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Synthesis of Novel Thia-Oxadiazolophanes

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ABSTRACT: *The novel thia-1,3,4-oxadiazolophanes were synthesized regioselectively from 1,4-bis(5-mercapto-1,3,4-oxadiazol-2-yl)butane and various 1,ω-dihaloalkanes in presence of potassium hydroxide.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:273–275, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10141

INTRODUCTION

Since the discovery of crown ethers by Pedersen [1], the chemistry of macrocyclic compounds has developed in a new dimension, viz. cation complexation using the legating macrocycles and their applications to biological and physical sciences [2]. In the pursuit of obtaining macrocycles having maximum legating ability and applicability, a large number of macrocycles have been synthesized and reported till date [3]. The field of heterophanes where heteroaromatic subunits are incorporated in the macrocycles is not an exception to this [4]. The special ability of sulfur-containing macrocycles to form stronger complexes with transition metals has been recognized [2]. A large number of sulfur-containing macrocycles have been synthesized so far. We have earlier reported the regioselective synthesis of *N*-amino triazolophanes [5] and oxadiazolophanes [6].

In continuation to this work, we now report the regioselective synthesis of thia-bis-1,3,4-oxadiazolophanes.

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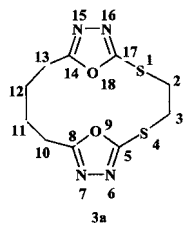
RESULTS AND DISCUSSION

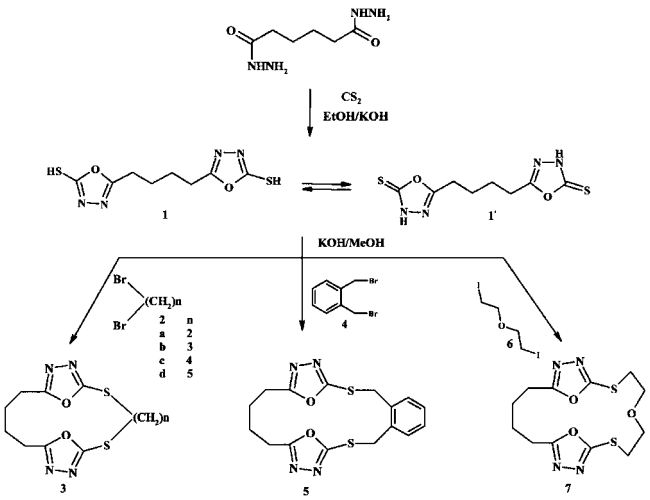
The biological activity of the mercapto-oxadiazole unit has given it a significant importance [7]. The starting synthon 1,4-bis(5-mercapto-1,3,4-oxadiazol-2-yl)butane (**1**) was prepared in good yields by refluxing adipic acid dihydrazide and carbon disulphide with ethanolic potassium hydroxide (Scheme 1).

^{13}C NMR of the compound exhibited the predominance of thione form **1′** as was evident by the appearance of the peak for C=S at δ 178.0 ppm. When compound **1** was treated with various 1,ω-dihalocompounds in the presence of organic bases like triethylamine or pyridine, a mixture of products with sticky polymeric nature was obtained, which could not be characterized. However, in the presence of alcoholic potassium hydroxide under high dilution conditions, a single product was obtained after work up. For example, the reaction of **1** with 1,2-dibromoethane **2a** resulted in the formation of the desired heterophane **3a**, confirmed on the basis of NMR spectra.



3a

The absence of a peak for C=S in the ^{13}C NMR spectra confirmed the S-alkylated product. The ^{1}H NMR showed peaks for 2,3-H at δ 3.10; for 10,13-H at δ 2.91; and for 11,12-H at δ 1.91. ^{13}C NMR showed signals of C-2,3 at δ 32.02; C-10,13 at 25.31; and C-11,12 at 24.89 ppm. The signals of the oxadiazole carbon



SCHEME 1 Synthesis of oxadiazolophanes.

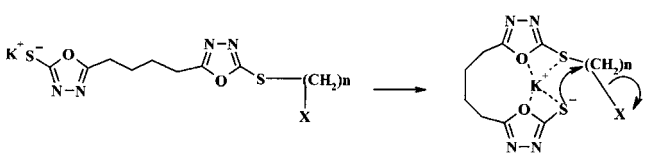
atoms were observed at δ 164.64 and 167.76 ppm. Compound **3a** was identified as 1,4-dithia-(2′,5′)-1′,3′,4′-oxadiazolo[4.4]phane [8].

The other 1,ω-dibromoalkanes ($n = 3$–5) similarly afforded the desired heterophanes **3b–d**. 1,2-Bis-(bromomethyl)benzene (**4**) and bis-iodoethylether (**6**) also reacted with compound **1** in similar manner to afford compounds **5** and **7**, respectively. Details of compounds **5** and **7** are given in the Experimental section with the other heterophanes.

We assume that the potassium ions help in the formation of template under high dilution conditions for the second intramolcular alkylation reaction which regioselectively occurred at sulfur (Scheme 2).

EXPERIMENTAL

The NMR spectra were recorded on Bruker AMX 500 spectrometer. Melting points were taken in open capillaries and are uncorrected. Mass spectrum of compound **3d** was recorded on Shimadzu GC-MS instrument. The C, H, N, S analysis of the compounds is in agreement with the theoretical values. The 1,ω-dihaloalkanes were obtained from E-Merck.



SCHEME 2

*Synthesis of 1,4-Bis(5-mercapto-1,3,4-oxadiazol-2-yl)butane (**1**)*

Adipic acid dihydrazide (8.7 g, 0.05 mol) and potassium hydroxide (8.4 g, 0.15 mol) were added to dry ethanol in a round-bottom flask fitted with a reflux condenser and the mixture was refluxed for 30 min. It was then cooled to room temperature and carbon disulfide (12 ml, 0.15 mol) was added in portions over 15 min. The mixture was again refluxed for 6 h and concentrated to half volume. A yellow-colored crystalline solid separated on cooling. It was filtered and redissolved in water. The cold aqueous solution was neutralized with dilute hydrochloric acid to obtain a white powder. It was filtered, washed with cold water, and dried on air. Yield 60%, m.p. 204°C. ^{1}H NMR: (DMSOd_6) δ 1.73 (m, 4H, 2 × C=N−CH_2−C$\underline{H}_2$), 2.77 (m, 4H, 2 × C=N−CH_2), 13.9 (broad peak, 2H, −NH, D_2O exchangeable). ^{13}C NMR: 24.4 (C=N−CH_2-$\underline{C}H_2$), 24.7 (C=N−$\underline{C}H_2$), 164.4 (−CH_2−$\underline{C}$=N), 178.0 ppm (C=S).

Synthesis of Oxadiazolophanes **3a–d**

Compound **1** 1.3 g (0.005 mol) was dissolved in aq. methanol (200 ml, 95:5) containing 0.56 g (0.01 mol) of potassium hydroxide. 1,ω-Dihaloalkane **2** (0.005 mol) was added to it dropwise over a period of 30 min. The mixture was then refluxed with stirring for 6–8 h; it was then concentrated to 1/4th volume and then dumped into water. A semisolid compound was obtained, which was triturated with acetone to afford low melting solid **3a–d**. Compound **5** was synthesized in a similar manner where bis-bromomethyl benzene **4** was added as methanolic solution.

*1,5-Dithia-(2′,5′)-1′,3′,4′-oxadiazolo[5.4]phane (**3b**)*

^{1}H NMR: ($CDCl_3$) δ 1.86 (m, 4H, 2 × C=N−CH_2−C$\underline{H}_2$), 2.31 (p, J = 7 Hz, 2H, −S−CH_2−C$\underline{H}_2$), 2.85 (m, 4H, 2 × C=N−C$\underline{H}_2$), 3.31 (t, 4H, 2 × S−C$\underline{H}_2$). ^{13}C NMR: 24.90 (2 × C=N−CH_2−C$\underline{H}_2$), 25.44 (2 × C=N−$\underline{C}H_2$), 28.64 (−S−CH_2−$\underline{C}H_2$), 30.90 (−S−$\underline{C}H_2$−), 163.82 (−CH_2−$\underline{C}$=N), 167.40 ppm (S−$\underline{C}$=N).

*1,6-Dithia-(2′,5′)-1′,3′,4′-oxadiazolo[6.4]phane (**3c**)*

^{1}H NMR: ($CDCl_3$) δ 1.89 (m, 4H, 2 × S−CH_2−C$\underline{H}_2$), 1.97 (m, 4H, 2 × C=N−CH_2−C$\underline{H}_2$), 2.88 (m, 4H, 2 × C=N−C$\underline{H}_2$), 3.25 (m, 4H, 2 × S−C$\underline{H}_2$). ^{13}C NMR: 24.93 (2 × C=N−CH_2−C$\underline{H}_2$), 25.51 (2 × C=N−$\underline{C}H_2$), 28.15 (−S−CH_2−$\underline{C}H_2$), 31.70 (−S−$\underline{C}H_2$), 163.75 (−CH_2−$\underline{C}$=N), 167.27 ppm (S−$\underline{C}$=N).

*1,7-Dithia-(2′,5′)-1′,3′,4′-oxadiazolo[7.4]phane (**3d**)*

^{1}H NMR: ($CDCl_3$) δ 1.75–1.88 (m, 10H, $-S-CH_2-(C\underline{H}_2)_3$ and 2 × $C{=}N-CH_2-C\underline{H}_2$), 2.77 (m, 4H, 2 × $C{=}N-CH_2$), 3.21 (m, 4H, 2 × $S-C\underline{H}_2$). ^{13}C NMR: 24.92 (2 × $C{=}N-CH_2-C\underline{H}_2$), 25.51 (2 × $C{=}N-\underline{C}H_2$), 27.43 ($-S-CH_2-CH_2-\underline{C}H_2$), 28.63 ($-S-CH_2-\underline{C}H_2$), 32.13 ($-S-\underline{C}H_2$), 164.32 ($-CH_2-\underline{C}{=}N$), 167.18 ppm ($S-\underline{C}{=}N$). GC-MS: retention time 4.1 min. M^+ *m/z* 326.

*3,4-Benz-1,6-dithia-(2′,5′)-1′,3′,4′-oxadiazolo-[6.4]phane (**5**)*

^{1}H NMR: ($CDCl_3$) δ 1.87 (m, 4H, 2 × $C{=}N-CH_2-C\underline{H}_2$), 2.88 (m, 4H, 2 × $C{=}N-C\underline{H}_2$), 4.60 (s, 4H, 2 × $S-C\underline{H}_2$), 7.26–7.44 (m, 4H, aromatic protons); ^{13}C NMR: 24.98 (2 × $C{=}N-CH_2-\underline{C}H_2$), 25.43 (2 × $C{=}N-\underline{C}H_2$), 34.22 ($S-C\underline{H}_2$), 129.03, 131.19, and 134.00 (aromatic carbons), 163.51 ($-CH_2-\underline{C}{=}N$), 167.47 ppm ($S-\underline{C}{=}N$).

*Synthesis of 4-Oxa-1,7-dithia-(2′,5′)-1′,3′,4′-oxadiazolo[7.4]phane (**7**)*

Bis-2-chloroethyl ether (0.01 mol, 1.1 ml) and KI (0.03 mol, 5 g) in dry acetone were heated together under reflux for 8 h. The solution was filtered and excess of acetone was then removed. The residue was dissolved in methanol (30 ml) and added dropwise to the solution of potassium salt of compound **1** (0.01 mol). The mixture was refluxed with stirring for 10 h and worked up as mentioned earlier to obtain compound **7**. ^{1}H NMR: ($CDCl_3$) δ 1.90 (m, 4H, 2 × $C{=}N-CH_2-C\underline{H}_2$), 2.88 (m, 4H, 2 × $C{=}N-C\underline{H}_2$), 3.42 (t, 4H, 2 × $S-C\underline{H}_2$), 3.86 (t, 4H, 2 × $S-CH_2-C\underline{H}_2-O$), ^{13}C NMR: 24.77 (2 × $C{=}N-CH_2-C\underline{H}_2$), 25.34 (2 × $C{=}N-\underline{C}H_2$), 31.99 ($-S-\underline{C}H_2$), 68.83 ($-S-CH_2-\underline{C}H_2-O$), 164.00 ($-CH_2-\underline{C}{=}N$), 167.19 ppm ($S-\underline{C}{=}N$).

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