



Stannathianes as activated polythiols for the synthesis of functionalized macrocyclic polythiolactones



Zuly Y. Delgado Espinosa, Mauricio F. Erben*

CEQUINOR (UNLP, CONICET-CCT La Plata), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Bv. 120 e/ 60 y 64 N°1465, La Plata (1900), Argentina

ARTICLE INFO

Article history:

Received 31 January 2017

Revised 21 February 2017

Accepted 27 February 2017

Available online 28 February 2017

Keywords:

Template synthesis

Stannathiane

Macrocyclic compounds

Thiolactone

Sulfur chemistry

ABSTRACT

We synthesized novel macrocyclic dithiolactones bearing endocyclic ether, polyether and lactone groups using new stannadithianes as tin templates in the condensation reaction with acid dichlorides and demonstrated an extension of this method toward synthesizing spiro-tetrathiolactones of controlled size. The structures of all synthesized compounds were characterized by spectroscopic methods.

© 2017 Elsevier Ltd. All rights reserved.

Introduction

Because of the so-called macrocyclic effect,¹ macrocyclic compounds—like polyactones, polythiolactones, and thiocrown ethers—have attracted attention as ligands for transition-metal ions because these compounds coordinate metal centers better than their acyclic counterparts.² In these compounds, the ring size and strain energy strongly influence the structural features and binding properties.^{3,4}

Polythiolactones are cyclic compounds having at least two endocyclic –SC(O)– groups.⁵ A few procedures are available for the preparation of macrocyclic thiolactones, including: 1) the use of benzyltriethylammonium tetrathiomolybdate as an efficient sulfur-transfer reagent to ω-halo acid chlorides for preparation of small-sized thiolactones, with polythiolactones being obtained as by-products⁶ and 2) the Shanzer-and-Libman method for macrocyclic polythiolactones by the reaction of cyclic stannadithianes with α,ω-dicarboxylic acid chlorides.⁷ The use of stannadithianes as tin templates enables control of the cycloaddition reaction leading to the formation of monomers (dithiolactones) and dimers (tetrathiolactones), depending on the size of the reagent and the ring strain of the products.⁸ Furthermore, polymerization reactions are spontaneous, highly exothermic processes; and upon ring

opening and poly condensation with dicarboxylic acid dichlorides, 2-stanna-1,3-dithiacycloalkanes yield polythioesters with number-average molecular weights above 30,000.⁹ The kinetics of the double-ring-closure reaction determines the influence of the mixing procedure on the ratio of the final products.¹⁰ More recently, stannathianes having polythioether chains have been prepared by using the reaction between dibutyltin oxide with dithiols in the presence of *p*-toluenesulfonic acid as a catalyst.^{11,12} In turn, these dithiols serve as templates for the preparation of di- and tetrathiolactones containing polythioether chains.

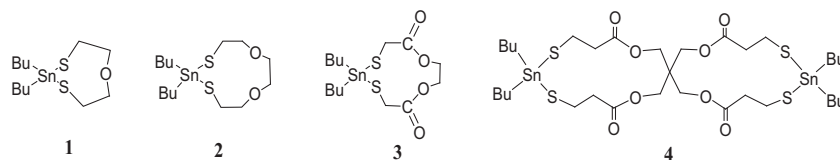
In this article, we report the synthesis of four cyclic 2-stanna-1,3-dithianes (cf. Scheme 1) containing endocyclic-ether (compounds **1** and **2**) and lactone (compound **3**) groups. We also describe the preparation of the first spiro compound, bis-stanna (tetra)thiane (compound **4**) and demonstrate the usefulness of these compounds as activated dithiol intermediates for preparing macrocyclic dithiolactone compounds via ring-opening condensation.

Results and discussion

Stannathianes **1** and **2** were prepared by the condensation reaction of dibutyltin oxide [(Bu)₂SnO] with the corresponding dithiols [2-mercaptoethyl ether and 2,2'-(ethylenedioxy)diethanethiol, respectively] in boiling toluene.¹³ After 24 h, an oily liquid (**1**) and a greasy compound (**2**) were obtained in good yields,

* Corresponding author.

E-mail address: erben@quimica.unlp.edu.ar (M.F. Erben).



Scheme 1. The 2-stanna-1,3-dithianes prepared in this work.

ca. 90%. According to the nuclear-magnetic-resonance (NMR) and Fourier-transform-infrared (FTIR) spectroscopies, the reaction went to completion, with the crude products obtained being already pure enough. The ^{119}Sn -NMR spectra indicated signals at 95.1 and 131.0 ppm, while the $\nu(\text{C}-\text{Sn})$ stretching absorptions were clearly observed at 593 and 597 cm^{-1} in the infrared spectra, for compounds **1** and **2**, respectively. The 2-dimensional-heteronuclear-single-quantum-coherence (2D-HSQC) NMR spectra allowed for an accurate and simultaneous assignment of the ^1H and ^{13}C chemical shifts of the ether carbon chain (cf. the [Experimental Section](#)). Both compounds were stable and could be stored indefinitely at room temperature without noticeable decomposition.

To the best of our knowledge, stannathianes containing endocyclic lactone groups have not yet been synthesized. Stannathiane **3** was prepared by treatment of $(\text{Bu})_2\text{SnO}$ with ethylene glycol bis-thioglycolate in boiling toluene at a 93% yield. The stable solid product could be further purified by recrystallization from dimethyl sulfoxide. The endocyclic lactone group was characterized by the presence of an intense absorption at 1736 cm^{-1} in the infrared spectrum and a signal at 170.7 ppm in the ^{13}C NMR spectrum.

These successful preparations prompted us to synthesize the related bis-stannathiane **4**, using the related tetrathiolpentaerythritoltetrakis(3-mercaptopropionate). Spiro compounds containing two $>\text{S}_2\text{Sn}$ moieties had not been synthesized up to that time. The reaction went smoothly, and excellent yields (96%) of the desired product were obtained upon heating in refluxing toluene overnight. After removing the solvent, a plastic-like compound remained, which product proved to be stable and could be further purified by recrystallization from hot toluene and chloroform (1:1). The ^1H NMR spectrum was consistent with a highly symmetric compound confirmed with the help of the 2D-HSQC NMR spectrum (cf. Supporting Information) and the presence of resonance at 171.4 ppm in the ^{13}C NMR spectrum as a result of the $\text{C}=\text{O}$ carbon. The presence of the lactone group was further evidenced in the infrared spectrum by the observation of the $\nu(\text{C}=\text{O})$ stretching at 1733 cm^{-1} .

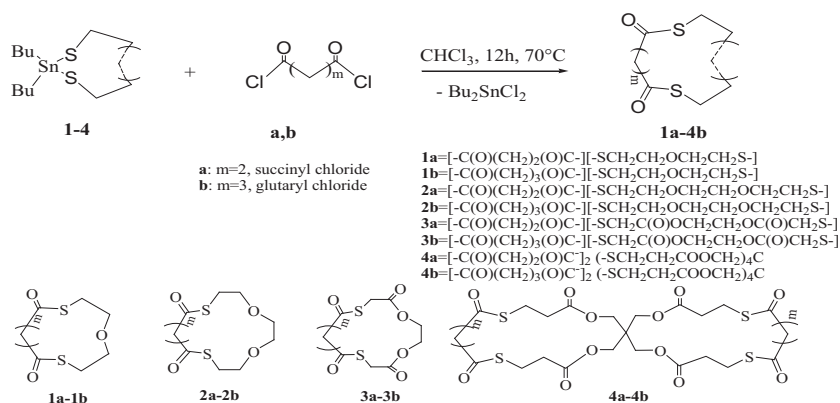
A second aim of this study was to determine the feasibility of using compounds **1–4** as tin “covalent templates” in Shanzer and

Libman’s general method for the preparation of macrocyclic polythiolactones.¹⁴ The procedure involved treating the stannathiane compounds **1–4** with diacyl dihalides, as illustrated in [Scheme 2](#). Two diacyl dihalides—i.e., succinyl chloride (**a**) and glutaryl dichloride (**b**)—were used as chemical probes to validate the potential of these novel templates.

Depending on the specific reaction conditions (i.e., reagent concentrations, molar ratio, and temperature, among others), macrocyclization to di-, tetra-, or even higher thiolactones can be achieved by using stannathiane tin templates and diacyl dihalides.^{10,15} In the present work, when the reaction conditions were deliberately adjusted to favor the formation of dithiolactones,¹⁶ no evidence for the formation of higher polythiolactones was found. To carry out a typical macrocyclization reaction, we used a slow addition of the diacyldihalide dissolved in chloroform (0.1 M) to a refluxing chloroform solution of the appropriate stannathiane template. The final stannathiane:diacyldihalide ratio used was 1:3, and the reaction mixture was refluxed overnight with stirring. The new polythiolactones were characterized by FTIR, multinuclear- ^1H , and ^{13}C NMR spectroscopy and mass spectrometry, as detailed in the [Experimental Section and Supplementary data](#).

Thus, stannathianes **1** and **2** reacted with diacyldihalides **a–b** to produce the novel dithiolactones **1a–1b** and **2a–2b**, respectively, having endocyclic ether groups. The presence of a single signal around $\delta = 197.0$ ppm in the ^{13}C NMR spectra and the intense absorptions between 1686 and 1694 cm^{-1} in the infrared spectra of the compounds isolated were indicative of the formation of thiolactones.

Two novel compounds, **3a** and **3b**, were obtained by the reaction of stannathiane **3** with succinyl chloride and glutaryl dichloride, respectively. In this instance, the cyclic compounds consisted in endocyclic dilactone and dithiolactone groups, as revealed by the detailed analysis of the ^{13}C NMR [$\delta(\text{C}(\text{O})-\text{O}) = 206.8, 208.8$ ppm and $\delta(\text{C}(\text{O})-\text{S}) = 191.8, 200.2$ ppm for **3a** and **3b**, respectively] and by the infrared spectra for **3a**—where the $\nu(\text{C}=\text{O})$ carbonyl-stretching modes, as intense absorptions were observed at 1693 and 1723 cm^{-1} for thiolactone and lactone groups, respectively—and **3b**—where the $\nu(\text{C}=\text{O})$ carbonyl



Scheme 2. Synthesis of macrocyclic poly-thiolactones.

stretching modes as intense absorptions were clearly observed at 1684 and 1740 cm^{-1} for the thiolactone and lactone groups, respectively.

Finally, the tetralactone/tetrathiolactone spiro compounds **4a** and **4b** were prepared by reaction of stannathiane **4** with two equivalents of the corresponding acid dichlorides (**a–b**). The direct reaction between pentaerythritoltetra(mercaptoacetate) and several acid dichlorides had been studied previously by Kricheldorf et al.,¹⁷ demonstrating that multicyclic polythioester polymers and gels were obtained in the absence of tin templates. In the present experiment, the analysis of the ^{13}C NMR [$\delta = 171$ ppm (COO) and $\delta = 197$ (COS)] and infrared spectra, with intense stretching absorptions observed at around 1690 cm^{-1} (thiolactone group) and 1740 cm^{-1} (lactone group), demonstrated the formation of the corresponding spiro compounds. To the best of our knowledge, this present report is the first describing the preparation of tetrathiolactones of controlled size through the use of the stannathiane-template method.

Conclusion

In summary, the novel stannathiane compounds **1–4** have been prepared and their feasibility as tin templates for the synthesis of macrocyclic thiolactones demonstrated, including an extension of Shanzer and Libman's general method to the preparation of dithiolactones containing endocyclic ethers (**1a–1b**), polyethers (**2a–2b**), and lactone groups (**3a–3b**) as well as tetralactone and tetrathiolactone spiro compounds (**4a–4b**).

Author contributions

All the authors contributed to the writing of the manuscript and have given approval to its final version.

Acknowledgement

ZYDE is a postdoctoral fellow and MFE is member of the Carrera del Investigador of CONICET (Argentina). The authors thank the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET),

the Agencia Nacional de Promoción Científica y Tecnológica (ANPCYT, PICT-2130), and the Facultad de Ciencias Exactas, Universidad Nacional de La Plata for financial support. Dr. Donald F. Haggerty, a retired academic career investigator and native English speaker, edited the final version of the manuscript.

A. Supplementary data

Supplementary data (Experimental details, infrared spectra and multinuclear and 2D-HSQC-NMR-spectroscopic data including ^1H , ^{13}C , and ^{119}Sn (**1–4**) spectra for all the synthesized compounds as well as analyses by chromatography and mass spectrometry for the polythiolactone compounds) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2017.02.086>. These data include MOL files and InChIKeys of the most important compounds described in this article.

References

1. Cabiness DK, Margerum DW. *J Am Chem Soc.* 1969;91:6540–6541.
2. Shanzer A, Libman J, Frolow F. *Acc Chem Res.* 1983;16:60–67.
3. Dugarte NY, Erben MF, Hey-Hawkins E, et al. *J Phys Chem A.* 2013;117:5706–5714.
4. Vujasinovic I, Veljkovic J, Mlinaric-Majerski K, Molcanov K, Kojic-Prodic B. *Tetrahedron.* 2006;62:2868–2876.
5. Noel A, Delpech B, Crich D. *J Org Chem.* 2014;79:4068–4077.
6. Bhar D, Chandrasekaran S. *Tetrahedron.* 1997;53:11835–11842.
7. Vujasinovic I, Mlinaric-Majerski K, Bertosa B, Tomic S. *J Phys Org Chem.* 2009;22:431–437.
8. Kricheldorf HR, Gomourashvili Z, Langanke D. *J Macromol Sci.* 2000;37A:1531–1545.
9. Kricheldorf HR, Probst N, Schwarz G, Schulz G, Krüger R-P. *J Polym Sci A Polym Chem.* 2000;38:3656–3664.
10. DallaCort A, Ercolani G, Iamiceli AL, Mandolini L, Mencarelli P. *J Am Chem Soc.* 1994;116:7081–7087.
11. Vujasinovic I, Veljkovic J, Mlinaric-Majerski K. *J Org Chem.* 2004;69:8550–8553.
12. Vujasinovic I, Veljkovic J, Molcanov K, Kojic-Prodic B, Mlinaric-Majerski K. *J Org Chem.* 2008;73:9221–9227.
13. Abel EW, Brady DB. *J Chem Soc.* 1965;1192–1197.
14. Shanzer A, Shochet N, Rabinovich D, Frolow F. *Angew Chem Int Ed.* 1980;19:326–327.
15. Cort AD, Ercolani G, Mandolini L, Mencarelli P. *J Chem Soc Chem Commun.* 1993;538–540.
16. DallaCort A, Mandolini L, Roelens S. *J Org Chem.* 1992;57:766–768.
17. Kricheldorf HR, Bornhorst K, Schwarz G. *J Macromol Sci A.* 2008;45:511–515.