A Novel and Green Method for the Synthesis of Benzo-15-crown-5 Containing Sulphonylthiourea-Based Receptors

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The nucleophilic reaction of 4'-aminobenzo-15-crown-5 and carbon disulphide in aqueous KOH afforded corresponding dithiocarbamate salt. Subsequent nucleophilic substitution reactions with sulfonamides aqueous NaOH provided benzo-15-crown-5-containing sulphonylthioureas. This novel, green method has the advantages of simple operation, high yields, easy product-isolation and environmental friendliness.

Key Words: Aqueous media, Benzo-15-crown-5-dithiocarbamate salt, Sulfonamides, Sulphonylthioureas.

INTRODUCTION

Thioureas-based anion receptors¹ via hydrogen-bonding interactions including benzo-15-crown-5-containing thioureas^{2,3} are well known. The continued interest in novel thiourea ligands stems from their applications in many areas of chemistry and biochemistry, such as chromoionophore⁴, bifunctional organo-catalyst⁵, solar cell⁶ and easy complexation of Ni(II)⁷ and anions⁸. Our ongoing studies are concerned with the simple, convenient preparation of these compounds. Several traditional methods have been developed for the synthesis of sulphonylthioureas involving: (a) reaction of sulphonylisothiocyanate and amine in dry CCl₄, CHCl₃ or CH₂Cl₂⁹⁻¹³; (b) reaction of sulfonamide and isothiocyanate in anhydride acetone, DMF or DMSO in the presence of strong base¹⁴⁻¹⁷. These traditional methods¹⁸ involve volatile and toxic organic solvent, hyper-toxic thiophosgene or unstable sulphonylisothiocyanate and cumbersome product-isolation procedures.

We have recently reported the synthesis of sulphonyl-imidazolidinethione from monosulphonyldiamine and carbon disulphide by intramolecularly nucleophilic substitution in water¹⁹. In continuation of our ongoing research on the development of new eco-friendly organic reactions, we utilized water as green solvent to present a novel method for the synthesis of benzo-15-crown-5-sulphonylthioureas from sulfonamides and benzo-15-crown-5-dithiocarbamate salts by intermolecularly nucleophilic substitution affording the desired products in excellent yields with a practical and easy workup procedure. The synthetic route is outlined in **Scheme-I**.

Scheme-I: Synthesis of sulphonylthiourea-functionalized benzo-15-crown-5 (**4a-g**) in water

EXPERIMENTAL

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. The progress of the reactions was monitored by TLC using silica-gel SIL G/UV₂₅₄ plates and also by HPLC on RIGOL L-3000 instrument using THF-MeOH as the mobile phase on PGC column. NMR spectra were recorded at 400 (¹H) 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} . High resolution mass spectrum (HRMS) was recorded on PESCIEX API 2000 (triple quadrupole) mass spectrophotometer.

Typical procedure: To a solution of compound **1** (2.83 g, 10 mmol) and KOH (0.56 g, 10 mmol) in H_2O (40 mL) was added CS_2 (50 mmol, 3 mL) and the mixture solidified in an ice-salt bath after stirring for 0.5 h at 35°C . The dithiocarbamate salt was filtered, washed with a minimal amount of Et_2O -ethanol and added to little amount of warm water, thus aqueous compound **2** was isolated and obtained. A mixture of compounds **3a-g** (10 mmol) and NaOH (0.84 g, 21 mmol) in H_2O (60 mL) was heated at 50°C . Agitation was continued for a further 45 min followed by dropwise addition of aqueous compound **2** with the reaction temperature being controlled at 50°C . The reaction mixture was cooled to room temperature and acidized with 2 M HCl. The precipitated product was filtered off, washed with little amount of ethanol, dried and recrystallized from ethanol to give pale yellow needles **4a-g**.

Spectroscopic data of compound **4a**: yield, 84 %; IR (KBr, ν_{max} , cm^{-1}): 1090 (C=S), 1360 and 1180 (SO_2), 1142 (CH_2OCH_2), 1048 (ArOCH_2), 860 (TsArH), 3220, 3280 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 2.34 (s, 3H, TsCH₃), 3.34-4.11 (m, 16H, CH_2OCH_2), 6.60-6.84 (m, 2H, OArH), 7.23 (s, 1H, OArH), 7.48-7.56 (m, 4H, TsArH), 8.86 (s, 1H, NH), 11.23 (s, 1H, SO_2NH). HRMS calcd. (%) for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_7\text{S}_2$ m/z 496.1315, found m/z 496.1310.

Compound 4b: Yield, 83 %; IR (KBr, ν_{max} , cm^{-1}): 1092 (C=S), 1363 and 1182 (SO_2), 1145 (CH_2OCH_2), 1049 (ArOCH_2), 770 (*o*-MeArH), 3225, 3283 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 2.35 (s, 3H, *o*-CH₃PhSO₂), 3.33-4.12 (m, 16H, CH_2OCH_2), 6.59-6.83 (m, 2H, OArH), 7.22 (s, 1H, OArH), 7.46-7.52 (m, 4H, *o*-MeArH), 8.85 (s, 1H, NH), 11.20 (s, 1H, SO_2NH). HRMS calcd. (%) for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_7\text{S}_2$ m/z 496.1315, found (%) m/z 496.1312.

Compound 4c: Yield, 85 %; IR (KBr, ν_{max} , cm^{-1}): 1094 (C=S), 1365 and 1184 (SO_2), 1143 (CH_2OCH_2), 1047 (ArOCH_2), 760, 710 (SO_2ArH), 3222, 3282 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.35-4.14 (m, 16H, CH_2OCH_2), 6.61-6.85 (m, 2H, OArH), 7.25 (s, 1H, OArH), 7.49-7.57 (m, 5H, SO_2ArH), 8.87 (s, 1H, NH), 11.24 (s, 1H, SO_2NH). HRMS calcd. (%) for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_7\text{S}_2$ m/z 482.1255, found (%) m/z 482.1250.

Compound 4d: Yield, 85 %; IR (KBr, ν_{max} , cm^{-1}): 1093 (C=S), 1364 and 1183 (SO_2), 1144 (CH_2OCH_2), 1046 (ArOCH_2), 850 (*p*-ClArH), 3223, 3281 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.36-4.15 (m, 16H, CH_2OCH_2), 6.63-6.87 (m, 2H, OArH), 7.24 (s, 1H, OArH), 7.47-7.54 (m, 4H, *p*-ClArH), 8.84 (s, 1H, NH), 11.22 (s, 1H, SO_2NH). HRMS calcd. (%) for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_7\text{S}_2\text{Cl}$ m/z 517.0213, found (%) m/z 517.0211.

Compound 4e: Yield 82 %; IR (KBr, ν_{max} , cm^{-1}): 1095 (C=S), 1361 and 1181 (SO_2), 1148 (CH_2OCH_2), 1048 (ArOCH_2), 3224, 3285 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.05 (s, 3H, CH_3SO_2), 3.32-4.10 (m, 16H, CH_2OCH_2), 6.62-6.86 (m, 2H, OArH), 7.21 (s, 1H, OArH), 8.83 (s, 1H, NH), 11.19 (s, 1H, SO_2NH). HRMS calcd. (%) for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_7\text{S}_2$ m/z 420.5013, found (%) m/z 420.5010.

Compound 4f: Yield 81 %; IR (KBr, ν_{max} , cm^{-1}): 1091 (C=S), 1362 and 1185 (SO_2), 1147 (CH_2OCH_2), 1045

(ArOCH_2), 750 (*o*-ClArH), 3225, 3284 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.37-4.16 (m, 16H, CH_2OCH_2), 6.64-6.88 (m, 2H, OArH), 7.26 (s, 1H, OArH), 7.48-7.55 (m, 4H, *o*-ClArH), 8.88 (s, 1H, NH), 11.25 (s, 1H, SO_2NH). HRMS calcd. (%) for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_7\text{S}_2\text{Cl}$ m/z 517.0213, found (%) m/z 517.0210.

Compound 4g: Yield 80 %; IR (KBr, ν_{max} , cm^{-1}): 1096 (C=S), 1366 and 1186 (SO_2), 1144 (CH_2OCH_2), 1050 (ArOCH_2), 810 (SO_2NAH), 3226, 3287 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.31-4.13 (m, 16H, CH_2OCH_2), 6.66-6.90 (m, 2H, OArH), 7.27 (s, 1H, OArH), 7.50-7.58 (m, 7H, SO_2NAH), 8.90 (s, 1H, NH), 11.26 (s, 1H, SO_2NH). HRMS calcd. (%) for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_7\text{S}_2$ m/z 532.6316, found (%) m/z 532.6313.

RESULTS AND DISCUSSION

Starting material **1** was prepared according to the published procedures². A modification of the procedure of Aksac²⁰ was used to obtain aqueous solution of compound **2**, which was used for the following reactions. Benzo-15-crown-5-based ligand³ used as Na^+ receptor and phase transfer catalyst could improve the water-solubility of **1** and nucleophilicity of TsNH-Na^+ moiety. The novel reaction for the preparation of title compounds **4a-g** was carried out based on the procedures shown in **Scheme-I**.

The structures of compounds **4a-g** were characterized by spectral (IR, ^1H NMR, HRMS) data. The infrared spectra of the thioureas **4a-g** revealed a C=S stretching vibration at 1090-1096 cm^{-1} , two bands for the symmetrical and asymmetrical vibrations of the SO_2 group at 1186-1180 and 1366-1360 cm^{-1} as well as *p*-MePhSO₂ and *p*-ClPhSO₂ out-of-plane Ph-H bending vibration with two adjacent hydrogens at 850-860 cm^{-1} in compounds **4a** and **4d**, *o*-MePhSO₂ and *o*-ClPhSO₂ out-of-plane Ph-H bending with four adjacent hydrogen at 750-770 cm^{-1} in case of compounds **4b** and **4f**, PhSO₂ C-H bending with five adjacent hydrogen at 710, 760 cm^{-1} in case of compound **4c** and 1-naphthyl SO_2 C-H bending with four and three adjacent hydrogen at 810 cm^{-1} in case of compound **4g**. The N-H *bis*-protons bands appeared at 3226-3220 and 3287-3280 cm^{-1} . The ^1H NMR data showed two broad singlets in the region δ 8.83-8.90 and 11.19-11.26 ppm for corresponding NH and SO_2NH moieties, multiplets at δ 3.31-4.16 ppm for CH_2OCH_2 of **4a-g**. Multiplets at δ 7.46-7.52 and 7.48-7.55 ppm for four hydrogens of the *o*-CH₃Ph and *o*-ClPh rings in compounds **4b** and **4f**, at δ 7.48-7.56 and 7.47-7.54 ppm for four hydrogens of the *p*-CH₃Ph and *p*-ClPh rings in compounds **4a** and **4d** as well as a singlet at 3.05 ppm for the three hydrogens of the CH_3SNO_2 moiety in **4e**. Further evidence about the structure of the foregoing compounds **4a-g** has been derived from their HRMS spectra which revealed the expected m/z number of signals for thiourea-based receptors, respectively.

Conclusion

In summary, an operationally simple and environmentally benign protocol for the synthesis of sulphonylthiourea-functionalized benzo-15-crown-5 in aqueous media is described. The mildness and eco-friendly nature of the reaction, short reaction times and impressive yields are the considerable

advantages that make the present method superior to the existing methods for the preparation of sulphonylthioureas. More detailed studies on the mechanism and synthetic applications of this supramolecular receptors for cooperative binding of sodium ions and anions are currently under investigation.

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REFERENCES

1. A.-F. Li, J.-H. Wang, F. Wang and Y.-B. Jiang, *Chem. Soc. Rev.*, **39**, 3729 (2010).
2. S. Nishizawa, K. Shigemori and N. Teramae, *Chem. Lett.*, 1185 (1999).
3. F.D. Sokolov, D.A. Safin, M.G. Babashkina, N.G. Zabiroy, V.V. Brusko, N.A. Mironov, D.B. Krivolapov, I.A. Litvinov, R.A. Cherkasov and B.N. Solomonov, *Polyhedron*, **26**, 1550 (2007).
4. T. Hayashita, T. Onodera, R. Kato, S. Nishizawa and N. Teramae, *Chem. Commun.*, 755 (2000).
5. B. Wu, G.-G. Liu, M.-Q. Li, Y. Zhang, S.-Y. Zhang, J.-R. Qiu, X.-P. Xu, S.-J. Ji and X.-W. Wang, *Chem. Commun.*, 3992 (2011).
6. Z. Ning, C. Yuan, H. Tian, Y. Fu, L. Li, L. Sun and H. Ågren, *J. Mater. Chem.*, **22**, 6032 (2012).
7. M.G. Babashkina, D.A. Safin, K. Robeyns and Y. Garcia, *J. Chem Soc., Dalton Trans.*, **41**, 1451 (2012).
8. W.-X. Liu, R. Yang and A.-F. Li, Z. Li, Y.F. Gao, X.X. Luo, Y.B. Ruan and Y.B. Jiang, *Org. Biomol. Chem.*, **7**, 4021 (2009).
9. J.W. McFarland and R.W. Houser, *J. Org. Chem.*, **33**, 340 (1968).
10. J.W. McFarland, T.H. Kozel, K.R. Stuhlmacher and T.S. Chevalier, *J. Heterocycl. Chem.*, **17**, 273 (1980).
11. C. Levallet, J. Lerpiniere and S.Y. Ko, *Tetrahedron*, **53**, 5291 (1997).
12. A.M. Bowser and J.S. Madalenoitia, *Org. Lett.*, **6**, 3409 (2004).
13. I.-J. Kang, L.-W. Wang, S.-J. Hsu, C.-C. Lee, Y.-C. Lee, Y.-S. Wu, T.-A. Hsu, A. Yueh, Y.-S. Chao and J.-H. Chern, *Bioorg. Med. Chem. Lett.*, **19**, 4134 (2009).
14. H.-B. Zhang, Y.-A. Zhang, G.-Z. Wu, J.-P. Zhou, W.-L. Huang and X.-W. Hu, *Bioorg. Med. Chem. Lett.*, **19**, 1740 (2009).
15. K.-H. König, C. Holzner and J. Boßlet, *Chem. Ber.*, **121**, 1771 (1988).
16. J. Li, G. Zhang, Z. Zhang and E. Fan, *J. Org. Chem.*, **68**, 1611 (2003).
17. S.A.F. Rostom, *Bioorg. Med. Chem.*, **14**, 6475 (2006).
18. C.-W. Ding, M.-J. Zhang and N. Ma, *Youji Huaxue*, **30**, 173 (2010).
19. C.-W. Ding, M.-J. Zhang and N. Ma, *Chin. Chem. Lett.*, **20**, 1166 (2009).
20. Z. Aksac, E. Pinar and S. Icli, *Org. Magn. Reson.*, **21**, 548 (1983).