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A New Class of Sulfur-Linked Bis-1,2,3-selenadiazoles, 1,2,3-Thiadiazoles, and 2*H*-diazaphospholes

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ABSTRACT: *Novel sulfur-linked bis-heterocycles, bis-1,2,3-selenadiazoles* **4**, *1,2,3-thiadiazoles* **5**, *and 2H-diazaphospholes* **7**, *were synthesized from bis(2-oxo-2-phenylethanone)sulfide* **2** *by adopting a simple and well-versed methodology.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:261–265, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20425

INTRODUCTION

The chemistry of compounds having α-ketomethylene group has evoked considerable interest because of their utility as building blocks for the development of heterocyclic ring systems. A number of heterocyclic compounds containing nitrogen and sulfur exhibit a variety of biological activities. The concept of isosteric exchange is a tool for modifying the activity of biologically important molecules. One such isosteric pair constitutes sulfur and selenium. The medicinal applications of isosterism have been reviewed by Schatz [1]. Substitution of selenium for oxygen and sulfur in chemotherapeutically active compounds is impeded by the toxic nature of selenium. In general, when selenium is part of a functional group, namely, —SeH and $-SeO_3H$, it tends to be more toxic than their sulfur analogs [2]. But when selenium is part of a ring system, the toxicity of sulfur and selenium does not differ widely. This paves the way toward the development of selenium-containing drugs like ^{75}Se-selenomethionine used in pancreatic scanning [3]. Some arylsulfonyl-1,2,3-selenadiazoles and arylsulfonyl-1,2,5-selenadiazoles exhibit antimicrobial activity [4] Besides, sulfur-containing heterocycles such as thiadiazoles are well known for their pronounced biological activity [4d,5]. In view of our successful results toward the development of a variety of heterocycles of this type [6], herein we wish to report bis-heterocycles incorporating 1,2,3-selenadiazole, thiadiazole, and 2*H*-diazaphosphole moieties.

RESULTS AND DISCUSSION

The general synthetic pathway is depicted in Scheme 1. Bis(2-oxo-2-phenyl-ethane)sulfide **2** was taken as a substrate to prepare bis-heterocycles. In fact, **2** was obtained by the reaction of 2 equivalents of phenacyl bromide **1** with 1 equivalent of Na_2S in methanol. Treatment of **2** with semicarbazide hydrochloride gave bis(1-phenyl-ethanonesemicarbazone)sulfide **3**. The compound **3** displayed bands in the region 3208–3484 (NHCO and $CONH_2$) and 1635–1650 cm^{-1} (C=N) corresponding to a semicarbazone moiety. The ^{1}H NMR

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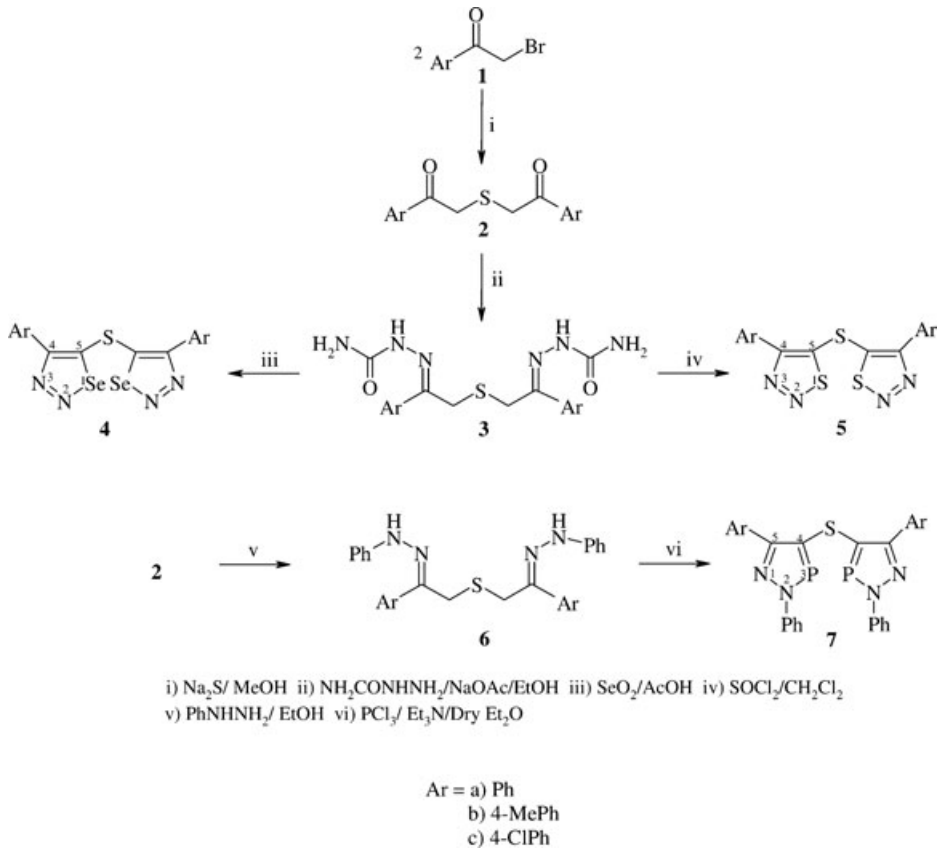

SCHEME 1

spectrum of **3a** showed a sharp singlet at 3.95 ppm for methylene protons and two broad singlets at 9.89 and 6.62 ppm for NH and NH_2, respectively, that disappeared on deuteration. Oxidative cyclization of **3** with SeO_2 in AcOH gave bis(4-phenyl-1,2,3-selenadiazole-5-yl)sulfide **4**. On the other hand, the Hurd–Mori reaction of **3** with $SOCl_2$ produced bis(4-phenyl-1,2,3-thiadiazole-5-yl)sulfide **5.** The IR spectra of **4** and **5** exhibited bands around 1420–1440 (N=N) and 675–720 cm^{-1} (C—Se/S). A multiplet corresponding to aromatic protons in the ^1H NMR spectra of **4** and **5** was observed in the region 7.20–7.93 ppm. Thus, the absence of a singlet due to a methylene group and broad singlets due to NH and NH_2 confirmed their formation. Similarly, the reaction of **2** with 2 equivalents of phenylhydrazine gave bis(1-phenylethanonephenylhydrazone)sulfide **6**. The absorption bands present in the IR spectra of **6** in the region 3285–3300 and 1632–1639 cm^{-1} were assigned to NH and C=N functional groups, respectively. The ^1H NMR spectrum of **6a** displayed two singlets at 2.31 ppm due to methylene protons. Apart from this, a broad singlet was observed at 9.89 ppm due to NH that was disappeared on deuteration. Heterocyclization of **6** with PCl_3 in Et_3N at −5°C to −10°C [7] resulted in bis(2,5-diphenyl-2*H*-1,2,3-diazaphosphole-4-yl)sulfide **7**. The ^1H NMR spectrum of **7a** displayed a multiplet at 7.12–7.72 ppm due to aromatic protons. The structures of **4, 5**, and **7** were further ascertained by ^{13}C NMR spectra. The ^{31}P NMR spectra of **7** displayed a signal between −209 and −211 ppm due to the di-coordinated phosphorous of 2*H*-diazaphospholes.

The lead compounds **4, 5**, and **7** were tested for antimicrobial activity at three different concentrations 25, 75, and 100 μg per disk. The compounds were evaluated for antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive bacteria), and *Escherichia coli* and *Klebsiella pneumoniae* (Gram-negative bacteria) on nutrient agar plates at 37°C for 24 h using Gentamycin as a reference drug. The antifungal activity was screened against *Fusarium solani*, *Curvularia lunata*, *Asperigillus niger*, and *Cunninghemella elegans* using Nystatin (25 μg per disk) as a standard drug. Fungal cultures were grown on potato dextrose broth at 25°C for 3 days. Then, the spore suspension was adjusted to 10^6 pores mL^{-1} (fungi) at 0.1 and 0.2 mg mL^{-1} concentration by using the Vincent and Vincent method [8].

All the compounds possessed moderate to high antibacterial activity toward both Gram-positive and Gram-negative bacteria. In general, all the compounds showed more activity against Gram-positive bacteria when compared to Gram-negative bacteria. It was also observed that compounds having diazaphosphole moiety exhibited comparatively high-antibacterial activity than other compounds. The results revealed that majority of the synthesized compounds showed various degrees of inhibition against the tested microorganisms. The compounds having diazaphophole moiety exhibited high-antibacterial activity against both Gram-positive (36–39 mm) and Gram-negative (24–32 mm) bacteria than the other compounds. The compounds having selenadiazole and thiadiazole units displayed moderate activity against both the bacteria (18–23 mm).

All the test compounds effectively inhibit germination against tested fungi at higher concentrations. It was observed that there was no marked difference in antifungal activity of compounds having 1,2,3-selenadiazole and 1,2,3-thiadiazole units. Further bioassay studies on these compounds are in progress.

EXPERIMENTAL

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, British Drug House (BDH), ethyl acetate–hexane (0.5:2)). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets, and the wave numbers are given in cm^{-1}. The ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian EM-360 spectrometer. The ^{13}C NMR spectra were run on a Varian VXR spectrometer operating at 75.5 MHz with $CDCl_3$ as solvent. All chemical shifts are reported in ppm from TMS as an internal standard. Microanalyses were performed using Perkin-Elmer 240C elemental analyzer. The starting compounds, phenacyl bromides, were prepared as per the procedure reported earlier [9].

*Bis(2-oxo-2-phenyl-ethane)sulfide (**2**)*

A solution of sodium sulfide (1.1 mmol) in methanol (25 mL) was taken and stirred at 0–10°C. To this, phenacyl bromide **1** (1 mmol) in methanol (30 mL) was added dropwise while stirring over a period of 30–40 min. The stirring was continued for an additional period of 3 h, maintaining the same temperature. The separated solid was collected by filtration, washed with water, dried and purified by recrystallization from aqueous methanol: bis(1-phenyl-ethanonesemicarbazone)sulfide (1.67 g, 62%): mp 66–68°C; bis(1-*p*-tolyl-ethanonesemicarbazone)sulfide (2.02 g, 68%): mp 82–84°C; bis(1-*p*-chlorophenyl-ethanonesemicarbazone)sulfide (2.4 g, 71%): mp 76–78°C.

*Bis(1-phenyl-ethanonesemicarbazone)sulfide (**3**)*

A mixture of **2** (1.0 mmol), semicarbazide hydrochloride (2.4 mmol), and sodium acetate (2.4 mmol) in 20 mL of ethanol was refluxed for 1–2 h. It was concentrated, cooled, and poured onto crushed ice. The separated solid was filtered, washed with water, and dried and purified by recrystallization from methanol.

*Bis(1-phenyl-ethanonesemicarbazone)sulfide (**3a**).* White solid, yield: 68%, mp 101–103°C. IR(KBr) ν: 1685, 1571 (NHCO), 1635 (C=N), 3482, 3215 (NH and NH_2). ^1H NMR (DMSO-d_6): δ 3.95 (s, 4H, S-CH_2), 6.62 (s, 4H, NH_2), 7.32–7.83 (m, 10 arom. H), 9.89 (bs, 2H, NH).

*Bis(1-p-tolyl-ethanonesemicarbazone)sulfide (**3b**).* White solid, yield: 62%, mp 111–113°C. IR(KBr) ν: 1690, 1568 (NHCO), 1642 (C=N), 3478, 3210 (NH and NH_2). ^1H NMR (DMSO-d_6): δ 2.45 (s, 3H, $-CH_3$), 3.92 (s, 4H, S-CH_2), 6.60 (s, 4H, NH_2), 7.62–7.82 (m, 8 arom. H), 9.43 (bs, 2H, NH).

*Bis(1-p-chlorophenyl-ethanonesemicarbazone)sulfide (**3c**).* White solid, yield: 72%, mp 122–124°C. IR(KBr) ν: 1695, 1574 (NHCO), 1650 (C=N), 3484, 3208 (NH and NH_2). ^1H NMR (DMSO-d_6): δ 3.99 (s, 4H, S-CH_2), 6.66 (s, 4H, NH_2), 7.38–7.93 (m, 10 arom. H), 9.71 (bs, 2H, NH).

*Bis(4-phenyl-1,2,3-selenadiazole-5-yl)sulfide (**4**)*

The compound bis(1-phenyl-ethanonesemicarbazone)sulfide **2** (1 mmol) was dissolved in glacial acetic acid (10 mL) and warmed gently with stirring. To this, selenium dioxide (2 mmol) was added portionwise during a period of 20 min at 60–70°C, and stirring was continued for 4–5 h. The reaction mixture was cooled and poured onto crushed ice. The separated solid was collected by filtration, washed with saturated sodium bicarbonate solution followed by water and dried. The resultant solid was purified by column chromatography (silica gel, hexane–ethyl acetate (2:1)).

*Bis(4-phenyl-1,2,3-selenadiazole-5-yl)sulfide (**4a**).* Red solid, yield: 65%, mp 130–132°C. IR (KBr) ν: 712 (C—Se), 1437 (N=N). ^1H NMR (DMSO-d_6): δ 7.32–

7.56 (10H, m, H_{arom}). ^{13}C NMR (DMSO-d_6): δ 145.5 (C-5), 154.6 (C-4), 127.4, 128.9, 132.2, 134.7 (aromatic carbons). Anal. Calcd for $C_{16}H_{10}N_4SSe_2$ (448.26): C, 42.87; H, 2.25; N, 12.50. Found: C, 42.98; H, 2.20; N, 12.62.

*Bis(4-p-tolyl-1,2,3-selenadiazole-5-yl)sulfide (**4b**).* Red solid, yield: 71%, mp 126–128°C. IR (KBr) ν: 699 (C—Se), 1432 (N=N). ^1H NMR (DMSO-d_6): δ 2.25 (s, 6H, —CH_3), 7.21–7.63 (m, 8 arom. H).^{13}C NMR (DMSO-d_6): δ 26.7 (Ar-CH_3), 144.8 (C-5), 154.3 (C-4), 126.1, 128.4, 132.9, 133.5 (aromatic carbons). Anal. Calcd for $C_{18}H_{14}N_4SSe_2$ (476.32): C, 45.39; H, 2.96; N, 11.76. Found: C, 45.54; H, 3.00; N 11.73.

*Bis(4-p-chlorophenyl-1,2,3-selenadiazole-5-yl)-sulfide (**4c**).* Red crystals, yield: 62%, mp 138–140°C. IR(KBr) ν: 719 (C—Se), 1439 (N=N). ^1H NMR (DMSO-d_6): δ 7.41–7.93 (m, 8 arom H). ^{13}C NMR (DMSO-d_6): δ 146.3 (C-5), 155.1 (C-4), 125.4, 128.1, 131.5, 133.9 (aromatic carbons). Anal. Calcd for $C_{16}H_8Cl_2N_4SSe_2$ (517.15): C, 37.16; H, 1.56; N, 10.83. Found: C, 37.04; H, 1.51; N, 10.94.

*Bis(4-phenyl-1,2,3-thiadiazole-5-yl)sulfide (**5**)*

To a well-cooled solution of bis(1-phenyl-ethanone-semicarbazone)sulfide **2** (1 mmol) in dichloromethane (20 mL), an excess of thionyl chloride (9 mL) was added portionwise while stirring and the mixture was allowed to attain room temperature. After stirring for 2–3 h, the excess thionyl chloride was decomposed with cold saturated sodium carbonate solution. The organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The resultant solid was purified by column chromatography (silica gel, hexane–ethyl acetate, (2:0.5)).

*Bis(4-phenyl-1,2,3-thiadiazole-5-yl)sulfide (**5a**).* White solid, yield: 65%, mp 146–148°C. IR (KBr) ν: 677 (C—S), 1432 (N=N). ^1H NMR (DMSO-d_6): δ 7.42–7.86 (m, 10 arom H). ^{13}C NMR (DMSO-d_6): δ 142.7 (C-5), 152.3 (C-4), 125.5, 127.3, 131.4, 133.6 (aromatic carbons). Anal. Calcd for $C_{16}H_{10}N_4S_3$ (354.48): C, 54.21; H, 2.84; N, 15.81. Found: C, 54.33; H, 2.90; N, 15.75.

*Bis(4-tolyl-1,2,3-thiadiazole-5-yl)sulfide (**5b**).* White solid, yield: 74%, mp 152–154°C. IR(KBr) ν: 683 (C—S), 1422 (N=N). ^1H NMR (DMSO-d_6): δ 2.35 (6H, s, —CH_3), 7.20–7.45 (m, 8 arom. H). ^{13}C NMR (DMSO-d_6): δ 25.4 (Ar-CH_3), 140.3 (C-5), 151.6 (C-4), 125.8, 126.6, 129.2, 132.4 (aromatic carbons). Anal. Calcd for $C_{18}H_{14}N_4S_3$ (382.53): C, 56.52; H, 3.69; N, 14.65. Found: C, 56.38; H, 3.65; N, 14.60.

*Bis(4-p-chlorophenyl-1,2,3-thiadiazole-5-yl)sulfide (**5c**).* White solid, yield: 76%, mp 168–170°C. IR(KBr) ν: 714 (C—S), 1436 (N=N). ^1H NMR (DMSO-d_6): δ 7.58–7.90 (m, 8 arom. H); ^{13}C NMR (DMSO-d_6): δ 141.5 (C-5), 152.7 (C-4), 126.3, 127.7, 131.9, 133.3 (aromatic carbons). Anal. Calcd for $C_{16}H_8Cl_2N_4S_3$ (423.37): C, 45.39; H, 1.90; N, 13.23. Found: C, 45.31; H, 1.99; N, 13.32.

*Bis(1-phenyl-ethanonephenylhydrazone)sulfide (**6**)*

To a solution of bis(2-oxo-2-phenyl-ethane)sulfide **2** (1 mmol) in ethanol (15 mL), phenylhydrazine (2.2 mmol) was added and refluxed for 2–3 h. The reaction mixture was concentrated and cooled. The solid separated was filtered, washed with water, dried, and purified by recrystallizition from ethanol.

*Bis(1-phenyl-ethanonephenylhydrazone)sulfide (**6a**).* White solid, yield: 69%, mp 112–114°C. IR(KBr) ν: 1635 (C=N), 3285 (NH). ^1H NMR (DMSO-d_6): δ 2.31 (s, 4H, S-CH_2), 7.32–7.83 (m, 20 arom. H), 9.89 (bs, 2H, NH).

*Bis(1-p-tolyl-ethanonephenylhydrazone)sulfide (**6b**).* White solid, yield 77%, mp 121–124°C. IR(KBr) ν: 1632 (C=N), 3290 (NH). ^1H NMR (DMSO-d_6): δ 2.21 (s, 6H, —CH_3), 2.35 (s, 4H, S-CH_2), 7.62–7.81 (m, 18 arom. H), 9.75 (bs, 2H, NH).

*Bis(1-p-chlorophenyl-ethanonephenylhydrazone)-sulfide (**6c**).* White solid, yield: 75%, mp 135–137°C. IR(KBr) ν 1639 (C=N), 3300 (NH). ^1H NMR (DMSO-d_6): δ 2.40 (s, 4H, S-CH_2), 7.52–7.93 (m, 18 arom. H), 9.71 (bs, 2H, NH).

*Bis(2,5-diphenyl-2H-1,2,3-diazaphosphole-4-yl) sulfide (**7**)*

To a well-cooled solution of phosphorus trichloride (3 mmol) in dry ether (15 mL) under nitrogen atmosphere maintained at –5 to –10°C, the compound **6** (1 mmol) in dry ether (10 mL) was added dropwise and stirred well. To this, triethylamine (1.2 mmol) was added and stirring was continued for 3–4 h. The ethereal layer was separated, washed with sodium bicarbonate solution, water and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The resulting solid was purified by column chromatography (silica gel, hexane–ethyl acetate (2:1)).

*Bis(2,5-diphenyl-2H-1,2,3-diazaphosphole-4-yl)-sulfide (**7a**).* White solid, yield: 64%, mp 166–

168°C. IR(KBr) ν: 1629 (C=N). ^{1}H NMR (DMSO-d_6): δ 7.12–7.72 (m, 20 arom. H). ^{13}C NMR (DMSO-d_6): δ 146.3 (C-5), 159.7 (C-4, J_{cp} = 54 Hz), 115.1, 118.5, 128.6, 129.0, 129.3, 130.8, 131.2, 134.7 (aromatic carbons). Anal. Calcd for $C_{28}H_{20}N_4P_2S$ (506.50): C, 66.40; H, 3.98; N, 11.06. Found: C, 66.32; H, 3.92; N, 11.16.

*Bis[2-phenyl(5-p-tolyl-2H-1,2,3-diazaphosphole-4-yl)sulfide (***7b***).* White solid, yield: 67%, mp 152–154°C. IR(KBr) ν: 1638 (C=N). ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 6H, –CH_3), 7.10–7.68 (m, 18 arom. H). ^{13}C NMR (DMSO-d_6): δ 25.4 (–CH_3), 145.9 (C-5), 156.8 (C-4, J_{cp} = 53 Hz), 114.7, 116.3, 129.1, 129.8, 130.4, 131.2, 132.5, 135.2 (aromatic carbons). Anal. Calcd for $C_{30}H_{24}N_4P_2S$ (534.55): C, 67.41; H, 4.53; N, 10.48. Found: C, 67.50; H, 4.58; N, 10.57.

*Bis[2-phenyl(5-p-chlorophenyl-2H-1,2,3-diazaphosphole-4-yl)sulfide (***7c***).* White solid, yield: 72%, mp 175–177°C. IR(KBr) ν: 1641 (C=N). ^{1}H NMR (DMSO-d_6): δ 7.21–7.73 (m, 18 arom. H). ^{13}C NMR (DMSO-d_6): δ 146.4 (C-5), 157.6 (C-4, J_{cp} = 57 Hz), 115.4, 118.9, 128.1, 129.5, 129.9, 130.4, 131.6, 136.3 (aromatic carbons). Anal. Calcd for $C_{28}H_{18}Cl_2N_4P_2S$ (575.39): C, 58.45; H, 3.15; N, 9.74. Found: C, 58.57; H, 3.18; N, 9.70.

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