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

Congwen Ding, Mingjie Zhang,* Lijun Geng, and Ruimin Li

Chemistry Department of Science School, Tianjin University, Weijin Road 92#, Tianjin 300072, People's Republic of China
E-mail: zmjtjuoc@163.com

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.b05

Abstract

The nucleophilic reaction of diamines and carbon disulfide in aqueous NaOH afforded a series of bis-dithiocarbamate salts. Activation of these with aqueous $ClCH_2COOK$ 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.

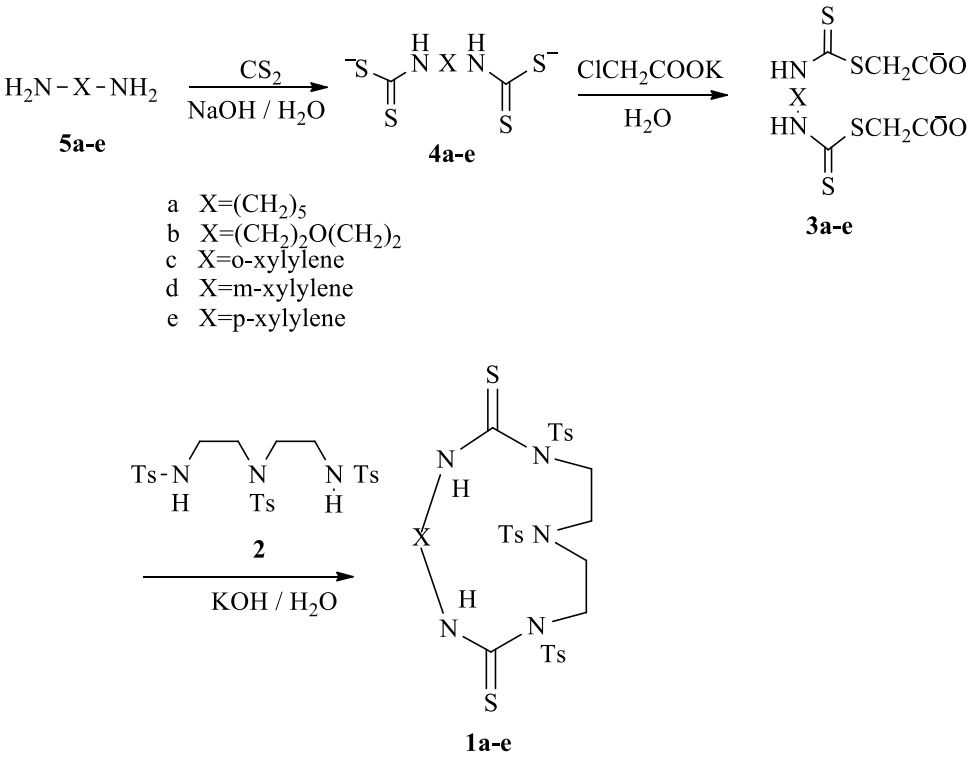
Keywords: Trisulfonamide, activated bis-dithiocarbamate salt, N-tosyl-macrocycle containing two thiourea moieties, green synthesis

Introduction

Macrocyclic anion receptors[1] 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,[2] their easy complexation of anions[3] and N-protected glutamate dianion,[4] and antimicrobial studies.[5] Our ongoing studies are concerned with the simple, convenient preparation of these macrocycles. We have noted that the traditional methods[6] 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.[7] 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 bio-transformations of the widely applied thioglycolate ion[8] 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**[9] and **2**[10] were prepared according to literature procedures. A modification of the procedure of Aksac[11] was used to obtain yellowish aqueous solutions of compounds **3a-e**,.which were used for the following reactions. Aqueous $ClCH_2COOK$ was prepared by using $ClCH_2COOH$ 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_2O 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_2O without organic solvents is an environmentally friendly procedure.

The structures of **1a-e** were characterized by melting point, IR, ^{1}H NMR, ^{13}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 cm^{-1} and 1380–1395 cm^{-1}, two bands for the symmetrical and asymmetrical vibrations of the SO_2 group at 1145–1158 cm^{-1} and 1345–1355 cm^{-1} as well as a Ts-H out-of-plane C-H bending vibration with two adjacent hydrogens at 852–856 cm^{-1} and C-O stretching with broad and strong absorption at 1090 cm^{-1} in compound **1b**, *ortho*-xylylene out-of-plane C-H bending with four adjacent hydrogen at 755 cm^{-1} in case of compound **1c**, *meta*-xylylene C-H bending with three adjacent hydrogen and one isolated hydrogen at 770 cm^{-1} in case of compound **1d**, and *para*-xylylene C-H bending with two adjacent hydrogen at 830 cm^{-1} in case of compound **1e**. The N-H bands appeared at 3332–3347 cm^{-1}. The ^{1}H NMR data showed a broad singlet in the region δ 7.65–7.83 ppm for NH, multiplets at δ 3.47–3.61 ppm and δ 3.61–3.64 ppm for the NCH_2 and OCH_2 of **1a** and **1b**, respectively. Multiplets at δ 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}C NMR spectra which revealed the expected number of signals for the mentioned compounds as well as C= S signals at δ 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[12] and then oxidation[13] 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}H) and 100 (^{13}C) MHz, respectively, on a Bruker Avance III Plus 400 spectrometer in DMSO-d_6 using TMS as internal reference. Chemical shifts (δ) 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 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 H_2O was added CS_2 (5.0 mmol, 0.3 mL), and the mixture solidified in an ice-salt bath after stirring for 1 h at 35 ºC. 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 H_2O. 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 H_2O were added dropwise simultaneously to 20 mL of H_2O. 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 H_2O (3×5 mL), then dried under vacuum over P_4O_{10} to afford macrocycles **1a-e** in high purity.

Macrocycle (1a). Yield, 82%, white crystalline solid, mp 278-280 ºC. IR (KBr, cm^{-1}) ν: 3332 (m, N-H), 2960 (s, C-H), 1380 (s, C=S), 1346 (s, SO_2), 1280 (s, C=S), 1146 (s, SO_2), 852 (vs, Ts-H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 70 ºC) δ (ppm): 1.32-1.58 (m, 6H, CH_2), 2.40 (s, 9H, CH_3), 3.47-3.61 (m, 4H, NCH_2), 3.31-3.52 (m, 8H, $TsNCH_2$), 7.48-7.56 (m, 12H, TsH), 7.65 (s, br, 2H, NH). ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 90 ºC) δ (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 $C_{32}H_{41}N_5O_6S_5$: 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 ºC. IR (KBr, cm^{-1}) ν: 3335 (m, N-H), 2962 (s, C-H), 1385 (s, C=S), 1345 (s, SO_2), 1285 (s, C=S), 1145 (s, SO_2), 1090 (bs, C-O), 853 (vs, Ts-H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 70 ºC) δ (ppm): 2.41 (s, 9H, CH_3), 3.28-3.48 (m, 8H, $TsNCH_2$), 3.61-3.64 (m, 8H, NCH_2 & OCH_2), 7.49-7.59 (m, 12H, TsH), 7.68 (s, br, 2H, NH). ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 90 ºC) δ (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 $C_{31}H_{39}N_5O_7S_5$: 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 ºC. IR (KBr, cm^{-1}) ν: 3341 (m, N-H), 2960 (m, C-H), 1390 (s, C=S), 1347 (s, SO_2), 1290 (s, C=S), 1147 (s, SO_2), 854 (vs, Ts-H), 755 (vs, Ar-H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 60 ºC) δ (ppm): 2.40 (s, 9H, CH_3), 3.30-3.45 (m, 8H, $TsNCH_2$), 4.75 (s, 4H, $ArCH_2$), 7.14-7.43 (m, 4H, ArH), 7.48-7.63 (m, 12H, TsH), 7.73 (s, br, 2H, NH). ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 80 ºC) δ (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 $C_{35}H_{39}N_5O_6S_5$: 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 ºC. IR (KBr, cm^{-1}) ν: 3347 (m, N-H), 2958 (s, C-H), 1385 (s, C=S), 1350 (s, SO_2), 1295 (s, C=S), 1152 (s, SO_2), 856 (vs, Ts-H), 770 (vs, Ar-H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 60 ºC) δ(ppm): 2.42 (s, 9H, CH_3), 3.31-

3.44 (m, 8H, $TsNCH_2$), 4.73 (s, 4H, $ArCH_2$), 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). ^{13}C NMR (100 MHz, DMSO-d_6, 80 ^oC) δ (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 $C_{35}H_{39}N_5O_6S_5$: 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 ^oC. IR (KBr, cm^{-1}) ν: 3337 (m, N-H), 2956 (s, C-H), 1395 (s, C=S), 1355 (s, SO_2), 1292 (s, C=S), 1158 (s, SO_2), 855 (vs, Ts-H), 830 (vs, Ar-H). ^1H NMR (400 MHz, DMSO-d_6, 60 ^oC) δ (ppm): 2.43 (s, 9H, CH_3), 3.30-3.43 (m, 8H, $TsNCH_2$), 4.74 (s, 4H, $ArCH_2$), 6.95 (d, 4H, *J* = 13.3 Hz, ArH), 7.48-7.62 (m, 12H, TsH), 7.83 (s, br, 2H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, 80 ^oC) δ (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 $C_{35}H_{39}N_5O_6S_5$: C 53.38, H 5.00, N 8.91. Found C 53.43, H 5.05, N 9.01%.

Acknowledgements

We are thankful for financial support from the National Natural Science Foundation of China (NNSFC) (No. 20802049).

References

1. Choi, K.; Hamilton, A. D. *Coord. Chem. Rev.* **2003**, *240*, 101.
2. Buhlmann, P.; Pretsch, E.; Bakker, E. *Chem. Rev*. **1998**, *98*, 1593.
3. Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609. (b) Matsumura, N.; Konishi, T.; Hayashi, H.; Yasui, M.; Iwasaki, F.; Mizuno, K. *Heterocycles* **2000**, *53*, 1239. (c) Okumura, Y.; Murakami, S.; Maeda, H.; Matsumura, N.; Mizuno, K. *Tetrahedron Lett.* **2003**, *44*, 8183.
4. Rossi, S.; Kyne, G. M.; Turner, D. L. ; Wells, N. J.; Kilburn, J. D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4233. (b) Ragusa, A.; Rossi, S.; Hayes, J. M.; Stein, M. ; Kilburn, J. D. *Chem. Eur. J.* **2005**, *11*, 5674. (c) Bartoli, S.; Mahmood, T.; Malik, A.; Dixon, S.; Kilburn, J. D. *Org. Biomol. Chem.* **2008**, *6*, 2340.
5. Annigeri, M.; Sathisha, M.P.; Revankar, V.K. *Transit. Met. Chem.* **2007**, *32*, 81. (b) Chandra, S.; Verma, S.; Dev, U.; Joshi, N. *J. Coord. Chem.* **2009**, *62*, 1327.
6. Ding, C.; Zhang, M.; Ma, N. *Youji Huaxue* **2010**, *30(2)*, 173.
7. Ding, C.; Zhang, M.; Ma, N. *Chin. Chem. Lett.* **2009**, *20*, 1166.
8. Osamu, S.; Susumu T. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 801. (b) Zhong, Z.; Du, D.; Liang, X. *Huaxue Fenxi Jiliang* **2002**, *11(2)*, 22. (c) Ning, M.S.; Price, S. E.; Ta, J.; Davies, K. M. *J. Phys. Org. Chem.* **2010**, *23*, 220.
9. Atkinson, I. M.; Lindoy, L. F.; Matthews, O. A.; Meehan, G. V.; Sobolev, A. N.; White, A. H. *Aust. J. Chem.* **1994**, *47*, 1155. (b) Gamsow, O. A.; Kausar, A. R.; Triplett, K. B. *J.*

Heterocl. Chem. **1981**, *18*, 297. (c) Nair, M. K. M.; Radhakrishnar, P. K. *Synth React Inorg. Met.-Org. Chem*. **1995**, *25*, 1077.
10. Koyama, H.; Yoshino, T. *Bull. Chem. Soc. Jpn*. **1972**, *45*, 481.
11. Aksac, Z.; Pinar, E.; Icli, S. *Organic Magnetic Resonance* **1983**, *21*, 548.
12. Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 220. (b) Taber, D. F.; Wang, Y.N. *J. Am. Chem. Soc.* **1997**, *119*, 22. (c) Nadir, U. K.; Krishna, R. V. *J. Heterocycl. Chem.* **2004**, *41*, 737.
13. Li, Z.; Wang, X.; Da, Y.; Chen, J. *Synth. Commun.* **2001**, *31*, 1433. (b) Yang, G.; Chen, Z.; Zhang, H. *Green Chem.* **2003**, *5*, 441. (c) Wang, X.; Song, A.; Zhu, J.; Yang, Z.; Zhang, Z. *Synth. Commun.* **2007**, *37*, 1627.

