacetate), 120446-16-4; **14**, 15186-48-8; **15**, 22323-80-4; **16**, 120446-15-3; **17**, 120522-11-4; **18**, 120522-12-5; **19**, 120522-13-6; **20a**, 120522-14-7; **20b**, 120522-15-8; **21a**, 120522-16-9; **21b**, 120522-17-0; **22a**, 59893-93-5; **22b**, 112259-34-4; **23a**, 120522-18-1; **23b**, 120522-19-2; 24a, 120522-20-5; **24b**, 120522-21-6; **25a**, 120522-22-7; **25b**, 120522-23-8; **26a**, 120522-24-9; **26b**, 120522-25-0; **27a**, 120522-26-1; **27b**, 120522-27-2; $(PhO)_3P^+MeI^-$, 17579-99-6; L-(*S*)-erythrulose, 533-50-6.

Notes

Expedient Synthesis of Ebselen and Related Compounds

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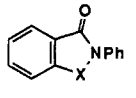
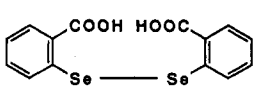
Introduction

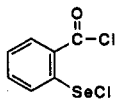
It was recently found that ebselen, 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one (**1b**), is effective for the treatment of diseases caused by cell damage due to increased formation of active oxygen metabolites.[1-3] These pharmacological effects have been attributed to glutathione peroxidase like[4] properties of the simple organoselenium compound. Previous syntheses of ebselen all rely on multistep reactions involving 2,2′-diselenobis(benzoic acid) (**2**) as an intermediate. In the earliest and shortest approach (still useful according to patent literature[5]), this material was converted to a selenenyl chloride benzoyl chloride **3**, which was treated with aniline to give ebselen.[6] Another more recent reaction sequence involves the three-step conversion of diselenide **2** to 2-(methylseleno)benzanilide (**4b**), which was cyclized to give ebselen by treatment with PCl_5 followed by hydrolysis.[7] In the following we describe an operationally simple one-pot preparation of ebselen and related compounds from benzanilide using ortholithiation[8] methodology.



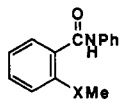
1 a X=S
b X=Se
c X=Te



2



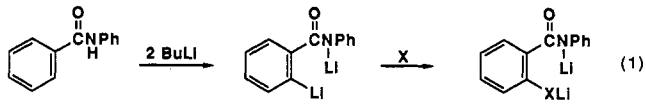
3



4 a X=S
b X=Se
c X=Te

Results

The chalcogens sulfur, selenium, and tellurium are all known to readily insert into the carbon–lithium bond of various organolithium compounds.[9] It was therefore not surprising to find that elemental selenium was rapidly consumed when added to a solution of the readily available[10] benzanilide-derived dianion **5** in THF at 0 °C (eq 1).



(1)

5

6 a X=S
b X=Se
c X=Te

Structure **6b** of the insertion product was confirmed by methylation which occurred exclusively on selenium to give, after aqueous workup, 2-(methylseleno)benzanilide (**4b**) in 76% yield. Similarly, the reaction of dianion **5** with sulfur and tellurium gave, after methylation, compounds **4a** (81%) and **4c** (70%), respectively.

The cyclization of dianion **6b** to ebselen was tried by using a variety of oxidants. Treatment with bromine or iodine in stoichiometric amounts at −78 °C, followed by warming to ambient temperature, produced ebselen in low yields (≤20%). A better result (42%) was obtained by using iron(III) chloride. However, the best yield of ebselen (63%) was obtained by using copper(II) bromide (2 equiv;

(1) Müller, A.; Cadenas, E.; Graf, P.; Sies, H. *Biochem. Pharmacol.* **1984**, *33*, 3235.
(2) Wendel, A.; Fausel, M.; Safayhi, H.; Tiegs, G.; Otter, R. *Biochem. Pharmacol.* **1984**, *33*, 3241.
(3) Parnham, M. J.; Graf, E. *Biochem. Pharmacol.* **1987**, *36*, 3095.
(4) For a recent study concerning the redox chemistry of a selenocysteine model system, see: Reich, H. J.; Jasperse, C. P. *J. Am. Chem. Soc.* **1987**, *109*, 5549.
(5) Eur. Pat. Appl. EP 44453.
(6) Lesser, R.; Weiss, R. *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1077.
(7) Weber, R.; Renson, M. *Bull. Soc. Chim. Fr.* **1976**, 1124.
(8) Gschwent, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(9) See: Engman, L.; Hellberg, J. S. E. *J. Organomet. Chem.* **1985**, *296*, 357 and references cited therein.
(10) Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 475.

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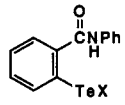
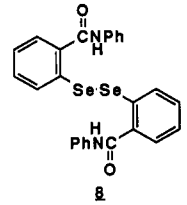
-78 °C to ambient). The $CuBr_2$-induced cyclization of dianion **6a** similarly produced 1-phenyl-1,2-benzisothiazol-3(2*H*)-one (**1a**) in 44% yield.

Our attempts to oxidatively cyclize the tellurium-containing dianion **6c** have so far been unsuccessful. Treatment with the above-mentioned oxidants instead yielded tellurenyl halides of structure **7**. Thus, iron(III) chloride

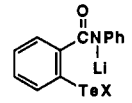


7 a X=Cl
b X=Br
c X=I



8

9



10 X=Cl,Br,I

gave compound **7a** in 48% yield whereas Br_2 and $CuBr_2$ produced compound **7b** in 66 and 43% yields, respectively. The reaction with iodine yielded compound **7c** in 72% yield as orange-brown glittering crystals.

When a tetrahydrofuran solution of dianion **6b** was poured into an aqueous solution of potassium hexacyanoferrate, 2,2′-diselenobis(benzanilide) (**8**) separated out as a yellowish solid (79% yield). Compounds of this type, prepared by multistep procedures, were recently shown in vitro to be even more effective than ebselen for the catalytic reduction of hydrogen peroxide.[11]

Discussion

As compared with previous syntheses of ebselen, the present method, involving ortholithiation,[12] selenium insertion, and oxidative cyclization, represents a significant improvement, producing the target molecule in a single one-pot operation. The method should also be useful for the preparation of derivatives of ebselen which could be more active than the parent compound.[5,13]

By using aqueous $K_3Fe(CN)_6$ instead of anhydrous $CuBr_2$ in the final oxidative conversion of dianion **6b**, diselenide **8a** was obtained in good yield instead of a cyclization product. This result can be explained by protonation of the dianion followed by oxidative dimerization of the resulting selenol.

The role of $CuBr_2$ in the oxidative cyclization step is not obvious. The reagent has previously been used for α-bromination of carbonyl compounds, bromination of aromatics, and 1,2-addition of bromine to olefins, thus mimicking the properties of bromine.[14] There are also reports that $CuBr_2$ can undergo electron-transfer reactions.[15,16] Since no diselenide **8** was isolated in the $CuBr_2$-induced oxidative cyclization of dianion **6b**, we feel that the copper reagent serves essentially as a source of bromine. The resulting arylselenenyl bromide **9** then undergoes cyclization to give ebselen.

The stability of the tellurenyl halides **7** and the apparent reluctance of intermediates **10** to undergo cyclization to give 2-phenyl-1,2-benzisotellurazol-3(2*H*)-one (**1c**) are surprising but can be understood in view of the well-known[17] ability of ortho donor substituents to stabilize aryltellurenyl halides.[18]

Experimental Section

Melting points (uncorrected) were determined by using a Büchi 510 melting point apparatus. ^1H NMR spectra were obtained with a Bruker WP 200 instrument operating at 200 MHz and recorded for $CDCl_3$ solutions containing tetramethylsilane as the internal standard. IR spectra were obtained by using a Perkin-Elmer 1710 FT infrared spectrometer. Elemental analyses were performed by Novo Microanalytical Laboratory, Bagsvaerd, Denmark. Tetrahydrofuran was distilled from potassium–benzophenone.

2-(Methylseleno)benzanilide (4b). To a stirred solution of benzanilide (1.0 g, 5.1 mmol) in dry tetrahydrofuran (35 mL) under N_2 at 0 °C was added *n*-butyllithium (4.1 mL, 2.5 M; 10.2 mmol). After 30 min, elemental selenium (0.40 g, 5.1 mmol) was added to the resulting orange-red solution of dianion **5** while a brisk stream of nitrogen was passed through the open system to exclude air. The solid material was rapidly consumed to give, after 30 min, a homogeneous dark orange-brown solution of dianion **6b**. The color faded considerably upon addition of methyl iodide (0.316 mL, 5.1 mmol), and when the reaction mixture was poured into water (100 mL), compound **4b** separated out as a solid. Recrystallization from EtOH afforded 1.11 g (76%) of the material, mp 176 °C (lit.[7] mp 177 °C).

2-(Methylthio)benzanilide (4a) was prepared in a similar manner by addition of elemental sulfur to the dianion **5**. Methylation (after 5 min) of dianion **6a** afforded compound **4a** in 81% yield, mp 149–50 °C (lit.[19] mp 149–50 °C).

2-(Methyltelluro)benzanilide (4c) was prepared in an analogous manner by addition of elemental tellurium to the dianion **5**. Methylation (after 1 h when only traces of the chalcogen remained) of dianion **6c** afforded compound **4c** in 70% yield, mp 184–5 °C. ^1H NMR: δ 1.98 (s, 3 H), 7.12–7.41 (several peaks, 5 H), 7.58–7.71 (several peaks, 4 H), 7.89 (s, 1 H). IR: 3303 and 1631 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NOTe$: C, 49.62; H, 3.87. Found: C, 49.91; H, 3.91.

2-Phenyl-1,2-benzisoselenazol-3(2*H*)-one (1b). To a solution of dianion **6b**, prepared as described above and cooled to -78 °C, was added $CuBr_2$ (2.28 g, 10.2 mmol). The cooling bath was removed after 30 min, and the temperature was allowed to rise to ambient. After 2 h, the reaction mixture was poured into water (100 mL) containing HOAc (1 mL) and, after filtration, extracted with CH_2Cl_2. Flash chromatography (SiO_2–CH_2Cl_2) afforded 1.01 g of crude product, which yielded 0.88 g (63%) of ebselen, mp 180–1 °C (lit.[6] mp 182–3 °C), after recrystallization from ethanol.

The cyclizations using $FeCl_3$ (2 equiv), Br_2 (1 equiv), and I_2 (1 equiv) were similarly performed.

2-Phenyl-1,2-benzisothiazol-3(2*H*)-one (1a) was prepared analogously to compound **1b** in 44% yield by starting from dianion **6a**; mp 142–3 °C (lit.[18a] mp 143–4 °C).

2-[(Phenylamino)carbonyl]benzenetellurenyl Chloride (7a). To a stirred solution of dianion **6c** (2.5 mmol), prepared in THF (20 mL) as described above and cooled to -78 °C, was added $FeCl_3$ (0.82 g, 5.0 mmol). The cooling bath was removed after 30 min, and the temperature was allowed to rise to ambient. After 2 h, the reaction mixture was poured into water (100 mL) containing HOAc (1 mL) and, after filtration, extracted with CH_2Cl_2. The semisolid obtained after drying ($CaCl_2$) and evaporation was recrystallized from $CHCl_3$ to give 0.44 g (48%) of compound **7a** as a yellow microcrystalline powder, mp 212 °C. ^1H NMR: δ 7.31 (m, 1 H), 7.42–7.75 (several peaks, 6 H), 7.88

(11) Eur. Pat. Appl. EP 198277.

(12) Ortholithiation has recently been used for the introduction of alkylchalcogeno groups into the ortho position of oxazolines, N–substituted benzamides (among them *N*-methylbenzamide), and related compounds. Christiaens, L.; Luxen, A.; Evers, M.; Thibaut, Ph.; Mbuyi, M. *Chem. Scr.* **1984**, *24*, 178.

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(14) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 161.

(15) Bansal, S. R.; Nonhebel, D. C.; Mancilla, J. M. *Tetrahedron* **1973**, *29*, 993.

(16) Okogun, J. I.; Okwute, K. S. *J. Chem. Soc., Chem. Commun.* **1975**, 8.

(17) Rauchfuss, T. B. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Ed.; Wiley: Chichester, 1987; Vol. 2, p 342.

(18) Compound **7b** did not cyclize to give **1c** using the conditions for the cyclization of the corresponding sulfenyl bromide.[18a] Treatment with silver salts ($AgNO_3$/DMF/Et_3N; AgOAc/HOAc) also did not yield the heterocycle. (a) Reissert, A.; Manns, E. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 1308.

(19) Sauter, F.; Dzerovicz, A. *Monatsh. Chem.* **1969**, *100*, 905.

(d, 1 H, J = 7.8 Hz), 8.35 (s, 1 H), 8.40 (d, 1 H, J = 8.0 Hz). IR: 3363, 1605, 1590, 1574, 1556, 1532 cm^{-1}. Anal. Calcd for $C_{13}H_{10}ClNOTe$: C, 43.46; H, 2.81. Found: C, 43.50; H, 2.77.

2-[(Phenylamino)carbonyl]benzenetellurenyl bromide (7b) was similarly prepared by treatment of dianion **6c** with $CuBr_2$ (2 equiv; 43% yield of **7b**) or Br_2 (1 equiv; 66% yield of **7b**); mp 198 °C. The material seemed to partly decompose during recrystallization, and no satisfactory elemental analysis was obtained. ^1H NMR: δ 7.31 (m, 1 H), 7.41–7.70 (several peaks, 6 H), 7.85 (d, 1 H, J = 7.7 Hz), 8.31 (s, 1 H), 8.43 (d, 1 H, J = 7.9 Hz). IR: 3366, 1605, 1590, 1573, 1554, 1532 cm^{-1}. Treatment of the material in CH_2Cl_2 with 1 equiv of bromine, followed by precipitation with hexane, caused separation of 2-[(phenylamino)carbonyl]-benzenetellurium tribromide. Anal. Calcd for $C_{13}H_{10}Br_3NOTe$: C, 27.71; H, 1.79. Found: C, 27.96; H, 1.78.

2-[(Phenylamino)carbonyl]benzenetellurenyl iodide (7c) was similarly prepared by treatment of dianion **6c** with I_2 (1 equiv) in 72% yield, mp 170–1 °C. ^1H NMR: δ 7.28 (m, 1 H), 7.42–7.62 (several peaks, 6 H), 7.75 (d, 1 H, J = 7.4 Hz), 8.24 (s, 1 H), 8.38, (d, 1 H, J = 7.7 Hz). IR: 3384, 1602, 1588, 1573, 1543 cm^{-1}. Anal. Calcd for $C_{13}H_{10}INOTe$: C, 34.64; H, 2.24. Found: C, 34.76; H, 2.27.

2,2'-Diselenobis(benzanilide) (8). When a solution of dianion **6b** (prepared as described for compound **4b**) was poured into a solution of $K_3Fe(CN)_6$ (1.70 g, 5.2 mmol) in water (100 mL), 1.10 g (79%) of compound **8** separated out as a yellowish solid, mp 256–7 °C (1,2-dichlorobenzene) (lit.[11] mp 263–5 °C). ^1H NMR (DMSO-d_6): δ 7.16 (m, 1 H), 7.38–7.47 (several peaks, 4 H), 7.77–7.81 (several peaks, 3 H), 7.96 (d, 1 H, J = 6.7 Hz), 10.6 (s, 1 H). IR: 3293 and 1639 cm^{-1}. Anal. Calcd for $C_{13}H_{10}NOSe$: C, 56.74; H, 3.66. Found: C, 56.65; H, 3.64.

Acknowledgment. Financial support by the National Swedish Board for Technical Development and the Swedish Natural Science Research Council is gratefully acknowledged.

Registry No. **1a**, 2527-03-9; **1b**, 60940-34-3; **4a**, 22978-26-3; **4b**, 60940-24-1; **4c**, 119796-32-6; **6a**, 119796-33-7; **7a**, 119796-34-8; **7b**, 119796-36-0; **7c**, 119796-35-9; **8**, 106663-84-7; benzanilide, 93-98-1; selenium, 7782-49-2; sulfur, 7704-34-9; tellurium, 13494-80-9.

A General Access to Acylstannanes

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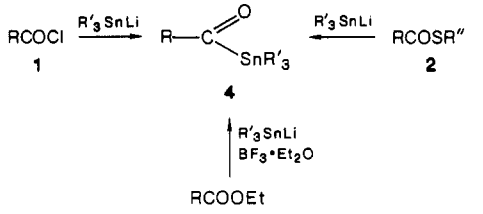
Received November 3, 1987

Much recent attention on acylmetallic compounds of group 14 elements has been focused upon their silicon derivatives, interesting both from the synthetic and the spectroscopic point of view.[1] Acylsilanes, in fact, have been shown to be very versatile organometallic reagents, participating in a number of interesting chemical transformations.[2]

Scheme I



On the contrary, very little is known about the corresponding acyltin derivatives,[3] despite their theoretical and practical interest in synthetic organic chemistry, deriving from the expected[4] greater reactivity of the tin–carbon compared to the silicon–carbon bond.

Our long-standing interest in the field of acylsilanes as "umpolung" reagents for nucleophilic acylation[5] has induced us to extend our attention to this promising and almost unexplored class of organometallic derivatives, in order to evaluate their potential in organic synthesis. Two reports dealing with the first examples of the reactivity of this class of compounds[3c,e] have recently appeared, but a general and efficient method for their preparation is still lacking. Furthermore, the very few methods available at present for the synthesis of acylstannanes are of limited interest due to the unavailability or high cost of the starting materials.[3,6]

We would like to report here the development of a new, simple, and possibly general method for the synthesis of acylstannanes.

Several attempts to obtain these tin derivatives through the usual hydrolytic methods[7] did not yield, for different reasons, the desired compounds. 2-(Trialkylstannyl)-2-phenyl-1,3-dithiane, in fact, when hydrolyzed, following several well-known procedures, led either to no reaction or to complete cleavage of the starting material. On the other hand, the difficulties encountered in the stannylation

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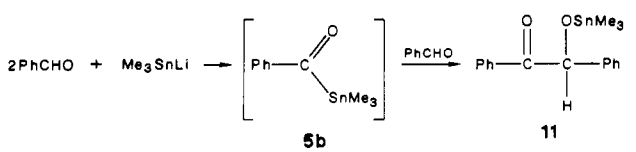
(3) (a) Peddle, G. J. D. *J. Organomet. Chem.* **1968**, *14*, 139. (b) Quintard, J. P.; Ellissondo, B.; Mouko-Mpegna, D. *J. Organomet. Chem.* **1983**, *251*, 175. (c) Verlhac, J. B.; Chanson, E.; Jousseaume, B.; Quintard, J. P. *Tetrahedron Lett.* **1985**, *26*, 6075. (d) Soderquist, J. A.; Hassner, A. *J. Am. Chem. Soc.* **1980**, *102*, 1577. (e) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657.

(4) Eaborn, C.; Seconi, G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 926 and references cited therein.

(5) (a) Degl'Innocenti, A.; Pike, S.; Walton, D. R. M.; Seconi, G.; Ricci, A.; Fiorenza, M. *J. Chem. Soc., Chem. Commun.* **1980**, 1201. (b) Ricci, A.; Degl'Innocenti, A.; Chimichi, S.; Fiorenza, M.; Rossini, G.; Bestmann, H. J. *J. Org. Chem.* **1985**, *50*, 130. (c) Ricci, A.; Fiorenza, M.; Degl'Innocenti, A.; Seconi, G.; Dembech, P.; Witzgall, K.; Bestmann, H. J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1068. (d) Ricci, A.; Degl'Innocenti, A.; Mordini, A.; Reginato, G.; Colotta, V. *Gazz. Chim. Ital.* **1987**, *117*, 645.

(6) An attempt to extend Quintard's[3b] procedure to the synthesis of aromatic acylstannanes by reacting Me_3SnLi with 2 equiv of benzaldehyde led only to the isolation of ((trimethylstannyl)oxy)benzoin in 48% yield, which is probably formed according to the following reaction:



(7) (a) Brook, A. G.; Duff, J. M.; Jones, P. F.; Davis, N. R. *J. Am. Chem. Soc.* **1967**, *89*, 431. (b) Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434.

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