Efficient Synthesis of New Sulfur Macrocyclic Diamides

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Abstract: Some new sulfur macrocyclic diamides and tetraamides were obtained via a simple and convenient method. This method consists of reacting a dicarboxylic acid dichloride with the appropriate diamine in dichloromethane. The cyclization does not require high dilution technique or template effect and the expected dilactams were obtained in high yields.

Key words: sulfur macrocyclic diamides, diamine, dicarboxylic acid dichloride

Macrocyclic polyethers ('crown-ethers') are well known for their complexation properties towards alkali and alkaline-earth metal ions. A quite remarkable selectivity can be achieved by changing the number and types of donor atoms and the size of the internal cavity of the ligands.¹⁻³ Many different modifications of the crowns have been made to enhance their cation-complexing properties. Some of these modifications involve the use of alkyl substituents, aromatic sub-cyclic units, nitrogen and/or sulfur atoms substituted for oxygen in the macro-ring and some other changes which provide crowns with unique complexing properties.⁴⁻¹⁰ Nitrogen and sulfur, naturally, are particularly interesting heterodonor atoms to investigate, and various studies were carried out with a series of oligooxa, oligo-aza or oligo-sulfur macrocycles in the last decade. Oxathio crown ethers, indeed, have been exploited for their ability to extract and transport heavy metal ions.11-15

Now, in continuing the synthesis of different modified crown ethers, herein, we report new studies on sulfur macrocyclic diamides, notably the synthetic routes and the structures of the target molecules that were intended to include two/three benzo-condensed systems, containing some additional structural feature such as a mixed set of S-, O-, pyridine and amide groups.

Numerous studies have been devoted to the preparation of different macrocyclic polylactams from diamines and diacids. Preparing sulfur macrocyclic polylactams from diamines and activated diacids requires a direct condensation reaction to form ring products over polymers. In an attempt to achieve this goal, there is a need for simple methods to prepare multifunctional crowns from inexpensive and available starting materials. Many different cyclization procedures have been developed; earlier high dilution techniques^{16,17} have been complemented by

various double-activation methods^{18,19} and by a series of consecutive 'Zipper- type' reactions.²⁰ In most of these methods the macrocyclic lactams and polylactams are obtained by cyclization of a polyfunctional, linear precursor to a ring product. The high dilution technique is however, inconvenient as it requires a simultaneous addition of the diamine and diacid dichloride to a large volume of solvent over an extended period of time. Morphy et al.²¹ and Jurczak et al.²² have reported that, consistent with the earlier findings of Tabushi et al.²³ that no high dilution technique was required for the reaction of dimethyl malonates with α,δ -diamines to form cyclic diamides. These facts promoted us to study and apply similar approaches and from these results an appropriate method was used for the synthesis of new sulfur macrocyclic diamides (5–12; Scheme 1).

Treatment of thia-salicylic acid (1) with potassium hydroxide in ethanol under reflux, gave the yellow solid of thia-salicylate salt 2 in 95% yield. Nucleophilic displacement of 1,2-diethylene glycol dibromide with thia-salicylate 2, provides the acyclic sulfur dicarboxylic acid 3 as white crystals in 90% yield.

In the next step, compound **3** was treated with thionyl chloride and gave dicarboxylic acid dichloride 4 in 85% yield. The cyclization between compound 4 and diamine 14b at first, was performed by the following high dilution method.¹³ A solution of **4** in dichloromethane (200 mL) and a solution of diamine 14b and triethylamine in dichloromethane (200 mL) were added dropwise over 5 hours into dichloromethane (1.5 L) at 0 °C. This was then stirred for 3 hours giving macrocyclic diamide 6 in 12% yield. However when the reaction time was shortened to 15 minutes, and triethylamine and diamine (14b) in dichloromethane (10 mL) were added dropwise to a solution of 4 in dichloromethane (10 mL) diamide 6 was obtained in, a much improved 75% yield. This result clearly indicates that, cyclization of compound 4 with diamine 14b does not need a high dilution method. Additionally, the cyclization was carried out with fast addition of a mixture of diamine 14b and triethylamine in dichloromethane (10 mL) into a solution of compound 4 in dichloromethane (10 mL) over 5 minutes with vigorous stirring at 0 °C and then the mixture was stirred at room temperature for 15 minutes to give compound 6 in even better yields of 95% yield. A low reaction time was observed for this macrocyclization reaction (15 mins). When this method was used at room temperature without triethylamine, the same result was obtained.

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Scheme 1

In a preliminary study, the effect of some solvents on the yield of the macrocyclization reaction was investigated with formation of sulfur macrocyclic diamide 6 as a model reaction (Table 1).

Table 1 clearly indicates, CH_2Cl_2 is a suitable solvent for this macrocyclization reaction.

Compounds 5–12 were readily obtained by reacting the compound 4 with appropriate diamine derivatives in high yields (Table 2).

It should be mentioned, the fast addition of diamine **14e** on dicarboxylic acid dichloride **4** in various solvents gave a mixture of products. After column chromatography both monomeric compound **9** [1:1], and dimeric compound **10** [2:2] were isolated in 75% and 15% yields, respectively. (Figure 1) (Table 2, entries 4 and 5)

Also for comparison of the conformational effects, we reacted dicarboxylic acid dichloride **4** with diamine **14c**. In contrast to fairly high yields of dilactams **5** and **6**, reaction of **4** with **14c** in CH_2Cl_2 , gave dilactam **7** with 21 ring atoms in 55% yield. These properties provide a measure of steric control and predictability in ligand design (Table 2, entry 3).

These results clearly indicate that the cyclization of dicarboxylic acid dichlorides with diamines does not need high dilution method. The question arises as to whether vigorous stirring and fast addition of reactant are indispensable for enforcing the cyclization of these substrates. To check this assumption the same reactions were performed under the modified conditions of slow addition and stirring, however a decrease in macrocyclization yield occurred. All the presented cyclization reactions proceed efficiently under vigorous stirring conditions as well as fast addition of reactants, in a properely selected solvent. The course of the reaction is assumed to depend on the occurrence of self-assembly phenomena,²⁶ which is probably stimulated by a properly selected solvent, and the yields are improved by application of high speed stirring and fast addition reactions.

The structure proposed for the sulfur macrocyclic compounds are consistent with data derived from IR, ¹HNMR, ¹³C NMR, UV-Vis, and MS spectra, along with elemental analysis.

The fast addition method for the preparation of sulfur macrocyclic diamides has the following advantages:

(i) Synthetic versatility – prepare even or odd membered dilactams.

(ii) High yields of cyclization without additional external cyclization factors (such as high dilution approach or template effect).

- (iii) Ease of purification.
- (iv) Short reaction time.

Petroleum ether used had a bp 60-80 °C.

Thia-salicylic Acid Salt 1

KOH (11.2 g, 20 mmol) in EtOH (200 mL) were placed in a 500 mL two necked flask fitted with stirrer and reflux condenser, and refluxed for 30 min. Then this salicylic acid (15.4 g, 10 mmol) was

 Table 1
 Solvent Effects in Macrocyclization Reaction Between Diamine 14b and Dicarboxylic Acid Dichloride 4

Solvent	Acetone	CH ₂ Cl ₂	CHCl ₃	CH ₃ CN	DMSO	Et ₂ O	EtOAc	THF	CH ₂ Cl ₂ / EtOAc
Yield (%)	60	95	50	35	26	15	70	50	75
Time (min)	15	15	20	15	20	20	15	15	15



Figure 1

	Table 2	Cyclization	Yields and Ph	ysical Prop	perties of N	Macrocycl	lic Dilactames	5 - 12
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Entry	Starting Materials	Dilactam	Time/ (min)	Yield (%) ^a	Melting Point (°C)	1 H NMR, δ^{c}
1	4 14a	5	15	63	175–177 (CH ₂ Cl ₂)	3.40 (t, 4 H, CH ₂), 3.57 (m, 4 H, CH ₂ S), 3.77(m, 4 H, CH ₂ O), 3.51(s, 2 H, NH), 6.8–7.9(m, 8 H, ArH)
2	4 14b	6	3	95	210–212 (CH ₂ Cl ₂)	1.60 (m, 2 H, CH ₂), 1.95(t, 4 H, CH ₂), 3.03 (t, 4 H, CH ₂ S), 3.55 (m, 4 H, CH ₂ O), 4.28 (s, 2 H, NH), 7.19–7.60 (m, 8 H, ArH)
3	4 14c	7	20	55	150–152 (CH ₂ Cl ₂)	1.10–1.56 (m, 12 H, CH ₂), 3.13–3.22 (m, 4 H, CH ₂ S), 3.72–3.78 (m, 4 H, CH ₂ O), 3.91 (s, 2 H, NH), 7.14–7.91 (m, 8 H, ArH)
4	4 14d	8	5	73	240–242 (CH ₂ Cl ₂)	2.33 (s, 3 H, CH ₃), 3.22 (m, 4 H, CH ₂ S), 3.78 (m, 4 H, CH ₂ O), 7.26–8.03 (m, 11 H, ArH), 10.04 (s, 2 H, NH)
5	4 14e	9	5	75	228–230 (acetone– CH ₂ Cl ₂)	3.18–3.22 (m, 4 H, CH ₂ S), 3.67–3.7 (m, 4 H, CH ₂ O), 7.32– 8.32 (m, 11 H, Ar), 10.18 (s, 2 H, NH) ^d
6	4 14e	10	5	15	178-180 (acetone–CH ₂ Cl ₂)	3.22 (m, 8 H, CH ₂ S), 3.68 (m, 8 H, CH ₂ O), 6.66–8.32 (m, 22 H, Ar), 10.56 (s, 4 H, NH) ^d
7	4 14f ^b	11	20	80	196–198 (EtOAc–CH ₂ Cl ₂)	1.41 (t, 3 H, CH ₃), 3.17 (m, 4 H, CH ₂ S), 3.74 (m, 4 H, CH ₂ O), 4.38 (m, 2 H, CH ₂), 6.96–8.8 (m, 11 H, Ar), 9.85 (s, 2 H, NH)
8	4 14g	12	20	75	205–208 (EtOAc– CH ₂ Cl ₂)	1.41 (t, 3 H, CH ₃), 3.15 (m, 4 H, CH ₂ S), 3.62 (m, 4 H, CH ₂ O), 4.36 (m, 2 H, CH ₂), 6.72–8.50 (m, 11 H, Ar), 10.10 (s. 2 H, NH)

^a Isolated yield. ^b Ref.^{24,25}

 $^{c \ 1}$ H NMR were recorded at 250 MHz in CDCl₃ unless otherwise stated. $^{d \ 1}$ H NMR were recorded in DMSO.

added dropwise and refluxed for 3–5 h. Then the mixture was cooled and the precipitate filtrated to give the yellowish-green salt of thia salicylic acid in 95% yield.

Sulfur Dicarboxylic Acid 3

Potassium thia-salicylate (1), (0.77g, 5 mmol) and diethylene glycol dibromide (1.16 g, 2.5 mmol) in DMF (10 mL) was heated under reflux for 15 min (precipitation of KBr occured). The solvent was then removed in vacuum and the remaining material was washed with water (20 mL) and recrystallized from dil. EtOH to give colorless crystals of diacid **3** in 90% yield; mp 182–184 °C.

IR (KBr): 698, 732, 914, 1114, 1272, 1413, 1465, 1562, 1693, 2958 cm⁻¹.

 1H NMR (DMSO, 250 MHz): δ = 3.11 (m, 4 H, CH_2S), 3.43 (m, 4 H, CH_2O), 7.18–8.04 (m, 8 H, ArH), 13.05 (s, 2 H, COOH).

¹³C NMR (DMSO, 62.9 MHz): δ = 30.81, 68.27, 123.89, 125.56, 128.51, 130.78, 139.60, 167.44.

MS: *m*/*z* (%) = 378 (M⁺, 0.1), 180, 153 (100), 137, 109, 97, 77, 69, 63, 45.

UV (EtOH): λ_{max} (ϵ) = 230.3 (2460), 261.9 (2186), 316.7 (856).

Sulfur Dicarboxylic Acid Dichloride 4

Sulfur dicarboxylic acid **3**, (9.45 g, 0.025 mol) was heated in SO₂Cl₂ (50 mL) for 8 h at 50–60 °C. The SO₂Cl₂was evaporated from the solution at low temperature and the residue was crystallized from petroleum ether to give **4** as a yellow cream solid in 85% yield; mp 82–87 °C.

IR (neat): 648, 657, 860, 1189, 1195, 1431, 1554, 1585, 1575, 2370, 3420 cm⁻¹.

¹H NMR (CDCl₃, 250 MHz): δ = 3.26 (m, 4 H, CH₂S) 3.75 (m, 4 H, CH₂O), 7.23–8.31 (m, 8 H).

¹³C NMR (CDCl₃, 62.9 MHz): δ = 32.22, 69.35, 124.88, 126.14, 130.72, 134.77, 135.57, 136.07.

Synthesis of Macrocyclic Diamides (5–12); General Procedure

A solution of diamine (2 mmol) in anhyd solvent (10 mL) was added quickly to a vigorously stirred solution of dicarboxylic acid dichloride (2 mmol) in anhyd solvent at r.t. The mixture was stirred for a further 5–20 min and then was washed with NaHCO₃ (2 × 10 mL) and water (2 × 10 mL). The organic layer was dried over MgSO₄ and the solvent was evaporated to give a solid product. The crude product was purified by column chromatography (petroleum ether–EtOAc).

1,15-Diaza-3,4;12,13-dibenzo-8-oxa-5,11-dithiacycloheptadecane-2,14-dione (5)

IR (KBr): 746, 1105, 1429, 1541, 1645, 3269 cm⁻¹.

 ^{13}C NMR (CDCl₃, 62.9 MHz): δ = 35.5, 45.0, 71.1, 126.7, 127.5, 132.1, 167.9.

MS: *m*/*z* (%) = 402 (M⁺, 2.5), 384, 35, 206, 192, 164, 136, 109, 91, 56 (100).

UV (CHCl₃): λ_{max} (ϵ) = 255.7 (750), 302.7 (532).

1,15-Diaza-3,4;12,13-dibenzo-8-oxa-5,11-dithiacyclooctadecane-2,14-dione (6)

IR (KBr): 686, 748, 862, 929, 1001, 1296, 1467, 1643, 2916, 3276 cm⁻¹.

¹³C NMR (CDCl₃, 62.9 MHz): δ = 32.15, 36.43, 69.1, 76.9, 127.73, 128.88, 130.82, 130.019, 162.86.

MS: *m*/*z* (%) = 416 (M⁺, 1.7), 398, 365, 220, 192, 164, 136, 109, 91, 56 (100).

UV (CHCl₃): _{max} () = 260.3 (2626), 310.3 (449).

1,15-Diaza-3,4;12,13-dibenzo-8-oxa-5,11-dithiacycloune-icosane-2,14-dione (7)

IR (KBr): 715, 1057, 1251, 1434, 1463, 1710, 2931, 2954, 3473 cm⁻¹.

 ^{13}C NMR (CDCl_3, 62.9 MHz): δ = 30.08, 31.00, 31.94, 52.51, 69.53, 76.96, 124.53, 126.10, 131.69, 132.79.

MS: *m*/*z* (%) = 458.2 (M⁺), 194, 181, 167 (100), 152, 135, 109, 91, 69, 59, 50, 45.

UV (CHCl₃): λ_{max} (ϵ) = 260.3 (2302), 323.0 (1139).

1, 15-Diaza-3,4;12,13-dibenzo-16,18-(*o*-methylbenzo)-8-oxa-5,11-dithiacyclooctadecane-2,14-dione (8)

IR (KBr): 748, 1105, 1253, 1315, 1525, 1633, 1604, 1658, 2864, 2929, 3278 $\rm cm^{-1}.$

 ^{13}C NMR (CDCl₃, 62.9 MHz): $\delta=29.75,\ 30.08,\ 70.14,\ 76.89,\ 77.40,\ 77.90,\ 88.60,\ 119.99,\ 128.93,\ 131.70,\ 134.91,\ 158.32.$

MS: *m*/*z* (%) = 464 (M⁺, 13.5), 283, 256, 225, 208, 163, 148, 137, 120, 56, 43 (100).

UV (CHCl₃): λ_{max} (ϵ) = 249 (1817).

1,15-Diaza-3,4;12,13-dibenzo-8-oxa-16,18-pyridine-5,1-dithiacyclooctadecane-2,14-dione (9)

IR (KBr): 695, 763, 1195, 1280, 1452, 1570, 1666, 2827, 3315cm⁻¹. ¹³C NMR (DMSO, 62.9 MHz): δ = 34.64, 38.87–40.88, 68.77, 77.51, 110.84, 126.94, 128.80, 130.95, 133.95, 138.25, 140.60, 150.27, 167.23.

MS: m/z (%) = 451 (M⁺, 5.9), 406, 377, 288, 163, 151, 137, 121, 109, 96, 83, 68, 57, 43(100).

UV (CHCl₃): λ_{max} (ϵ) = 250.6 (2809), 300.7 (2769).

Compound 10

IR (KBr): 740, 1047, 1110, 1257, 1415, 1465, 1562, 1677, 2987, 3035 cm⁻¹.

 ^{13}C NMR (DMSO, 62.9 MHz): $\delta = 35.44, \, 69.57, \, 78.51, \, 111.00, \, 128.04, 129.60, \, 131.05, \, 134.15, \, 139.95, \, 141.01, \, 151.17, \, 169.23.$

MS: m/z = 902 (M⁺), 552, 550, 538, 524, 451, 406, 364, 304, 239,193, 172 (100), 143, 109, 94, 77, 43.

UV (CHCl₃): λ_{max} (ϵ) = 246.4 (2010), 307.7 (1255).

1, 15-Diaza-3,4;12,13-dibenzo-16,18-(*p*-ethylbenzoato)-8-oxa-5,11-dithiacyclooctadecane-2,14-dione (11)

IR (KBr): 695, 897, 1115, 1475, 1600, 1654, 1712, 2878, 3255 cm⁻¹.

¹³C NMR (CDCl₃, 62.9 MHz): δ = 6.81, 14.76, 61.64, 67.61, 76.90, 77.9, 119.24, 129.32, 131.41, 135.81, 154.55, 164.38.

MS: *m*/*z* = 522 (M⁺,2.9), 477, 314, 236, 206, 180, 163, 137, 108, 83, 68, 57, 43 (100).

UV (CHCl₃): λ_{max} (ϵ) = 242.9 (831), 306.6 (474).

1,15-Diaza-3,4;12,13-dibenzo-16,18-(*m*-ethylbenzoato)-8-oxa-5, 11-dithiacyclooctadecane-2,14-dione (12)

IR (KBr): 667, 1020, 1205, 1217, 1228, 1365, 1726, 2858, 3280 cm⁻¹.

 ^{13}C NMR (CDCl_3, 62.9 MHz): δ = 6.51, 13.76, 63.54, 68.61, 76.90, 79.9, 119.14, 128.32, 132.41, 136.81, 155.55, 167.38.

MS: m/z (%) = 522 (M⁺, 4.7), 477, 314, 235, 206, 181, 163, 137, 108, 82, 68, 57, 43 (100).

UV (CHCl₃): λ_{max} (ϵ) = 244 (961), 307.4 (479).

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