Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 36–38

First isolation of 1,2-dithietan-3-one from α-dithiolactone

Toshiyuki Shigetomi,[a] Kentaro Okuma[a,*] and Yoshinobu Yokomori[b]

[a]*Department of Chemistry, Faculty of Science, Fukuoka University, Jonan-ku, Fukuoka 814-0180, Japan*
[b]*National Defense Academy, Hashirimizu, Yokosuka 239-8686, Japan*

Received 20 September 2007; revised 2 November 2007; accepted 5 November 2007
Available online 7 November 2007

Abstract—Treatment of α-dithiolactone **6** with ethoxycarbonylformonitrile oxide **7** resulted in the formation of 1,2-dithietan-3-one **4**. Compound **4a** was oxidized with *m*-CPBA to give 4,4-di-*tert*-butyl-1,2-dithietan-3-one 1-oxide **5a**. The reaction of **4a** with triphenylphosphine afforded the corresponding α-thiolactone **10**.

The chemistry of small rings containing sulfur atom and the associated concepts of distorted hybridization and strain are the current topics of interest.[1] Because of their unique structures and chemical reactivities, three- and four-membered rings containing an S–S bond have also received great attention from both experimental and theoretical perspectives.[2] 1,2-Dithietanes, in particular, have stimulated fundamental theoretical and chemical interests.[1] To our knowledge, isolated examples of compounds bearing the 1,2-dithietane ring system are dithiatopazine (1,2-dithietane) and 3,4-diethyl-1,2-dithietane 1,1-dioxide (1,2-dithietane 1,1-dioxide).[3,4] On the other hand, five-membered ring compounds containing an S–S bond such as 1,2-dithiolan-3-ones (**1**)[5] and 1,2-dithiolan-3-one 1-oxides (**2**) (containing Leinamycin **3** as antitumor antibiotic)[5,6] are well known, which are of interest because of their chemical behavior and biological activities. However, there was no report on the isolations of 1,2-dithietan-3-one (**4**) and 1,2-dithietan-3-one 1-oxide (**5**), which are four-membered analogues of **1** and **2**, respectively (Chart 1). Therefore, synthetic methods of 1,2-dithietan-3-one **4** and its 1-oxide **5** are desired to elucidate their chemical reactivities and biological activities. We recently reported the synthesis of α-dithiolactone (**6**) from thioketene S-oxide and Lawesson reagent (LR) and its chemical properties.[7] Rearrangements of oxaspiropentanes to cyclobutanones are well known.[8] We surmise that if spirocyclic oxathiiranes were formed by oxidizing **6**, 1,2-dithietan-3-one **4** would be obtained. Thus, we attempted to produce spirocyclic

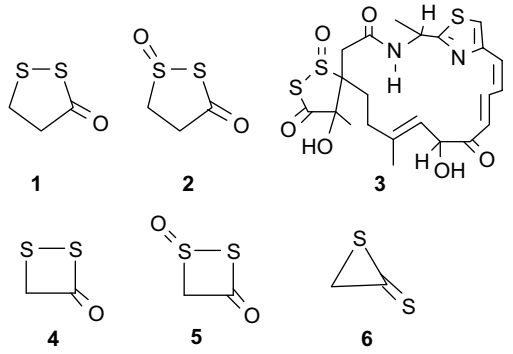


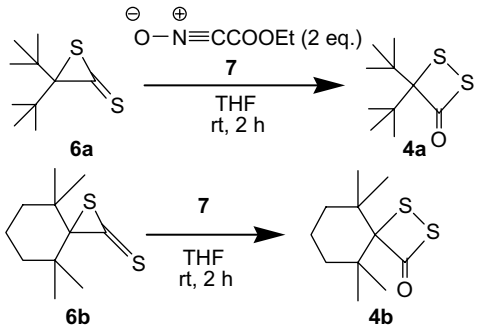
Chart 1.

oxathiirane by reacting **6** with nitrile oxide. Herein we describe the synthesis of 1,2-dithietan-3-one **4** by reacting **6** with ethoxycarbonylformonitrile oxide (**7**) and oxidation of **4**.

Treatment of 3,3-di-*tert*-butylthiirane-2-thione (**6a**) with nitrile oxide **7** (2 equiv) generated from ethyl chlorooxyimidoacetate and triethylamine[9] resulted in the formation of 4,4-di-*tert*-butyl-1,2-dithietan-3-one (**4a**) in 82% yield (Scheme 1). 4,4-(2′,2′,6′,6′-Tetramethylcyclohexyl)1,2-dithietan-3-one (**4b**) was also synthesized in a similar manner in 80% yield. The structure of **4b** was confirmed as follows. In the ^{1}H NMR spectrum, signals of methyl and methylene protons resonated at δ 1.10 (6H), 1.31 (6H), 1.47–1.61 (4H), and 1.73–1.79 (2H). The ratio of four methyl protons was divided into 6:6, suggesting that the product was an asymmetric compound. In the ^{13}C NMR spectrum, signals of C=O and quaternary ring carbon

* Corresponding author. Tel.: +81 92 871 6631; fax: +81 92 865 6030; e-mail: kokuma@fukuoka-u.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.025



Scheme 1.

resonated at δ 194.0 and 114.1, respectively. In the IR spectrum, a band assignable to C=O was observed at 1724 cm^{-1}. In MS analysis, the M^+ signal was observed at 230. The above results indicate that the product is 1,2-dithietan-3-one **4b**. X-ray crystallographic analysis of **4b** was carried out. Figure 1 shows the ORTEP drawing of **4b**. Comparison with the X-ray crystallographic data of dithiatopazine (bond lengths: C–S: 1.844 and 1.881, S–S: 2.084, and C–C: 1.571 Å. Bond angles: C–S–S: 82.2° and 80.7°, S–C–C: 97.4° and 96.8°) demonstrated that the C11–S2 bond (1.7851 Å) of **4b** is shorter than those of dithiatopazine. In addition, the C1–C11–S2 bond angle (102.25°) of **4b** is larger than those of dithiatopazine. In **4b**, the sum of the interior angles of the quadrangle C1–S1–S2–C11 is 360°, suggesting that **4b** is planar. Based on the report of isomerization of oxaspiropentane to cyclobutanone,[8] the reaction is speculated to proceed as follows: the initially formed 1,3,4-oxazathiolane (**8**) retrocyclized to give spirocyclic oxathiirane (**9**), which isomerized to **4** (Scheme 2).

Nicolaou et al. reported that dithiatopazine was thermally decomposed when heated in xylene at 140 °C for 1 h to give an olefinic compound and diatomic sulfur.[4] To compare the stability of dithiatopazine with that of **4a**, **4a** was refluxed in xylene-d_{10} at 140 °C for 2 days (Scheme 3). Surprisingly, **4a** was recovered unchanged, suggesting that **4a** was more stable than dithiatopazine.

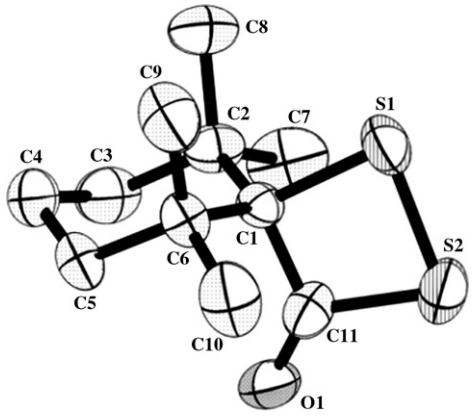
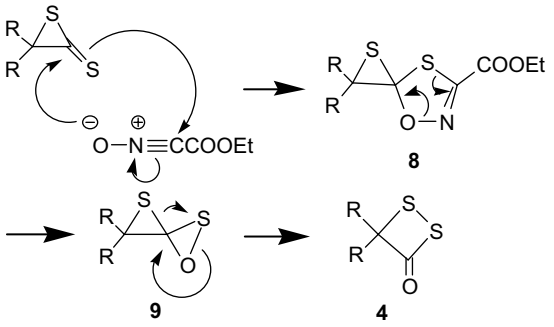
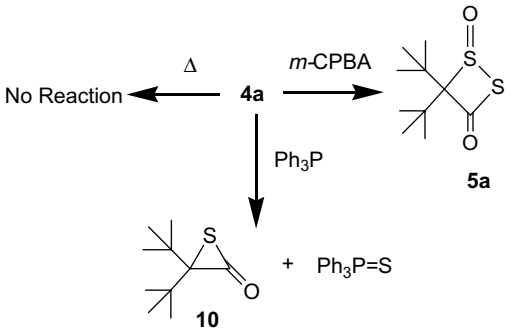


Figure 1. ORTEP drawing of 1,2-dithietan-3-one **4b**. Selected bond lengths: C1–S1 1.8718(15), C11–S2 1.7851(18), S1–S2 2.0855(8), C1–C11 1.542(2), C11–O1 1.166(2) Å. Selected bond angles: C1–S1–S2: 81.75(5)°, C11–S2–S1: 81.06(6)°, C11–C1–S1: 94.94(10)°, C1–C11–S2: 102.25(12)°, O1–C11–C1: 129.86(16)°, O1–C11–S2: 127.89(15)°.



Scheme 2.



Scheme 3.

Sublimation of **4a** was observed at 160 °C. The thermal reactivities of dithiatopazine and **4a** are quite different.

Leinamycin belongs to a class of 1,2-dithiolane-3-one 1-oxides, and is of interest because of its biological activities.[6,10] 1,2-Dithiolane-3-one 1-oxides are synthesized by reacting 1,2-dithiolane-3-one with *m*-chloroperbenzoic acid (*m*-CPBA) or dimethyldioxirane.[5] Therefore, we tried the synthesis of 1,2-dithietan-3-one 1-oxide **5** from **4a**. Oxidation of **4a** with *m*-CPBA afforded 4,4-di-*tert*-butyl-1,2-dithietan-3-one 1-oxide (**5a**) in 78% yield. By using excess amount of *m*-CPBA (5 equiv), only monoxide **5a** was isolated in 76% yield.

Nicolaou et al. reported that the reaction of dithiatopazine with triphenylphosphine gave an episulfide.[4] Meanwhile, Schaumann and Behrens were the first and only ones to report the synthesis and characterization of α-thiolactones by reacting thioketenes with nitrones.[11] Thus, we attempted the synthesis of α-thiolactone from 1,2-dithietan-3-one **4a** and triphenylphosphine. One sulfur atom in **4a** was eliminated by treatment with triphenylphosphine in $CDCl_3$ at room temperature for 4 days to give the main product (IR 1782 and 1809 cm^{-1} (C=O), mp 65–74 °C, and MS 186 (M^+)) in 82% yield along with triphenylphosphine sulfide. Comparison with the melting points (65–76 °C) and IR data (C=O: 1785 and 1810 cm^{-1}) of α-thiolactone (**10**) reported by Schaumann and Behrens[11] confirmed that the obtained product is identical with **10**.

In summary, we succeeded in synthesizing 1,2-dithietan-3-one **4** by reacting α-dithiolactone **6** with ethoxycarbonylformonitrile oxide **7**. The structure of **4b** was

determined by X-ray crystallographic analysis. Compound **4a** was oxidized with *m*-CBPA to give 4,4-di-*tert*-butyl-1,2-dithietan-3-one 1-oxide **5a**, which is a four-membered analogue of Leinamycin. The reaction of **4a** with triphenylphosphine is a new synthetic route to α-thiolactone **10**.

Synthesis of **4**: To a solution of **6a** (0.037 g, 0.18 mmol) and ethyl chlorooxyimidoacetate (0.055 g, 0.36 mmol) in THF (0.5 mL) was added a solution of triethylamine (0.041 g, 0.40 mmol) in THF (1.0 mL) in one portion at room temperature. After being stirred for 2 h, the reaction mixture was filtered and evaporated to give yellow oily crystals, which were chromatographed over silica gel by elution with hexane to give pure **4a** (0.032 g, 0.147 mmol). Compound **4b** was also synthesized in a similar manner. **4a**: yellow crystals: mp 87–92 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) $\delta = 1.34$ (s, 18H). ^{13}C NMR ($CDCl_3$ 100 MHz) $\delta = 30.08, 40.93, 117.20, 193.23$. IR $\nu = 1724\ cm^{-1}$ (C=O). UV/vis (hexane) λ_{max} (ε) 294.5 (919), 403.0 (105). Anal. Calcd for $C_{10}H_{18}OS_2$: C, 55.00; H, 8.31. Found: C, 54.60; H, 8.15. **4b**: yellow crystals: mp 100–105 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) $\delta =$ 1.10 (s, 6H), 1.31 (s, 6H), 1.47–1.61 (m, 4H), 1.73–1.79 (m, 2H). ^{13}C NMR ($CDCl_3$ 100 MHz) $\delta = 18.20$, 26.10, 29.25, 37.86, 38.90, 114.14, 193.94. IR $\nu =$ $1724\ cm^{-1}$ (C=O). UV/vis (hexane) λ_{max} (ε) 292.5 (711), 398.0 (106). Anal. Calcd for $C_{11}H_{18}OS_2$: C, 57.35; H, 7.87. Found: C, 57.04; H, 7.80. HRMS: (M^+) calcd for $C_{11}H_{18}OS_2$ 230.0799; found 230.0822. X-ray crystallographic data for **4b**: crystal data for $C_{11}H_{18}OS_2$ crystallized from acetonitrile. F_W 230.37, Orthorhombic, space group = *Pbca*, $a = 13.8799(3)$, $b = 11.8394(3)$, $c = 14.5197(3)$ Å, $\alpha = 90.00°$, $\beta =$ 90.00°, $\gamma = 90.00°$, $V = 2386.02(9)$ Å^3, $Z = 8$, $D_x =$ $1.283\ Mg\ m^{-3}$, μ(Mo Kα) = $0.414\ mm^{-1}$, the final *R* and *wR* were 0.0422 and 0.1123, respectively, using 3275 reflections.

Synthesis of **5a**: To a solution of **4a** (0.060 g, 0.28 mmol) in dichloromethane (2.0 mL) was added a solution of *m*-chloroperoxybenzoic acid (0.085 g, 0.49 mmol) in dichloromethane (1.0 mL) in one portion at room temperature. After being stirred for 1.5 h, the reaction mixture was evaporated to give pale yellow crystals, which were chromatographed over silica gel by elution with hexane–dichloromethane (1:1) to give pure **5a** (0.051 g, 0.218 mmol). **5a**: yellow crystals: mp 129–131 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) $\delta = 1.31$ (s, 9H), 1.51 (s, 9H). ^{13}C NMR ($CDCl_3$ 100 MHz) $\delta = 30.31, 30.92, 39.33, 40.99, 118.07, 188.51$. IR $\nu = 1097$ and $1705\ cm^{-1}$ (S=O and C=O). Anal. Calcd for $C_{10}H_{18}O_2S_2$: C, 51.24; H, 7.74. Found: C, 51.19; H, 7.68.

Synthesis of **10**: Triphenylphosphine (0.035 g, 0.138 mmol) was added to a solution of **4a** (0.030 g, 0.138 mmol) in $CDCl_3$ (0.6 mL). The solution was left for 4 days at room temperature. Formation of **10** and triphenylphosphine sulfide was monitored by NMR spectroscopy. The reaction mixture was evaporated to give a pale yellow solid, which was chromatographed over silica gel by elution with hexane–dichloromethane (1:1) to give pure **10** (0.021 g, 0.113 mmol). **10**: colorless crystals: mp 65–74 °C (lit.[11] mp 65–76 °C); ^{1}H NMR ($CDCl_3$ 400 MHz) $\delta = 1.25$ (s, 18H); ^{13}C NMR ($CDCl_3$ 100 MHz) $\delta = 30.22, 38.54, 59.39, 188.34$; IR $\nu = 1782$, $1809\ cm^{-1}$ (C=O) (lit.[11] C=O; 1785, $1810\ cm^{-1}$).

References and notes

1. (a) Nakayama, J.; Ishii, A. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Taylor, R., Eds.; Academic Press: New York–Tokyo, 2000; Vol. 77, pp 221–284; (b) Zoller, U. In Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Comprehensive Heterocyclic Chemistry II; Pergamon: New York, 1996; Vol. 1B, pp 1113–1138.
2. Ono, Y.; Sugihara, Y.; Ishii, A.; Nakayama, J. *J. Am. Chem. Soc.* **2003**, *125*, 12114–12115; Shimizu, T.; Murakami, H.; Kamigata, N. *J. Org. Chem.* **1999**, *64*, 8489–8494; Yu, H.; Chan, W. T.; Goddard, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 7529–7537; Ishii, A.; Akazawa, T.; Maruta, T.; Nakayama, J.; Hoshino, M.; Shiro, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 777–778; Shimada, K.; Kodaki, K.; Aoyagi, S.; Takikawa, Y.; Kabuto, C. *Chem. Lett.* **1999**, 695–696.
3. Block, E.; Bazzi, A. A.; Rsvelle, L. K. *J. Am. Chem. Soc.* **1980**, *102*, 2490–2491.
4. Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Carroll, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 3801–3802.
5. Pattenden, G.; Shuker, A. J. *Tetrahedron Lett.* **1991**, *32*, 6625–6628; Kanda, Y.; Saito, H. *Tetrahedron Lett.* **1992**, *33*, 5701–5704; Pattenden, G.; Shuker, A. J. *J. Chem. Soc., Perkin Trans.* **1992**, 1215–1221.
6. Mitra, K.; Kim, W.; Daniels, J. S.; Gates, K. S. *J. Am. Chem. Soc.* **1997**, *119*, 11691–11692; Wu, S.; Greer, A. *J. Org. Chem.* **2000**, *65*, 4883–4887; Behroozi, S. J.; Kim, W.; Dannaldson, J.; Gates, K. S. *Biochemistry* **1996**, *35*, 1768–1774.
7. Okuma, K.; Shigetomi, T.; Nibu, Y.; Shioji, K.; Yoshida, M.; Yokomori, Y. *J. Am. Chem. Soc.* **2004**, *126*, 9508–9509; Shigetomi, T.; Soejima, H.; Nibu, Y.; Shioji, K.; Okuma, K.; Yokomori, Y. *Chem. Eur. J.* **2006**, *12*, 7742–7748.
8. Tomilov, Y. V.; Guseva, E. V.; Kostuchenko, I. V.; Ugrak, B. I.; Shulishov, E. V.; Nefedov, O. M. *Eur. J. Org. Chem.* **2004**, *14*, 3145–3153; Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F. *Org. Lett.* **2003**, *5*, 2923–2926; Salaun, J. R.; Champion, J.; Conia, J. M. *Org. Synth.* **1977**, *57*, 36–40; Aue, D. H.; Meshishnek, M. J.; Shellhamer, D. F. *Tetrahedron Lett.* **1973**, *48*, 4799–4802; Crandall, J. K.; Paulson, D. R. *J. Org. Chem.* **1968**, *33*, 991–998.
9. Conti, P.; Amici, M. D.; Roda, G.; Pinto, A.; Tamborini, L.; Madsen, U.; Nielsen, B.; Osborne, H. B.; Micheli, C. D. *Tetrahedron* **2007**, *63*, 2249–2256; Rees, C. W.; Rakitin, O. A.; Marcos, C. F.; Torroba, T. *J. Org. Chem.* **1999**, *64*, 4376–4380; Rees, C. W.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 2189–2196; Marcos, C. F.; Polo, C.; Rakitin, O. A.; Rees, C. W.; Torroba, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 281–283; Marcos, C. F.; Polo, C.; Rakitin, O. A.; Rees, C. W.; Torroba, T. *J. Chem. Soc., Chem. Commun.* **1997**, 879–880; Alazard, J. P.; Leboff, A.; Thal, C. *Tetrahedron* **1986**, *42*, 1407–1412; Borsus, J. M.; L'Abbe, G.; Smets, G. *Tetrahedron* **1975**, *31*, 1537–1539.
10. Hara, M.; Takahashi, I.; Yoshida, M.; Asano, K.; Kawamoto, I.; Morimoto, M.; Nakano, H. *J. Antibiot.* **1989**, *42*, 333–335; Hara, M.; Asano, K.; Kawamoto, I.; Takiguchi, T.; Katsumoto, S.; Takahashi, K.; Nakano, H. *J. Antibiot.* **1989**, *42*, 1768–1774.
11. Schaumann, E.; Behrens, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 722–723.