Synthesis of novel disulfide-bridged dilactam crown ethers

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Abstract

The novel macrocyclic dilactams with redox-switched disulfide linkage were synthesized. These compounds were obtained from 2,2'-dithiodibenzoyl chloride in the macrocyclization step by fast addition method in moderate yields.

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There have been great advances in the chemistry of sulfur-substituted crown ethers [1]. Thiacrown ethers are known to coordinate to transition metals [1,2] whereas crown ethers prefer to coordinate with alkaline and alkaline earth metals [3]. Application of these compounds to molecular machines and devices has also attracted much attention [4]. In general, redox reactions between dithiol and disulfide are very useful to control molecular structures and functions simultaneously [5]. This phenomena is known to regulate enzymatic activity [6] and ion recognition of artificial hosts [5]. According to design and synthesis of several redox-switched crown ethers with disulfide linkage are reported, for examples, for zinc abstraction from proteins and disrupt their conformation for achieving maturation of HIV virus [7], paraquat and secondary ammonium salts recognitions [8], and selective electrode properties in laboratory [9] and in the biomembranes [10].

Here we report the synthesis of novel macrocyclic dilactams with disulfide linkage (2–7). In these switchable crown compounds, the 2,2'-dithiobisbenzamides were used as the constructing part of the systems which recently have been used as anti-HIV-1 agents [7].

1. Experimental

All materials and solvents were obtained from Merck chemical company (Germany) and Fluka (Switzerland). Melting points were determined in open capillary tubes in an Electrothermal IA 9000 melting point apparatus. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. 1H and 13C NMR spectra were recorded on a Bruker-500 MHz and Bruker-100 MHz instruments using tetramethylsilane (TMS) as an internal standard. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument at 70 eV.
1.1. Preparation of 2,2′-dithiodibenzoyl chloride 1

2,2′-Dithiodibenzoic acid (3.06 g, 10.0 mmol) and freshly distilled thionyl chloride (25 mL) were refluxed for 12 h. The thionyl chloride was evaporated at low temperature to give 2,2′-dithiodibenzoyl chloride 1 in 85% yields which applied in macrocyclization step without additional purification: IR (neat) 746, 786, 1109, 1160, 1245, 1560, 1600, 1725, 3080 cm⁻¹. 1H-NMR (CDCl₃, 100 MHz, δ ppm): 7.3–7.6 (m, 4H), 7.75 (d, J = 8.0 Hz), 8.4 (d, 2H, J = 8.0 Hz). MS (m/z): 342 (M⁺), 340, 338, 303, 233, 201, 179, 169, 167, 148, 133, 118, 102, 94.

1.2. General procedure for the synthesis of dilactam crown ethers (2–7)

A solution of diamine (2.0 mmol) and triethylamine (0.41 g, 4.0 mmol) in CHCl₃ (10 mL) was added quickly (5 s) to a vigorously stirring solution of 2,2′-dithiodibenzoyl chloride (1) (0.69 g, 2.0 mmol) in CHCl₃ (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 min. The precipitate was filtered off and the filtrate washed with water (2 mL × 20 mL) and 10% aqueous sodium hydroxide solution (20 mL) and then with water (50 mL). The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated to give a solid product. The crude product was flash purified by rinsing with cold acetone.

5,6,7,8,9,10-Hexahydridibenzo[c,k][1,2,6,9]dithiaazacyclododecine-5,10-dione (2): obtained from ethylene-diamine (0.12 g, 2 mmol) in 60% yield; white solids; m.p. = 205–210 °C; IR (KBr): 1431, 1463, 1507, 1552, 1592, 1624, 1680, 2993, 3062, 3340 cm⁻¹. 1H-NMR (DMSO-d₆, 500 MHz, δ ppm): 3.25 (6H, 100 MHz, δ ppm): 3.68 (bs, 2H, NH), 7.00 (d, J = 8.1 Hz), 7.22 (t, J = 8.0 Hz), 7.39 (t, 2H, J = 8.0 Hz), 7.84 (d, J = 8.0 Hz). 13C-NMR (DMSO-d₆, 125 MHz, δ ppm): 168.6, 134.6, 131.5, 130.7, 128.8, 127.9, 125.0, 38.2. MS (m/z): 330 (M⁺), 329, 328, 327, 173, 106, 81, 68, 56, 38, 30.

7-Methyl-5,6,7,8,9,10-hexahydridibenzo[c,k][1,2,6,9]dithiaazacyclododecine-5,10-dione (3): obtained from 1,2-diamino-2-methylpropane (0.17 g, 2 mmol) in 75% yield; white solids; m.p. = 219–220 °C; IR (KBr): 1446, 1469, 1524, 1602, 1689, 2977, 3047, 3322, 3360 cm⁻¹. 1H-NMR (DMSO-d₆, 500 MHz, δ ppm): 0.88 (d, 3H, J = 6.8 Hz), 3.19–3.26 (m, 3H), 6.81 (bs, 2H, NH), 7.02 (d, J = 8.0 Hz), 7.21 (t, J = 7.5 Hz), 7.35 (t, 2H, J = 7.5 Hz), 7.82 (d, 2H, J = 7.5 Hz). 13C-NMR (DMSO-d₆, 125MHz, δ ppm): 168.7, 134.9, 131.5, 130.5, 128.9, 127.8, 125.1, 38.5, 37.5, 23.7. MS (m/z): 347 (M⁺ + 4), 345 (M⁺ + 2), 343 (M⁺), 342, 305, 272, 235, 203, 168, 134, 107, 69, 63, 37.

6,7,8,9,10,11-Hexahydro-5H-dibenzo[c,l][1,2,6,10]dithiaazacyclotridecine-5,11-dione (4): obtained from 1,3-diaminopropane (0.15 g, 2 mmol) in 75% yield; white solids; m.p. = 214–215 °C; IR (KBr): 1426, 1460, 1500, 1535, 1589, 1617, 1683, 2885, 3075, 3358, 3384 cm⁻¹. 1H-NMR (DMSO-d₆, 500 MHz, δ ppm): 1.68 (m, 2H), 3.31 (q, 4H, J = 5.5), 7.05 (d, J = 8.0 Hz), 7.22 (t, J = 8.0 Hz), 7.32 (bs, 2H, NH), 7.43 (t, J = 7.7 Hz), 7.90 (d, J = 7.7 Hz). 13C-NMR (DMSO-d₆, 125MHz, δ ppm): 162.8, 135.0, 131.0, 130.5, 128.8, 127.9, 124.9, 36.9, 28.4. MS (m/z): 347 (M⁺ + 4), 345 (M⁺ + 2), 343 (M⁺), 342, 339, 303, 167, 174, 133, 106, 81, 68, 49, 39.

5,6,7,8,9,10,11,13,14,15,16-Decahydridibenzo[i,m][1,4,11,12,7,16]dioxadithiaazacycloctadecine-5,16-dione (5): obtained from 1,8-diaminonaphthalene (0.316 g, 2 mmol) in 54% yield; brown solids; m.p. = 270–272 °C; IR (KBr): 1449, 1484, 1537, 1593, 1685, 3068, 3350 cm⁻¹. 1H-NMR (DMSO-d₆, 500 MHz, δ ppm): 7.04 (d, 2H, J = 8.0 Hz), 7.13 (bs, 2H, NH), 7.23 (td, 2H, J₁ = 7.5 Hz, J₂ = 1.5 Hz), 7.41 (t, 2H, J = 8.0 Hz), 7.52 (d, 2H, J = 7.0 Hz), 7.74 (t, 2H, J = 7.0 Hz), 7.85 (dd, J₁ = 7.6 Hz, J₂ = 1.0 Hz). 13C-NMR (DMSO-d₆, 500 MHz, δ ppm): 169.6, 160.1, 135.5, 131.9, 131.2, 130.5, 128.7, 127.9, 124.9, 111.0. MS (m/z): 379 (M⁺), 377 (M⁺–2), 374, 239, 237, 220, 204, 189, 164, 134, 106, 81, 68, 38.

4,5,6,7,17-Tetraydrodibenzo[c,l]naphtho[1,8-gh][1,2,6,10]dithiaazacyclotridecine-5,16-dione (7): obtained from 1,8-diaminonaphthalene (0.316 g, 2 mmol) in 54% yield; brown solids; m.p. = 270–272 °C; IR (KBr): 1449, 1484, 1537, 1593, 1685, 3068, 3350 cm⁻¹. 1H-NMR (DMSO-d₆, 500 MHz, δ ppm): 6.88 (bs, 2H, NH), 7.05 (d, 2H,
\[ J = 7.5 \text{ Hz}, \] 7.14 (d, 2H, \( J = 7.5 \text{ Hz} \)), 7.24 (t, 2H, \( J = 7.5 \text{ Hz} \)), 7.37 (t, 2H, \( J = 7.5 \text{ Hz} \)), 7.46 (td, 2H, \( J_1 = 8.0 \text{ Hz}, \) \( J_2 = 1.5 \text{ Hz} \)), 7.53 (d, 2H, \( J = 8.0 \text{ Hz} \)), 7.83 (d, 2H, \( J = 8.0 \text{ Hz} \)). MS (m/z): 431 (M+ + 2), 428 (M+), 427, 389, 330, 269, 240, 208, 166, 149, 133, 106, 94, 68, 44, 39.

2. Results and discussion

The reaction of 2,2'-dithiodibenzoic acid with freshly distilled thionyl chloride gave 2,2'-dithiodibenzoyl chloride 1 in 85% yields. The cyclization was carried out with fast addition of a mixture of the diamines (2.0 mmol) and triethylamine (4.0 mmol) in CHCl₃ (10 mL) into a solution of 2,2'-dithiodibenzoyl chloride 1 (2.0 mmol) in CHCl₃ (10 mL) over 5 s with vigorous stirring at 0 °C. The mixture was then stirred at room temperature for 20 min to give 2,2'-dithiobisbenzamides 2–7 in 30–75% yields (Scheme 1).

The size of these macrocycles varied between 12 and 18 membered rings with mixed donor atoms. A fast reaction time was observed for this macrorcyclization reaction. Moderate yields of the 2,2'-dithiobisbenzamides in comparison with previously reported [11] dilactam crown ethers can be attributed to the conformational behavior of disulfide linkage which decreased the probability of the simultaneous reaction of both benzoyl chloride ends with diamines, particularly with the large and flexible diamine in the synthesis of 5. The structures proposed for the macrocyclic compounds are consistent with data derived from IR, ¹H-NMR and ¹³C-NMR in addition to satisfactory molecular weights that determined by mass spectrometric analysis.

3. Conclusion

In conclusion, the current method provides a very simple and convenient procedure for the efficient synthesis of novel disulfide-bridged macrocyclic dilactams without additional external cyclization factors such as high dilution approach, template effect or nitrogen protection. Moreover, synthetic versatility, no side reactions, ease of workup, and short reaction time can be considered as the advantages of this method. Thiol-disulfide exchange and ion recognition ability of these compounds are in progress in our laboratory.
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