2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (PTPS)[15] in anhydrous tetrahydrofuran at 20 °C is selective since the *tert*-butoxycarbonyl N-protecting group reacts with Lawesson's reagent at 110 °C[14] and ester is transformed into the thio ester function at 140 °C.[16] The thioamides **2** display an IR absorption decrease of approximately 10 cm^{-1} which is consistent with the amide (1620–1650 cm^{-1} range) → thioamide (1610–1640 cm^{-1} range) transformation.

The cyclization of thioamides **2** to thiazoles **3** was achieved by using ethyl bromopyruvate following the general procedure of Hantzsch already employed by us for the synthesis of bithiazoles related to bleomycin derivatives.[17,18] The NMR spectra of **3** show a single proton in the range δ 8.0–8.4 which is, with the 1220–1240 cm^{-1} IR absorption peak, indicative of the thiazolic moiety. A common feature for **2** and **3** lies in the weak intensity of the molecular peak as compared with the *m/e* 57 parent fragmentation in mass spectroscopy. The results are summarized in Table I.

The synthesis, here applied to six thiazole amino acids found in the structure of ulicyclamide, ulithiacyclamide, and patellamides, is very general and could be used starting from any L- or D-amino acids in good yields. The absence of any racemization during the two main steps of the synthesis has been verified using ^1H NMR and ^{13}C NMR. The least-square linear regression analyses of the C–multiple bond and α atoms for the amides and corresponding thioamides indicate the presence of a single enantiomer, as substantiated by the following relations:

$$\delta_{C=S} = 1.475 \times \delta_{C=O} - 48.136 \qquad (r = 0.983)$$

$$\delta_{C_\alpha(C=S)} = 1.008 \times \delta_{C_\alpha(C=O)} + 5.164 \qquad (r = 0.997)$$

Experimental Section

Melting points were determined on a Tottoli melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 177 grating infrared spectrophotometer using potassium bromide pellets. ^1H and ^{13}C spectra in $CDCl_3$ solutions were recorded on Cameca 350-MHz and Bruker WP 80 SY spectrometers, respectively, with tetramethylsilane as internal standard. Electron impact mass spectra were recorded on a Ribermag R10-10 (combined with Riber 400 data system) mass spectrometer at 70 eV by using direct insertion. TLC monitoring of all reactions was performed with Merck silica gel 60 F 254 precoated sheets (0.2 mm) with CH_2Cl_2–ethyl acetate (9:1, v/v) as developing system. Spots were detected with ultraviolet light and/or ninhydrin.

Typical Procedure for the Preparation of N-Protected α-Amino Carboxamides 1. *N*-Boc-valinamide (1c). To a solution of 2.18 g of di-*tert*-butyl dicarbonate (10 mmol) in dry CH_2Cl_2 (50 mL) were added 1.5 g of L-valinamide hydrochloride (10 mmol) and 2.1 g of triethylamine (20 mmol). The reaction mixture was refluxed for 3 h. Triethylamine salts were extracted twice by 10 mL of water, and the organic phase was evaporated in vacuo to give 1.9 g (90% yield) of an oily residue which readily crystallized upon standing at room temperature: R_f 0.03; mp 157 °C; IR 1630 (C=O), 1670 (Boc); ^{13}C NMR δ 59.6 (d, C_α), 174.5 (s, C=O). Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95; O, 22.19. Found: C, 55.66; H, 9.31; N, 12.83; O, 22.07.

Typical Procedure for the Preparation of N-Protected α-Amino Thiocarboxamides 2. *N*-(*tert*-Butoxycarbonyl)-valinethioamide (2c). To a solution of amide **1c** (1.365 g, 6.3 mmol) in dry THF (10 mL) was added PTPS (2.0 g, 3.8 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature until the starting material was consumed (6 h), as monitored by thin-layer chromatography (silica gel, 9:1 dichloromethane–ethyl acetate). The solvent was evaporated and the thick residue was chromatographed on a silica gel column (eluted with CH_2Cl_2–ethyl acetate, 9:1). The resulting oil (1.8 g, 66%) crystallized on standing (white crystals): R_f 0.16; mp 109 °C; IR 1630 (C=S), 1680 (Boc); ^{13}C NMR δ 65.5 (d, C_α), 209.4 (s, C=S); mass spectrum, *m/e* (relative intensity) 232 (26, M^+) 57 (100). Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C, 51.69; H, 8.68; N, 12.06; O, 13.77; S, 13.80. Found: C, 51.77; H, 8.73; N, 12.12; O, 13.89; S, 13.74.

Typical Procedure for the Preparation of 2-[(N-Protected)-1-aminoalkyl]thiazole-4-carboxylic Esters 3. Ethyl 2-[*N*-(Butoxycarbonyl)valyl]thiazole-4-carboxylate (3c). A mixture of 1.16 g (5 mmol) of **2c** and 0.63 mL (5 mmol) of ethyl bromopyruvate in 20 mL of dry ether was stirred at room temperature for 2 days. Filtration of the precipitate and evaporation of the filtrate afforded a residue which was submitted to column chromatography (silica gel, dichloromethane–ethyl acetate, 9:1). Evaporation of the solvents gave an oil which soon crystallized (0.7 g, 42%): R_f 0.64; mp 125.5 °C; IR 1235 (C–H thiazole), 1697 (Boc); ^1H NMR δ 4.9 (dd, H_α), 8.0 (s, 5-ThzH); mass spectrum, *m/e* (relative intensity) 328 (3, M^+), 57 (100). Anal. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.86; H, 7.37; N, 8.53; O, 19.49; S, 9.76. Found: C, 55.91; H, 7.43; N, 8.50; O, 19.53; S, 9.71.

Registry No. **1a**, 35150-09-5; **1b**, 81587-17-9; **1c**, 35150-08-4; **1d**, 96928-99-3; **1e**, 96929-00-9; **1f**, 88463-18-7; **2a**, 89226-13-1; **2b**, 96929-01-0; **2c**, 96929-02-1; **2d**, 96929-03-2; **2e**, 96929-04-3; **2f**, 88815-90-1; **3a**, 96929-05-4; **3b**, 96929-06-5; **3c**, 96929-07-6; **3d**, 96929-08-7; **3e**, 96929-09-8; **3f**, 96929-10-1; ethyl bromopyruvate, 70-23-5; L-valinamide hydrochloride, 3014-80-0.

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Synthesis and Reactivities of Trimethylsilyl-Substituted Tetrathia- and Tetraselenafulvalenes

Yoshiyuki Okamoto,* Hung Sui Lee, and S. T. Attarwala

Department of Chemistry, Polytechnic Institute of New York, Brooklyn, New York 11201

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Recently numerous investigations on "Organic metals" have been reported.[1] The term organic metals refers to organic compounds which exhibit electrical conductivity close to that of metals. The compounds mostly consist of donor–acceptor complexes of tetrathiafulvalene (TTF), tetraselenafulvalene (TSeF), and their derivatives. There has been an enormous amount of research on the synthesis and properties of TTF and TSeF compounds.[2] However, in general, the preparation methods require multistep routes and involve unstable intermediates.

We have disclosed recently a synthesis of alkoxycarbonyl-substituted TTF and TSeF compounds from the reactions of CS_2 or CSe_2 with bis(alkoxycarbonyl)-acetylenes under high pressure.[3,4] We now report the one-step synthesis and reactivity of versatile trimethylsilyl-substituted TTF and TSeF derivatives as shown in Scheme I. In a typical reaction, bis(trimethylsilyl)-acetylene and CS_2 were dissolved in hexane and the solution was pressurized under 5000 atm at 120–130 °C for 12

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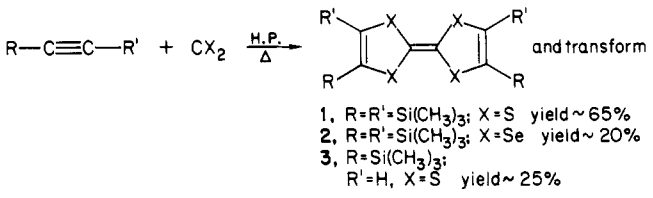
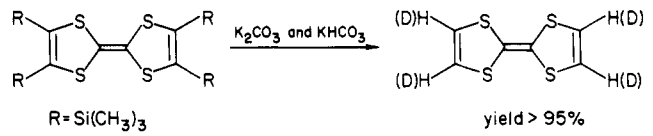
Scheme I

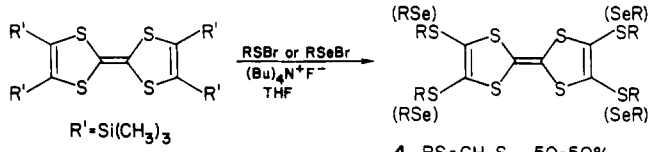


1, R=R'=Si(CH$_3$)$_3$; X=S yield~65%
2, R=R'=Si(CH$_3$)$_3$; X=Se yield~20%
3, R=Si(CH$_3$)$_3$; R'=H, X=S yield~25%

Scheme II



Scheme III



4, RS=CH$_3$S, 50-50%
5, RSe=CH$_3$Se, 40-45%
6, RSe=C$_6$H$_5$Se, 58-60%

h. The reaction products were separated by column chromatography using Florisil silica gel eluted with hexane. The eluted solution was orange in color and contained tetrakis(trimethylsilyl)tetrathiafulvalene (1). Other dark brown products remained in the column. 1 was recrystallized from hexane to give orange crystals in 60–65% yield. For the reaction with CSe_2 the hexane solution of bis(trimethylsilyl)acetylene and CSe_2 was reacted under a pressure of 6000 atm at 55–60 °C for 12 h. After the separation of the products by chromatography and recrystallization from hexane, dark reddish prismatic crystals of tetrakis(trimethylsilyl)tetraselenafulvalene were obtained in 20–25% yield. A large amount of polymeric product remained in the column. Similarly, (trimethylsilyl)acetylene was reacted with CS_2 and bis(trimethylsilyl)tetrathiafulvalene was obtained, Scheme I.

These trimethylsilyl-substituted TTF and TSeF were found to be stable in air and the trimethylsilyl group was readily replaced with hydrogen and other organic moieties. For example, a solution of 1 or 3 in ethanol and THF (1:1) was treated with aqueous K_2CO_3 and $KHCO_3$ solution under a nitrogen atmosphere at room temperature. After acidification and extraction with chloroform, pure TTF was obtained quantitatively. Using deuterated water under the same conditions afforded deuterated TTF (Scheme II).

When the THF solution of 1 and methanesulfenyl bromide was reacted with tetrabutylammonium fluoride, tetrakis(methylthio)tetrathiafulvalene (4) was obtained. With methaneselenyl bromide and benzeneselenenyl bromide, tetrakis(methylselenyl)tetrathiafulvalene (5) and tetrakis(phenylselenyl)tetrathiafulvalene (6) were obtained (Scheme III).

This work establishes that these trimethylsilyl-substituted TTF and TSeF derivatives and particularly compound 1 are valuable starting materials for the preparation of suitable TTF derivatives, which form complexes with TCNQ, AsF_6^-, and ClO_4^-. These complexes behave as organic metals and have interesting electrical properties.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 457 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 NMR spectrometer or a JEOL JNM-FX90Q spectrometer. Ultraviolet spectra were recorded on a Cary 15 UV-VIS spectrophotometer. Melting points were measured on an Electrothermal apparatus and are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

High-pressure experiments were performed in Teflon capsules (3 mL capacity) in a stainless steel die and compressed via a piston with a Clifton 200-ton hydraulic press.

Chemicals. Bis(trimethylsilyl)acetylene, (trimethylsilyl)-acetylene, and tetrabutylammonium fluoride were purchased from Aldrich and used without purification. CSe_2 was synthesized according to the literature[5] and was also obtained from Alfa Products. Methanesulfenyl bromide,[6] methaneselenyl bromide,[7] and benzeneselenyl bromide[8] were prepared by the methods described in the literature from dimethyl disulfide, dimethyl diselenide and diphenyl diselenide, respectively. These disulfides and diselenides were obtained from Aldrich.

Representative High-Pressure Reactions. Synthesis of Tetrakis(trimethylsilyl)tetrathiafulvalene (1). Bis(trimethylsilyl)acetylene, 0.7 g (5 mmol), and CS_2, 0.7 g (7 mmol), were dissolved in hexane (1.5 mL) and the solution was pressurized under 5000 atm at 120–130 °C for 12 h. The reaction products were separated by column chromatography using Florisil silica gel eluted with hexane. The eluted solution was orange in color and contained 1. Other dark brown products remained in the column. 1 was recrystallized from hexane to give orange crystals: mp 223–224 °C, in 65% yield. ^{1}H NMR ($CDCl_3$) δ 0.25 (s); IR (KBr, cm^{-1}) 2920, 1460, 1380, 1230, 925, 850, and 740; mass spectrum, m/e 492. Anal. Calcd for $C_{18}H_{36}S_4Si_4$: C, 43.84; H, 7.36; S, 26.00. Found: C, 43.69, H, 7.31; S, 26.65. 1 was found to form readily the complex with TCNQ upon mixing their acetonitrile solution. The complex which was black in color was found to be the resistivity (powder form) of 10^4 Ω/cm at room temperature.

Synthesis of Tetrakis(trimethylsilyl)tetraselenafulvalene (2). The hexane solution (3 mL) of bis(trimethylsilyl)acetylene, 1.0 g (7 mmol), and CSe_2, 1.0 g (6 mmol), was reacted under a pressure of 6000 atm at 55–60 °C for 12 h. After the separation of the products by chromatography and recrystallization from hexane, dark reddish prismatic crystals of 2 were obtained in 20% yield, mp 104–105 °C. A large amount of polymeric product remained in the column: ^{1}H NMR ($CDCl_3$) δ 0.25 (s); IR (KBr, cm^{-1}) 2950, 2890, 1710, 1660, 1480, 1450, 1250, 900, 850, and 750; mass spectrum, m/e 680 (based on ^{80}Se). Anal. Calcd for $C_{18}H_{36}Se_4Si_4$: C, 32.34; H, 5.39; Se, 47.90. Found: C, 32.50; H, 5.35; Se, 48.20.

Synthesis of Bis(trimethylsilyl)tetrathiafulvalene (3). (Trimethylsilyl)acetylene was reacted with CS_2 under similar condition described in the synthesis of 1. Compound 3 was obtained, in 20–25% yield (mp 131–133 °C). This reaction also gave a large amount of polymeric materials. ^{1}H NMR ($CDCl_3$) δ 0.25 (s), 5.28 (s); ms, m/e 348; IR (KBr, cm^{-1}) 2940, 1500, 1400, 930, 830, and 740. Anal. Calcd for $C_{12}H_{20}S_4Si_2$: C, 41.32; H, 5.78; S, 36.77; Si, 16.10. Found: C, 41.45; H, 6.00; S, 36.60.

Synthesis of Tetrathiafulvalene. A solution of 1 (100 mg) in 20 mL of ethanol and THF (1:1) was added to an aqueous buffer solution (1.5 mL) containing K_2CO_3 (0.13 mmol) and $KHCO_3$ (0.13 mmol) and the mixture was stirred for 2 h at room temperature under a nitrogen atmosphere. Then the solution was acidified with dilute HCl (5%) and extracted with $CHCl_3$. The chloroform solution was washed with water and then dried over Na_2SO_4. After removal of the solvent, a yellow crystalline material was obtained, 65 mg, mp 119–120 °C. The crystalline material obtained was identified as tetrathiafulvalene by IR spectroscopy and thin layer chromatography. The yield was >90%.

Synthesis of Deuterated Tetrathiafulvalene. Under similar conditions as described in the above, a solution of 1 (100 mg) in 20 mL of C_2H_5OD and THF (1:1) was reacted with a buffer

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solution of K_2CO_3 and $KHCO_3$ prepared in D_2O. Deuterated tetrathiafulvalene, 63 mg (95%), yield mp 118–119 °C (lit.[9] mp 119 °C), was obtained: IR (KBr, cm^{-1}) 2245 (C–D).

Synthesis of Tetrakis(methylthio)tetrathiafulvalene (4). To an ice-cold solution made from 400 mg of 1 in 10 mL of dried tetrahydrofuran was added 1 mL of 5 M methanesulfenyl bromide in methylene chloride under nitrogen. After the mixture was allowed to stand at room temperature for 0.5 h, tetrabutylammonium fluoride (4 mmol) in 4 mL of tetrahydrofuran was added. The solution was allowed to stand for 10 h and then the mixture was poured into ice water and extracted with CH_2Cl_2.

The product was isolated by chromatography using Florisil silica gel eluted with the mixed solvent of chloroform and hexane (1:2 by volume). A pure red-brown liquid product (190 mg) was obtained: yield 49%; IR (film, cm^{-1}) 3060, 2960, 1480, 1420, 1310, 1260, and 800; ^1H NMR ($CDCl_3$) δ 2.46 (s); mass spectrum, *m/e* 388. Anal. Calcd for $C_{10}H_{12}S_8$: C, 30.93; H, 3.09; S, 65.98. Found: C, 31.20; H, 3.12; S, 66.25.

Synthesis of Tetrakis(methylseleno)tetrathiafulvalene (5). To an ice-cold solution of 500 mg of 1 in 10 mL of dried tetrahydrofuran was added 5 mL of 1 M methaneselenenyl bromide in CH_2Cl_2 under nitrogen. After standing in an ice bath for 20 min, tetrabutylammonium fluoride (5 mmol) in 7 mL of dried tetrahydrofuran was added. The solution was allowed to stand at room temperature for 2 h. The product was purified by chromatography using Florisil silica gel eluted with the mixed solvent of hexane and methylene chlorine (2:1 by volume). A red-brown liquid (200 mg) was obtained: yield 35%; IR (film, cm^{-1}) 3060, 2920, 1400, 1265, 1245, 860, and 760; ^1H NMR ($CDCl_3$) δ 2.40 (s); mass spectrum, *m/e* 580 (based on ^{80}Se). Anal. Calcd for $C_{10}H_{12}S_4Se_4$: C, 20.69; H, 2.07; S, 22.07; Se, 55.17. Found: C, 21.20; H, 2.15; S, 22.28; Se, 54.20.

Synthesis of Tetrakis(phenylselenyl)tetrathiafulvalene (6). This compound was prepared from 1 with benzeneselenenyl bromide by a similar method to that described in above. 6 was obtained in 58–60% yield: IR (film, cm^{-1}) 3050, 1570, 1470, 1440, 1020, 740, and 680; ^1H NMR ($CDCl_3$) δ 6.7, 6.9; mass spectrum, *m/e* 825 (based on ^{80}Se). Anal. Calcd for $C_{30}H_{20}S_4Se_4$: C, 43.66; H, 2.44; S, 15.55; Se 38.30. Found: C, 43.50; H, 2.30; S, 16.10; Se, 37.50.

Acknowledgment. This research was financially supported by a generous grant from Koppers Company, Inc.

Registry No. 1, 96913-54-1; 1 (TCNQ complex), 96913-59-6; 2, 96913-55-2; 3, 96913-56-3; 4, 51501-77-0; 5, 96913-57-4; 6, 96913-58-5; TTF, 31366-25-3; TTF (deuterated), 51751-16-7; $Me_3SiC{\equiv}CSiMe_3$, 14630-40-1; $Me_3SiC{\equiv}CH$, 1066-54-2; CS_2, 75-15-0; CSe_2, 506-80-9; MeSBr, 41138-92-5; MeSeBr, 73501-41-4; PhSeBr, 34837-55-3.

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Synthesis and Physical Properties of 5,6-Dihydroxyindole

Bryan P. Murphy and Thomas M. Schultz*

Clairol Research Laboratory, P.O. Box 10213, Stamford, Connecticut 06922

Received August 8, 1984

5,6-Dihydroxyindole (2) is an important intermediate in melanogenesis, the process by which eumelanin, a black, intractable biopigment, is formed from L-3,4-dihydroxyphenylalanine (1) (Scheme I).[1] Generally, 2 is obtained either by saponification of 5,6-diacetoxyindole[2] or hydrogenolysis of 5,6-dibenzyloxyindole.[3] These methods yield only small quantities of pure 2, and until recently,[4,5] no attempts have been made to design a more efficient laboratory scale synthesis.

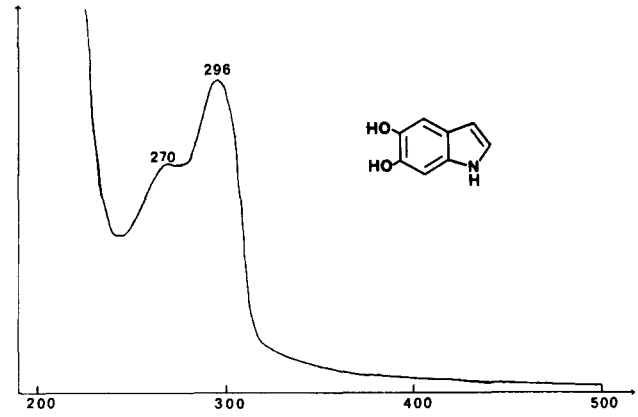
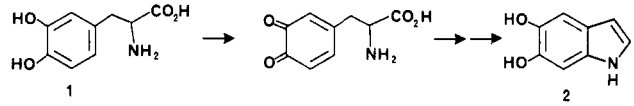
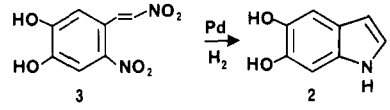


Figure 1. UV–vis spectrum of 5,6-dihydroxyindole in deaerated water.

Scheme I



Scheme II



A comprehensive summary of analytical data also is lacking, which makes in situ identification of 2 during melanogenesis difficult.

We have improved on the most recent technology: reductive cyclization of (*E*)-4,5-dihydroxy-2,β-dinitrostyrene (3) with noble metal catalysts in polar, hydroxylic solvents (Scheme II).[4,5] Herein we report these improvements and the first full summary of the physical properties of 5,6-dihydroxyindole from one source.

Results and Discussion

Catalytic hydrogenation of 3 in aqueous media gives variable yields of pure 5,6-dihydroxyindole, due to difficulty in isolation.[4] Our improvements have led to consistently higher yields of pure 2. In a typical synthesis, 3 was hydrogenated in methanol over 10% Pd/C at 50 psi, and the solvent was removed in vacuo, to give a black solid. Sonication of this material in dichloromethane produced a suspension, which yielded a golden colored solution after filtration. Concentration and chromatography (silica gel) with 1:1 dichloroethane/anhydrous diethyl ether gave nearly colorless crystals of 2.

The UV–visible spectrum (Figure 1) has λ_{max} = 296 nm in degassed H_2O (log ϵ 3.52).[6] The pK_a value for the first ionization (5-hydroxyl group) was found to be 8.9. The value for the second ionization (6-hydroxyl group) was difficult to determine accurately, due to eumelain formation at high pH, but is greater than 10.2. These assignments were based on the observation that 5,6-dihydroxy-

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