

# An expedient synthesis of N-tosyl macrocycles containing two thiourea moieties from trisulfonamide and bis-dithiocarbamate salts at room temperature in aqueous media

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## Abstract

The nucleophilic reaction of diamines and carbon disulfide in aqueous NaOH afforded a series of bis-dithiocarbamate salts. Activation of these with aqueous  $\text{ClCH}_2\text{COOK}$  and subsequent nucleophilic substitution reaction with trisulfonamide aqueous KOH at room temperature provided N-tosyl-macrocycles containing two thiourea units. This strategy has the advantages of simple operation, mild reaction condition, easy product-isolation and environmental friendliness.

**Keywords:** Trisulfonamide, activated bis-dithiocarbamate salt, N-tosyl-macrocycle containing two thiourea moieties, green synthesis

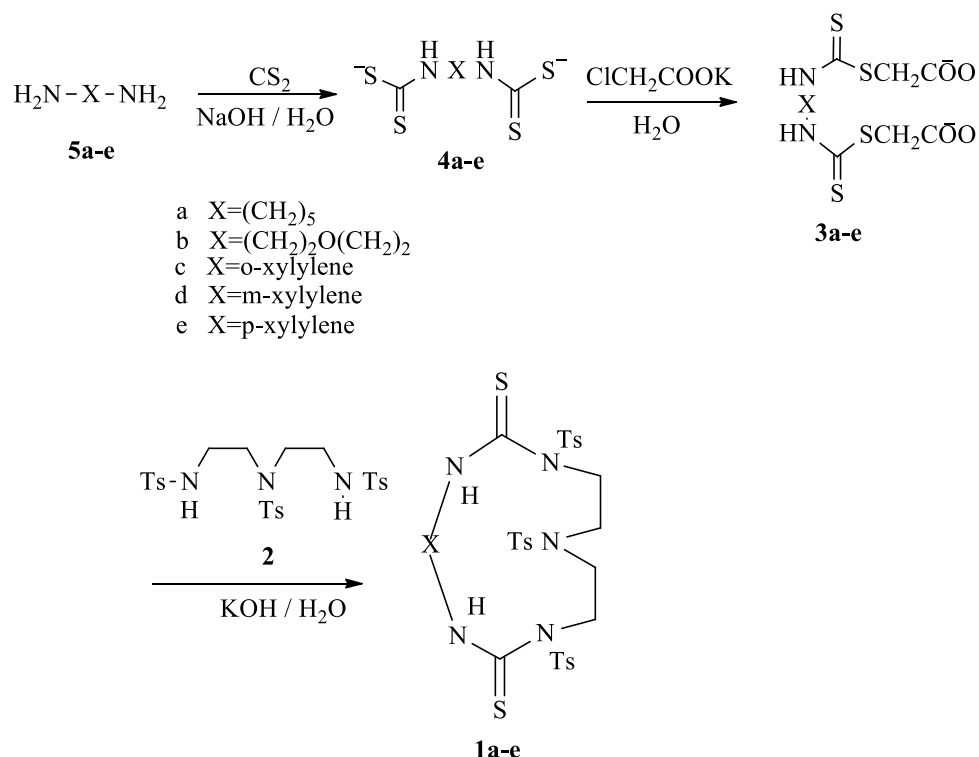
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## Introduction

Macrocyclic anion receptors<sup>1</sup> based on directed hydrogen-bonding interactions including macrocyclic thiourea are well known. The continued interest in novel macrocyclic thiourea ligands stems from their applications in many areas of chemistry and biochemistry, including ion-selective electrodes and optodes,<sup>2</sup> their easy complexation of anions<sup>3</sup> and N-protected glutamate dianion,<sup>4</sup> and antimicrobial studies.<sup>5</sup> Our ongoing studies are concerned with the simple, convenient preparation of these macrocycles. We have noted that the traditional methods<sup>6</sup> of this kind involve volatile and toxic organic solvent, hyper-toxic thiophosgene or unstable (sulfonyl) isothiocyanate, and cumbersome product-isolation procedures.

We have recently reported the synthesis of calix[4]crown-5-sulfonyl imidazolidinethione from calix[4]crown-5-monosulfonyldiamine and carbon disulfide by intramolecular cyclization at room temperature in water.<sup>7</sup> In our study of these N-sulfonyl macrocycles, we now report the synthesis of methylene-bridged cyclophane-thiones from trisulfonamide and activated bis-dithiocarbamate salts by intermolecular cyclization at room temperature in water (Scheme 1).

This may be of value for providing a simple and high-yielding preparation for this important category of macrocycles. Also, since this preparation is nucleophile-mediated with dithiocarbamate salt as the electrophile, it may provide information regarding the biotransformations of the widely applied thioglycolate ion<sup>8</sup> containing systems such as dithiocarbamate salts *in vivo*.



**Scheme 1.** Synthesis of N-tosyl macrocycles containing two thiourea moieties **1a-e**.

## Results and Discussion

The reagents **5b**<sup>9</sup> and **2**<sup>10</sup> were prepared according to literature procedures. A modification of the procedure of Aksac<sup>11</sup> was used to obtain yellowish aqueous solutions of compounds **3a-e**, which were used for the following reactions. Aqueous ClCH<sub>2</sub>COOK was prepared by using ClCH<sub>2</sub>COOH in aqueous KOH. We have tried slowly adding aqueous **3a-e** to **2** aqueous KOH. Unfortunately, there existed a spot of larger-ring by-products than compounds **1a-e** in the reaction mixture. Final protocol was opted that aqueous solution of **2** in KOH and aqueous solution of **3a-e** were added dropwise simultaneously to 20mL of H<sub>2</sub>O to avoid the side reaction. The result demonstrated that no by-product is produced, and the products are isolated directly by filtration. Moreover, the use of H<sub>2</sub>O without organic solvents is an environmentally friendly procedure.

The structures of **1a-e** were characterized by melting point, IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, thin-layer chromatography (TLC), and elemental analyses. The infrared spectra of the thiourea macrocycles **1a-e** revealed a C=S stretching vibration at 1280–1295  $\text{cm}^{-1}$  and 1380–1395  $\text{cm}^{-1}$ , two bands for the symmetrical and asymmetrical vibrations of the  $\text{SO}_2$  group at 1145–1158  $\text{cm}^{-1}$  and 1345–1355  $\text{cm}^{-1}$  as well as a Ts-H out-of-plane C-H bending vibration with two adjacent hydrogens at 852–856  $\text{cm}^{-1}$  and C-O stretching with broad and strong absorption at 1090  $\text{cm}^{-1}$  in compound **1b**, *ortho*-xylylene out-of-plane C-H bending with four adjacent hydrogen at 755  $\text{cm}^{-1}$  in case of compound **1c**, *meta*-xylylene C-H bending with three adjacent hydrogen and one isolated hydrogen at 770  $\text{cm}^{-1}$  in case of compound **1d**, and *para*-xylylene C-H bending with two adjacent hydrogen at 830  $\text{cm}^{-1}$  in case of compound **1e**. The N-H bands appeared at 3332–3347  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR data showed a broad singlet in the region  $\delta$  7.65–7.83 ppm for NH, multiplets at  $\delta$  3.47–3.61 ppm and  $\delta$  3.61–3.64 ppm for the  $\text{NCH}_2$  and  $\text{OCH}_2$  of **1a** and **1b**, respectively. Multiplets at  $\delta$  7.65–7.83 ppm for four hydrogens of the *ortho*-xylylene ring in compound **1c** as well as a singlet at 6.87 ppm for the isolated hydrogen of the *meta*-xylylene ring moiety in **1d**, and a doublet for four protons at 6.95 ppm for the *para*-xylylene ring in compound **1e**. Further evidence about the structure of the foregoing compounds **1a-e** has been derived from their  $^{13}\text{C}$  NMR spectra which revealed the expected number of signals for the mentioned compounds as well as C=S signals at  $\delta$  207.1–208.3 ppm for thiourea macrocycles, respectively. In addition, elemental analysis supported the suggested structures.

## Conclusions

We have demonstrated that our strategy for the green synthesis of large-ring compounds can be applied to the preparation of various N-tosyl macrocycles with two thiourea moieties using low-toxic, inexpensive, and easily available reagents in water. Our example show trisulfonamide **2** and bis-dithiocarbamate salts **3a-e** can be used as a very versatile synthon, prepared in facile steps in aqueous media, in order to synthesize derivatives of cyclam family including cyclophane-based cyclic thioureas. Five novel sulfonylthiourea macrocycles were synthesized and characterized using the method. These compounds offer the opportunity for selective desulfonylation<sup>12</sup> and then oxidation<sup>13</sup> allowing the possibility of the preparation of a range of macrocyclic (thio)ureas.

## Experimental Section

**General.** The reagents used were of reagent grade and used as purchased. Melting points were measured by using a XT-4 Electrothermal micro-melting-point apparatus and are uncorrected. NMR spectra were recorded at 400 ( $^1\text{H}$ ) and 100 ( $^{13}\text{C}$ ) MHz, respectively, on a Bruker Avance III Plus 400 spectrometer in  $\text{DMSO}-d_6$  using TMS as internal reference. Chemical shifts ( $\delta$ ) are

given in ppm. Infrared spectra were obtained on a Bio-Rad spectrophotometer using thin films on NaCl windows or in KBr pellets and are reported as  $\text{cm}^{-1}$ . Elemental analysis was determined on a Yanaco CHN Corder elemental analyzer.

### General preparation of compounds (1a-e)

To a solution of a diamine **5a-e** (0.5 mmol) and NaOH (50 mg, 1.3 mmol) in 0.5 mL of  $\text{H}_2\text{O}$  was added  $\text{CS}_2$  (5.0 mmol, 0.3 mL), and the mixture solidified in an ice-salt bath after stirring for 1 h at 35 °C. The bis-dithiocarbamate salts was filtered, washed with a minimal amount of diethyl ether and added to an aqueous solution of potassium chloroacetate (133 mg, 1.0 mmol) in 0.5 mL of  $\text{H}_2\text{O}$ . After 0.5 h stirring at room temperature, an aqueous solution of **3a-e** was obtained. The solution of **3a-e** and a solution of trisulfonamide **2** (283 mg, 0.5 mmol) dissolved in a solution of KOH (67 mg, 1.2 mmol) in 1.0 mL of  $\text{H}_2\text{O}$  were added dropwise simultaneously to 20 mL of  $\text{H}_2\text{O}$ . After the addition was finished, the reaction mixture was stirred for another 3-4 h at room temperature. The resulting white precipitate was collected by suction filtration and washed successively with  $\text{H}_2\text{O}$  (3×5 mL), then dried under vacuum over  $\text{P}_4\text{O}_{10}$  to afford macrocycles **1a-e** in high purity.

**Macrocycle (1a).** Yield, 82%, white crystalline solid, mp 278-280 °C. IR (KBr,  $\text{cm}^{-1}$ )  $\nu$ : 3332 (m, N-H), 2960 (s, C-H), 1380 (s, C=S), 1346 (s,  $\text{SO}_2$ ), 1280 (s, C=S), 1146 (s,  $\text{SO}_2$ ), 852 (vs, Ts-H).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ , 70 °C)  $\delta$  (ppm): 1.32-1.58 (m, 6H,  $\text{CH}_2$ ), 2.40 (s, 9H,  $\text{CH}_3$ ), 3.47-3.61 (m, 4H,  $\text{NCH}_2$ ), 3.31-3.52 (m, 8H,  $\text{TsNCH}_2$ ), 7.48-7.56 (m, 12H, TsH), 7.65 (s, br, 2H, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ , 90 °C)  $\delta$  (ppm): 207.9 (s), 141.8 (s), 137.0 (s), 129.7(d), 127.5 (d), 51.5 (t), 44.5 (t), 43.1 (t), 32.3 (t), 24.4 (q), 22.6 (t). Anal. Calcd for  $\text{C}_{32}\text{H}_{41}\text{N}_5\text{O}_6\text{S}_5$ : C 51.11, H 4.83, N 9.31. Found C 54.01, H 4.89, N 9.29%.

**Macrocycle (1b).** Yield, 85%, white crystalline solid, mp 282-284 °C. IR (KBr,  $\text{cm}^{-1}$ )  $\nu$ : 3335 (m, N-H), 2962 (s, C-H), 1385 (s, C=S), 1345 (s,  $\text{SO}_2$ ), 1285 (s, C=S), 1145 (s,  $\text{SO}_2$ ), 1090 (bs, C-O), 853 (vs, Ts-H).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ , 70 °C)  $\delta$  (ppm): 2.41 (s, 9H,  $\text{CH}_3$ ), 3.28-3.48 (m, 8H,  $\text{TsNCH}_2$ ), 3.61-3.64 (m, 8H,  $\text{NCH}_2$  &  $\text{OCH}_2$ ), 7.49-7.59 (m, 12H, TsH), 7.68 (s, br, 2H, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ , 90 °C)  $\delta$  (ppm): 207.1 (s), 142.1 (s), 137.5 (s), 129.5(d), 127.7 (d), 69.5 (t), 44.5 (t), 43.1 (t), 32.3 (t), 24.4 (q). Anal. Calcd for  $\text{C}_{31}\text{H}_{39}\text{N}_5\text{O}_7\text{S}_5$ : C 49.38, H 5.21, N 9.29. Found C 49.31, H 5.26, N 9.21%.

**Macrocycle (1c).** Yield, 80%, white crystalline solid, mp 262-264 °C. IR (KBr,  $\text{cm}^{-1}$ )  $\nu$ : 3341 (m, N-H), 2960 (m, C-H), 1390 (s, C=S), 1347 (s,  $\text{SO}_2$ ), 1290 (s, C=S), 1147 (s,  $\text{SO}_2$ ), 854 (vs, Ts-H), 755 (vs, Ar-H).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ , 60 °C)  $\delta$  (ppm): 2.40 (s, 9H,  $\text{CH}_3$ ), 3.30-3.45 (m, 8H,  $\text{TsNCH}_2$ ), 4.75 (s, 4H,  $\text{ArCH}_2$ ), 7.14-7.43 (m, 4H, ArH), 7.48-7.63 (m, 12H, TsH), 7.73 (s, br, 2H, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ , 80 °C)  $\delta$  (ppm): 207.3 (s), 142.3 (s), 138.5 (s), 136.7 (s), 129.3 (d), 127.2 (d), 126.7 (d), 126.6 (d), 53.3 (t), 44.5 (q), 43.1 (q), 24.3 (q). Anal. Calcd for  $\text{C}_{35}\text{H}_{39}\text{N}_5\text{O}_6\text{S}_5$ : C 53.38, H 5.00, N 8.91. Found C 53.35, H 5.05, N 8.89%.

**Macrocycle (1d).** Yield, 81%, white crystalline solid, mp 258-260 °C. IR (KBr,  $\text{cm}^{-1}$ )  $\nu$ : 3347 (m, N-H), 2958 (s, C-H), 1385 (s, C=S), 1350 (s,  $\text{SO}_2$ ), 1295 (s, C=S), 1152 (s,  $\text{SO}_2$ ), 856 (vs, Ts-H), 770 (vs, Ar-H).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ , 60 °C)  $\delta$ (ppm): 2.42 (s, 9H,  $\text{CH}_3$ ), 3.31-

3.44 (m, 8H, TsNCH<sub>2</sub>), 4.73 (s, 4H, ArCH<sub>2</sub>), 6.87 (s, 1H, ArH), 6.90 (d, 2H,  $J = 13.2$  Hz, ArH), 7.09 (dd, 1H,  $J = 15.6, 6.6$  Hz, ArH), 7.49-7.62 (m, 12H, TsH), 7.80 (s, br, 2H, NH). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>, 80 °C)  $\delta$  (ppm): 207.2 (s), 142.4 (s), 141.3 (s), 136.6 (s), 129.2 (d), 128.4 (d), 127.2 (d), 126.7 (d), 124.9 (d), 56.3 (t), 44.4 (q), 43.1 (q), 24.2(q). Anal. Calcd for C<sub>35</sub>H<sub>39</sub>N<sub>5</sub>O<sub>6</sub>S<sub>5</sub>: C 53.38, H 5.00, N 8.91. Found C 53.15, H 4.95, N 9.00%.

**Macrocycle 1e.** Yield, 79%, white crystalline solid, mp 248-250 °C. IR (KBr, cm<sup>-1</sup>)  $\nu$ : 3337 (m, N-H), 2956 (s, C-H), 1395 (s, C=S), 1355 (s, SO<sub>2</sub>), 1292 (s, C=S), 1158 (s, SO<sub>2</sub>), 855 (vs, Ts-H), 830 (vs, Ar-H). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 60 °C)  $\delta$  (ppm): 2.43 (s, 9H, CH<sub>3</sub>), 3.30-3.43 (m, 8H, TsNCH<sub>2</sub>), 4.74 (s, 4H, ArCH<sub>2</sub>), 6.95 (d, 4H,  $J = 13.3$  Hz, ArH), 7.48-7.62 (m, 12H, TsH), 7.83 (s, br, 2H, NH). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>, 80 °C)  $\delta$  (ppm): 208.3 (s), 142.6 (s), 140.6 (s), 136.8 (s), 129.3 (d), 127.3 (d), 126.8 (d), 57.4 (t), 44.3 (q), 43.2 (q), 24.3 (q). Anal. Calcd for C<sub>35</sub>H<sub>39</sub>N<sub>5</sub>O<sub>6</sub>S<sub>5</sub>: C 53.38, H 5.00, N 8.91. Found C 53.43, H 5.05, N 9.01%.

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