Convergent Synthesis of Macrocycles Composed of 5-Amino-2H-1,2,4-thiadiazolin-3-one or 5-Amino-2H-1,2,4-thiadiazolone-3-thione and 1,3-Benzenedimethanethiol

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Transition metal complexes with peripheral sites capable of hydrogen-bonding or π-stacking interactions to form groups have recently been used as hosts to bind neutral guests, such as aliphatic amines, aromatic amines, hydrazines, DNA nucleobases, amino acids, and barbiturate. This form of host is referred to as a metalloreceptor. The construction of hosts with metal ions in the scaffold has allowed the binding of many structurally sophisticated guests. Consequently, the design and study of various metal-containing macrocycles is one of the most active and interesting areas in modern supramolecular chemistry. Coordinate covalent bond formation offers new prospects for interesting areas in modern supramolecular chemistry.

Results and Discussion

Compound (1) is regiospecifically O-alkylated under NaH basic conditions to give 5-amino-3-alkoxy-1,2,4-thiadiazole. Using this reaction, a macrocycle 5, containing two 5-amino-1,2,4-thiadiazole subunits linked to the 3- and 5-positions of the heterocyclic unit was prepared from 1, as shown in Scheme 1. The anion of compound 1 was prepared in the presence of NaH in 1-methyl-2-pyrrolidinone and DMF; it was alkylated with ethylene glycol dimethanesulfonate to afford the O-alkylated compound (3). The formation of 3 was confirmed by its 1H and 13C NMR spectra. In 3, the NH of compound 1 was replaced by an OCH2CH2OCH2CH2OMs signal at 4.44, 4.38, 3.80, and 3.09 ppm in the 1H NMR spectrum and 69.4, 69.2, 68.8, 67.8, and 37.6 ppm in the 13C NMR spectrum. To provide possible chelation sites that allow the formation of complexes with metal ions, the 1,3-benzenedimethanethiol anion was produced in a 2-propanol solution of sodium 2-propanoxide and alkylated with 3 to give an S-alkylated compound (4). The formation of 4 was also confirmed by its 1H and 13C NMR spectra. In 4, the SH of 1,3-benzenedimethanethiol was replaced by a SCH2CH2OCH2CH2O-1,2,4-thiadiazole signal at 6.64, 4.42, 3.74, 3.62, and 2.60 ppm in the 1H spectrum and 138.6, 129.6, 128.6, 127.6, and 36.7 ppm in the 13C NMR spectrum. The disappearance of the mesyl group of compound 3 at 3.09 and 37.6 ppm in the 1H and 13C NMR spectra, respectively and the appearance of a 1,3-xylenyl group at 7.27-7.17 and 3.74 ppm in the 1H spectrum and 138.6, 129.6, 128.6, 127.6, and 36.7 ppm in the 13C NMR spectrum also supported the formation of 4. The target macrocycle was obtained via cyclization involving N,N-diaclylation of 4 at the NH2 of the 1,2,4-thiadiazole rings using diglycolyl chloride with a high dilution technique. The diglycolyl chloride solution was added to CH2Cl2 solution of 4 over a 24 hr period. The structure of the macrocycle was firmly established by 1H and 13C NMR, IR, and HRMS. The successful macrocyclization of 4 to 5 was supported by evidence of N-acylation, indicated by the NHCOCH2 group that replaced NH2 at 12.91, and 4.51 ppm in the 1H spectrum and 167.2
We reported the synthesis of bis(5-amino-1,2,4-thiadiazolyl)-3,3'-disulfide (7) and the S-alkylation of compound (7) at the 3-position under basic conditions to afford 3-alkylthio-5-amino-1,2,4-thiadiazole. Using this reaction, macrocycle 8 was synthesized, and it had the same scaffold as macrocycle 5. The only structural difference between 8 and 5 was the atom linking the 1,2,4-thiadiazole subunit, which is sulfur in 8 and oxygen in 5. Macrocycle 8 was synthesized as shown in Scheme 2. The synthesis sequence of 8 differs from that of 5. The chelation sites were built first and then the 1,2,4-thiadiazole rings were introduced. Therefore, the S-alkylation of 1,3-benzenedimethanethiol was performed with 1,5-dichloro-3-oxapentane, which was the similar method as used to convert 3 to 4, to prepare 6. The formation of 6 was confirmed by its \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra. In 6, the SH of 1,3-benzenedimethanethiol was replaced by a SCH_2CH_2OCH_2CH_2Cl signal at 3.71, 3.63, 3.56, and 2.56 ppm, and 70.2, 69.9, 43.6, and 30.3 ppm in the \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra, respectively.

To introduce the 1,2,4-thiadiazole rings, the S-alkylation of bis(5-amino-1,2,4-thiadiazolyl)-3,3'-disulfide (7) was performed at the 3-position of 7 in the presence of K_2CO_3. The structure of 8 was confirmed by \(^1\text{H}\) and \(^{13}\text{C}\) NMR. The chlorine of 6 was replaced by a 1,2,4-thiadiazole ring signal.

![Scheme 1](image1.png)  
**Scheme 1.** Synthesis of macrocycle containing two 5-amino-2H-1,2,4-thiadiazolin-3-one subunits.

![Scheme 2](image2.png)  
**Scheme 2.** Synthesis of macrocycle containing two 5-amino-2H-1,2,4-thiadiazoline-3-thione subunits.
at 8.03 ppm and 183.7 and 166.5 ppm, respectively. The S-alkylation was strongly supported by the typical chemical shift in which CH₂Cl changes to 3.24 and 30.9 ppm from 3.72 and 42.8 ppm in the ¹H and ¹³C NMR spectra, respectively. Target macrocycle 9 was obtained by cyclization using N,N-diacylation following the acylation procedure used for 4. The structure of 9 was determined using the same method as for 5.

**Experimental Section**

The IR spectra were recorded on a Jasco Report-100 spectrophotometer. The ¹H and ¹³C NMR spectra were obtained using a JEOL JNM-AL400 spectrometer at 400 MHz and 100 MHz respectively with tetramethylsilane as the internal reference. NMR measurements were performed at the Central Research Facilities of Chungnam National University. Elemental analyses were carried out on an EA 1110 (CE Instrument). FAB-HRMS spectra were obtained on a JEOL-JMS HX-100/110A spectrometer at Korea Basic Science Institute, Taeduk, Taejon.

The synthesis of 5-amino-2H-1,2,4-thiadiazolin-3-one (1) and bis(5-amino-1,2,4-thiadiazolyl)-3,3’-disulfide followed the previous literature procedures.

**5-(5-Amino-1,2,4-thiadiazol-3-yl)oxa-3-oxapentyl methanesulfonate (3).** Compound (1) (5.0 g, 42.68 mmol) was dissolved in heated anhydrous 1-methyl-2-pyrrolidinone (150 mL) and DMF (35 mL) at 50 °C. The clear reaction solution was cooled to room temperature, and 60% NaH (2.6 g, 64.00 mmol) was added to the above solution and the reaction mixture was stirred for 60 min at room temperature. The ethylene glycol dimethanesulfonate (16.8 g, 64.00 mmol) was added to the reaction mixture and heated to 55-60 °C for 3 hr. The reaction mixture was cooled to room temperature and ice water (300 mL) was added to the reaction mixture. The aqueous solution was extracted with chloroform (300 mL × 3). The organic solution was dried with MgSO₄. The solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂, eluent n-hexane : ethyl acetate = 1 : 9) to afford the product (3.5 g, 29.7%).

**1,3-Bis[5-(5-amino-1,2,4-thiadiazol-3-yl)oxa-3-oxapentylthiomethyl]benzene (4).** 1,3-Benzenedimethanethiol (0.50 mL, 3.38 mmol) was dissolved in a freshly prepared 2-propanol solution (70 mL) of sodium 2-propanoxide (0.59 g, 7.13 mmol). Compound (3) (0.30 g, 6.81 mmol) was added to the above solution and the reaction mixture was heated at reflux over 3 hr. After cooling the reaction mixture at room temperature, solvent was removed under reduced pressure.

The residue was purified by chromatography (SiO₂; eluent CHCl₃ : MeOH = 15 : 1) to afford product (0.30 g, 16.3%).

Liquid, Rf: 0.10 (CHCl₃ : MeOH = 15 : 1). IR (KBr, cm⁻¹): 3400, 3018, 1506, 1336, 1215, 1052, 1027. ¹H NMR (400 MHz, CDCl₃, δ): 7.27-7.17 (4H, m, C₆H₄), 6.46 (4H, br, 2NH₂), 4.43 (4H, m, 2CH₂OH), 3.74 (8H, m, 2CH₂ + 2CH₂C₆H₄H), 3.62 (4H, t, J = 6.64 Hz, 2CH₂), 2.60 (4H, t, J = 6.41 Hz, 2CH₂S). ¹³C NMR (100 MHz, CDCl₃, δ): 183.0 (O-C=O), 175.4 (O-C=N), 168.7 (C=O), 167.2 (S-C=N), 139.9, 129.4, 128.5, 127.9 (C₆H₄), 71.8 ((C=O)CH₂O), 69.0 (HetOCH₂CH₂OC₆H₄S), 68.8 (HetOCH₂CH₂OC₆H₄S), 36.7 (C₆H₄CH₃), 30.9 (SCH₂). FAB-HRMS: C₂₃H₂₉OₐₙS₄, (M+1) 545.1133, found: 545.1138.

11,14,20,23,38,39-Hexaaza-6,9,17,25,28-pentaaza-3,12,22,31-tetrahydrotricyclo-[31,3,1,1⁵,1⁹]-21,24-dionia-13(3),10(11),13(38),21(39),23(24),33(34),35(36)-heptaene-19,15-dione (5). Compound (4) (0.3 g, 0.55 mmol) was dissolved in dichloromethane (100 mL) and pyridine (90 mL, 1.10 mmol) and diglycolyl chloride (0.094 g, 0.55 mmol) was added to the above solution over 24 hr. The solution was heated at reflux for additional 20 hr. After cooling the reaction mixture at room temperature, ice water (50 mL) was added to the reaction mixture and the mixture was stirred for 30 min. The organic layer was separated and dried with MgSO₄. The solvent was removed under reduced pressure and the residue was purified by chromatography (SiO₂; eluent CHCl₃ : MeOH = 30 : 1) to afford colorless solid product (0.070 g, 19.7%).

Mp: 176.5-178.0 °C, Rf: 0.49 (CHCl₃ : MeOH = 30 : 1), IR (KBr, cm⁻¹): 3435, 3165, 3090, 2929, 1729, 1517, 1279, 1120, 1086. ¹H NMR (400 MHz, CDCl₃ + DMSO-d₆, δ): 12.91 (2H, 2NH), 7.29 (1H, s, CH of C₆H₄), 7.27-7.19 (3H, m, CH₃ of C₆H₄), 4.48 (4H, m, 2CH₂OH), 4.41 (4H, s, (CO)CH₂O), 3.79 (4H, m, CH₃CH=CH₂S), 3.77 (4H, m, CH₂CH₂OH), 3.68 (4H, t, J = 6.23 Hz, SCH₂CH₂O), 2.28 (4H, t, J = 6.23 Hz, CH₂S). ¹³CNMR (75 MHz, CDCl₃ + DMSO-d₆, δ): 175.4 (O=C=N), 168.7 (C=O), 167.2 (S-C=N), 139.9, 129.4, 128.5, 127.9 (C₆H₄), 71.8 ((C=O)CH₂O), 70.2 (CH₂OH), 69.0 (HetOCH₂CH₂OC₆H₄S), 68.8 (HetOCH₂CH₂OC₆H₄S), 36.7 (C₆H₄CH₃), 31.0 (SCH₂). FAB-HRMS Calcd for C₆₂H₇₉N₉O₁₅S₄, 643.1137. Found: 643.1134.

1,3-Bis[5-chloro-3-oxapentylthiophenyl]benzene (6). The reaction mixture of 1,3-benzenedimethanethiol (20.0 g, 0.117 mol), 2-chloroethyl ether (87.8 g, 0.470 mol) and ethanol (150 mL) was added to the above solution over 3 hr. The solvent was removed under reduced pressure and the residue was purified by chromatography (SiO₂; eluent CHCl₃ : MeOH = 15 : 1) to afford a colorless oil product (1.2 g, 55%).

Liquid, Rf: 0.46 (n-hexane : ethyl acetate = 1 : 9), IR (KBr, cm⁻¹): 3231, 1617, 1539, 1507, 1334, 1173. ¹H NMR (400 MHz, CDCl₃, δ): 6.82 (2H, s, NH₂), 4.44 (2H, m, CH₂O), 4.38 (2H, m, CH₂OMs), 3.80 (4H, m, 2 x CH₂O), 3.09 (3H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃, δ): 183.0 (O=C=N), 166.8 (H₃N=C=N), 69.4 (NH₂=COCH₂), 69.2 (MsOCH₂), 68.8 (MsOCH₂CH₂), 67.8 (NH₂=N=COCH₂CH₂), 37.6 (CH₃). FAB-HRMS cald for C₁₅H₁₃N₃O₁₅S₂, 284.0375, found 284.0378.

**Notes**

(4H, t, J = 5.50 Hz, 2CH2CH3Cl), 3.56 (4H, t, J = 6.60 Hz, 2CH2CH2SC6H4). 13C NMR (100 MHz, CDCl3, δ): 138.8, 129.4, 128.4, 127.5 (C6H5), 71.2, 69.9 (CH2OCH3), 43.6 (CH2), 35.3 (C6H4CH2S), 30.0 (C6H4CH2SCH2). Anal. Calc. for C11H16Cl2O2S2: C 50.70; H 6.31; Found: C 50.75; H 6.34; S 17.08.

1.3-Bis[5-(5-aminol,1,2,4-thiadiazol-3-ylthio]-3-oxapentylthiomethyl]-benzene (8). To a suspension of K2CO3 (3.27 g, 23.66 mmol) in anhydrous DMF (60 mL), were added compound (6) (2.26 g, 5.89 mmol) and compound (7) (7, 3.21 g, 12.14 mmol) in DMF (10 mL) over 10 min. The reaction mixture was heated at 50-55 °C for 5 hr and then heated at 70 °C for 15 hrs. The solvent was removed under reduced pressure and the residue was dissolved in H2O (50 mL) and ethyl acetate (200 mL). The organic layer was separated and dried with anhydrous MgSO4. Solvent was removed under reduced pressure to afford product. The crude product was purified by chromatography (silicagel; eluent chloroform : methanol = 20 : 1) to give oil product (1.18 g, 34.7%).

Notes