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RESEARCH ARTICLE

PUMMERER REACTION OF 4,7-DI-*TERT*-BUTYL-3*H*,8*H*-1,2,5,6-DITHIADIAZOCINE 1-OXIDE; FORMATION OF 1,4-DITHIINS

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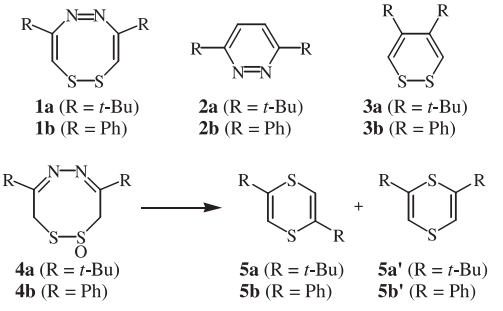
The Pummerer reaction of 4,7-di-*tert*-butyl-3*H*,8*H*-1,2,5,6-dithiadiazocine 1-oxide (**4a**) with $(CF_3CO)_2O$ in the presence of DBU has produced 2,5-di-*tert*-butyl-1,4-dithiin (**5a**) in 67% yield, whereas the reaction of **4a** with $(CF_3CO)_2O$ alone gave a 5:2 mixture of **5a** and 2,6-di-*tert*-butyl-1,4-dithiin (**5a′**) in 61% yield.

Keywords: Eight-membered heterocycles; Pummerer reaction; Thiosulfinates; 1,4-Dithiins; DFT calculations

INTRODUCTION

In our continuing studies on sulfur-containing heterocycles [1], we have investigated the preparation of 1,2,5,6-dithiadiazocines (**1**). We expected thermolysis of **1** to furnish either pyridazines **2** with liberation of $^1S_2$ (diatomic sulfur) or 1,2-dithiins **3** with liberation of N_2. We report here that the Pummerer dehydration of thiosulfinates **4** produces 1,4-dithiins **5** and not the expected dithiadiazocines **1** (Scheme 1). Some other results found during this study are also reported.



SCHEME 1

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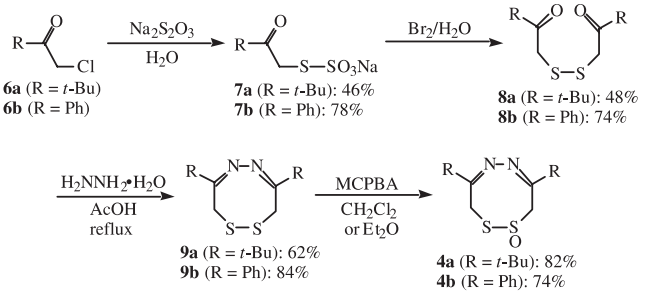


SCHEME 2

RESULTS AND DISCUSSION

Thiosulfinates **4** were prepared as shown in Scheme 2. Disulfides **8** were prepared from α-chloroketones **6** through **7** in reasonable overall yields [2]. Heating **8** with hydrazine monohydrate in boiling acetic acid provided 3*H*,8*H*-1,2,5,6-dithiadiazocines **9**. Oxidation of **9** with a slight excess of *m*-chloroperbenzoic acid (MCPBA) produced **4** in reasonable yields. Thiosulfinates **4** are thermally labile, although storable without appreciable decomposition in a refrigerator.

The ^{1}H NMR spectra determined with $CDCl_3$ as the solvent, shows the methylene protons of **9b** as two sharp doublets at δ3.53 and 4.21 with $J = 13.0$ Hz, whereas those of **9a** appear as a sharp singlet at δ3.59. DFT calculations [B3LYP/6-31+G(d) level] [3] revealed that the methylene protons of both **9a** and **9b** are nonequivalent if these compounds are frozen in the calculated optimized conformations (Figures 1 and 2). Thus, the appearance of the methylene protons of **9a** as the sharp singlet would be attributed to the coincidence of the chemical shift values of the two methylene protons rather than a rapid conformational change that makes these protons equivalent. Indeed, the spectrum of **9a** in C_6D_6 as the solvent shows the methylene protons as two doublets at δ3.07 and 3.26 with $J = 10.1$ Hz. 2*H*,7*H*-1,4,5-Thiadiazepines (**10**), a seven-membered, lower analog of **9**, exist in a frozen conformation (Figure 3) regardless

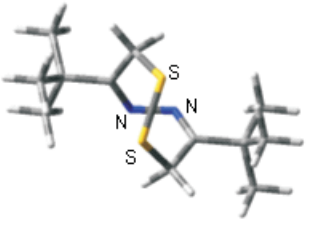


FIGURE 1 Optimized structure of **9a**.

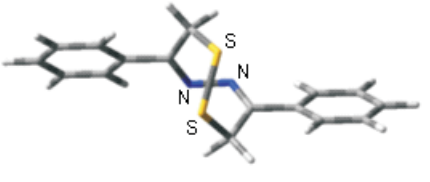
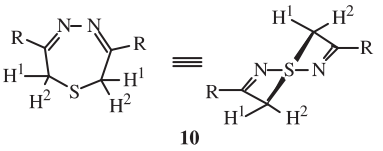


FIGURE 2 Optimized structure of **9b**.



10

FIGURE 3 Conformation of **10**.

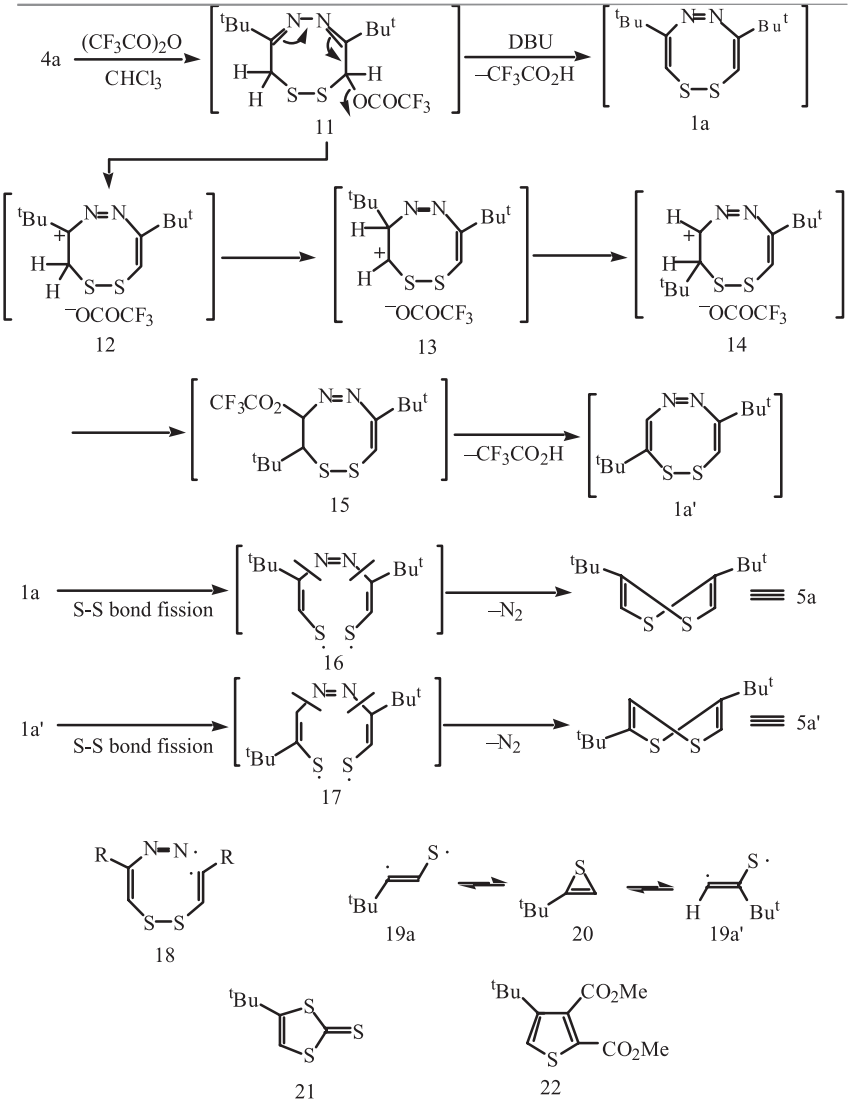
of the substituent, thus the methylene protons of many **10** appear as two doublets at room temperature [4].

When, after a solution of **4a** and DBU (1,8-diazabicyclo[6.4.0]undecene) in $CHCl_3$ had been stirred for a while at room temperature, $(CF_3CO)_2O$ was added to this solution and then the resulting mixture was stirred for an additional 1.5 hr, the reaction furnished 2,5-di-*tert*-butyl-1,4-dithiin (**5a**) [5] in 67% yield as the sole product. In contrast, when **4a** was allowed to react with $(CF_3CO)_2O$ alone in refluxing $CHCl_3$, a mixture of **5a** and 2,6-di-*tert*-butyl-1,4-dithiin (**5a**′) [5c, 6] was formed (5:2) in 61% yield; the reaction at room temperature gave a 1:1 mixture of **5a** and **5a**′ in 20% yield. Incidentally, **4a** does not react with DBU. In addition, although the Pummerer reaction produces free CF_3CO_2H in the absence of DBU, a separate experiment revealed that CF_3CO_2H does not bring about the isomerization of **5a** to **5a**′.

The following is a tentative explanation of the observed results (Scheme 3). Initially, the expected Pummerer reaction takes place to give **11**. In the presence of a strong base (DBU), elimination of CF_3CO_2H of **11** proceeds efficiently to provide the expected dithiadiazocine **1a**. S−S bond fission of **1a** gives resonance-stabilized thiyl radical **16**. An intramolecular reorganization of **16** with simultaneous elimination of N_2 would produce the dithiin **5a**. However, in the absence of DBU, elimination of CF_3CO_2H is sluggish, thus allowing the rearrangement of **11** into **15** to take place through carbocation intermediates **12**–**14**. Elimination of CF_3CO_2H from **15** provides dithiadiazocine **1a**′ whose decomposition furnishes the dithiin **5a**′. This explains why a mixture of **5a** and **5a**′ is formed in the absence of DBU. The C–N bond fission of **1a** that produces a biradical **18** is less probable since its two radical centers are of a σ-type, and thus **18** is expected to be highly unstable. In addition, if **18** were formed, it might produce a 1,3-biradical **19a** with extrusion of N_2, and then **19a** might isomerize to **19a**′ through thiirene **20**. The head-to-tail dimerization of **19a** and the head-to-tail reaction of **19a** with **19a**′ explain the formation of **5a** and **5a**′, respectively. However, this is ruled out by the following observations. Reportedly, biradicals such as **19a** are trapped by carbon disulfide [7] and dimethyl acetylenedicarboxylate (DMAD) [8]. However, the Pummerer reaction of **4a** with $(CF_3CO)_2O$ in carbon disulfide did not furnish the expected adduct **21**; it gave a 5:2 mixture of **5a** and **5a**′ in 48% yield. Similarly, the reaction in the presence of DMAD did not produce the expected thiophene **22**.

Similar results were also obtained for the Pummerer reaction of **4b**. In the presence of DBU, the reaction of **4b** with $(CF_3CO)_2O$ produced a 15:1 mixture of dithiins **5b** [9] and **5b**′ [10] in 32% yield. However, in the absence of DBU, the reaction was less selective, giving a 5:2 mixture of **5b** and **5b**′ in 11% yield.

Finally, DFT calculations [B3LYP/6-31+G(d) level] [3] were carried out on the hypothetical dithiadiazocine **1a**. Figure 4 shows the optimized structure of **1a**. The compound adopts a distorted tub conformation. Any anomaly that renders **1a** so unstable is not found in the predicted structure. Although steric repulsion between bulky *tert*-butyl groups might make **1a** partly unstable, this does not hold for **1b**. Therefore, although we proposed the mechanism that involves **1** as the intermediate, we cannot rule out the possibility that another mechanism is operative.



SCHEME 3

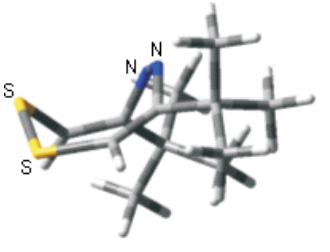


FIGURE 4 Predicted structure of **1a** (S−S bond length, 2.11 Å; N=N bond length, 1.24 Å; C−S−S−C dihedral angle, 63.6°).

EXPERIMENTAL

Melting points were determined on a Mel-Temp capillary tube apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400, a Bruker AC300P, or a Bruker AC200 spectrometer; $CDCl_3$ was used as the solvent, unless otherwise stated, with TMS as the internal standard. IR spectra were taken on a Perkin–Elmer System 2000 FT-IR spectrometer. Elemental analyses were performed by the Material and Life Science Research Center of Saitama University.

Preparation of Thiosulfites 7

A mixture of **6a** (10.0 g, 74 mmol) and $Na_2S_2O_3 \cdot 5H_2O$ (18.4 g, 74 mmol) in water (25 mL) was heated under stirring at 60 °C for 3 h. The reaction mixture was then washed with diethyl ether to remove the unreacted **6a**. The water layer was subsequently evaporated under reduced pressure, and the resulting residue was crystallized from EtOH–H_2O to provide 8.0 g (46%) of pure **7a** [5c]. Similarly, the known compound **7b** [2] was prepared from **6b** in 78% yield.

Preparation of Disulfides 8

A saturated aqueous solution of bromine was added to a solution of **7a** (2.0 g, 8.6 mmol) in water (5 mL) at 0 °C until the added bromine was consumed no longer. The resulting white solid was collected by filtration, dried, and crystallized from MeOH to give 545 mg (48%) of pure **8a**: mp 60–61 °C; ^{1}H NMR ($CDCl_3$) δ1.19 (s, 18H), 3.93 (s, 4H) ppm. The known compound **8b** [2], mp 79–80 °C, was similarly prepared, in 74% yield.

Preparation of 3*H*,8*H*-1,2,5,6-Dithiadiazocines 9

A mixture of **8a** (500 mg, 1.9 mmol) and hydrazine monohydrate (168 mg, 3.4 mmol) in acetic acid (15 mL) was heated under reflux for 5 h. The acetic acid was then removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel with CH_2Cl_2-hexane (1:1) as the eluent to give 326 mg (62%) of **9a**. In a similar way, **9b** was prepared in 84% yield.

9a: mp 88–89 °C; ^{1}H NMR δ (ppm): 1.19 (s, 18H), 3.59 (s, 4H); ^{1}H NMR (C_6D_6) δ (ppm): 1.10 (s, 18H), 3.07 (d, J = 10.1 Hz, 2H), 3.26 (d, J = 10.1 Hz, 2H); ^{13}C NMR δ (ppm): 27.3, 32.5, 38.3, 161.6; IR (KBr) ν(cm^{-1}) 2962, 2865, 1612, 1594, 1476, 463, 1419, 1391, 1361, 1223, 1198, 1158, 1093, 1085, 1019, 979, 893, 885, 830. Calcd. (%) for $C_{12}H_{14}N_2S_2$: C; 55.77, H; 8.58, N; 10.84. Found: C; 55.95, H; 8.65, N; 10.78.

9b: mp 140–141 °C; ^{1}H NMR δ (ppm): 3.53 (d, J = 13.0 Hz, 2H), 4.21 (d, J = 13.0 Hz, 2H), 7.42–7.79 (m, 10H); ^{13}C NMR δ (ppm): 36.3, 126.8, 128.6, 129.8, 136.4, 149.0; IR (KBr) ν(cm^{-1}): 3036, 1561, 1495, 1443, 1415, 1287, 1181, 1066, 1039, 1018, 962, 917, 895, 838, 774, 737, 708, 689, 605, 592, 483, 442. Calcd. (%) for $C_{16}H_{14}N_2S_2$: C; 64.39, H; 4.73, N; 9.39. Found: C; 64.48, H; 4.65, N; 9.45.

Preparation of 3*H*,8*H*-1,2,5,6-Dithiadiazocine 1-Oxides 4

A solution of MCPBA (310 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of **4a** (200 mg, 0.78 mmol) in CH_2Cl_2 (5 mL) at −15 °C. After the mixture had been stirred for 15 min, the reaction was quenched by addition of aqueous sodium hydrogensulfite solution. The organic layer was then washed with water, dried over $MgSO_4$, and evaporated. The

resultant residue was chromatographed on a column of Florisil with CH_2Cl_2 as eluent to give 178 mg (82%) of **4a** (attempted purification by silica-gel column chromatography resulted in the decomposition of **4a**). Intractable orange oily mixtures were obtained by heating neat purified crystalline **4a** at 80 °C for a short period of time or by letting purified **4a** stand at room temperature for a few days. In a similar way, **4b** was prepared in 74% yield.

4a: mp 79–81 °C (dec); ^{1}H NMR δ (ppm): 1.26 (s, 9H), 1.29 (s, 9H), 3.40 (d, J = 12.1 Hz, 1H), 3.66 (d, J = 12.1 Hz, 1H), 3.89 (d, J = 13.1 Hz, 1H), 4.32 (d, J = 13.1 Hz, 1H); ^{13}C NMR δ (ppm): 23.9, 28.1, 28.6, 38.3, 38.5, 57.8, 155.4, 157.3; IR (KBr) ν(cm^{-1}) 2965, 2871, 1621, 1574, 1480, 1462, 1414, 1400, 1363, 1212, 1202, 1158, 1107, 1078, 1090, 978, 897, 828, 769, 568, 436, 418. Calcd. (%) for $C_{12}H_{22}N_2OS_2$: C; 52.52, H; 8.08, N; 10.20. Found: C; 52.38, H; 8.11, N; 10.07.

4b: mp 161–163 °C (dec); ^{1}H NMR δ (ppm): 3.78 (d, J = 13.2 Hz, 1H), 4.03 (d, J = 14.8 Hz, 1H), 4.08 (d, J = 14.8 Hz, 1H), 5.30 (d, J = 13.2 Hz, 1H), 7.41–7.91 (m, 10H); ^{13}C NMR δ (ppm): 21.1, 54.0, 127.0, 127.5, 128.4, 128.8, 129.9, 130.2, 134.3, 137.0, 137.7, 143.5; IR (KBr) ν(cm^{-1}) 3056, 1557, 1495, 1444, 1422, 1410, 1298, 1186, 1058, 1020, 900, 773, 743, 688, 604, 440. Calcd. (%) for $C_{16}H_{14}N_2OS_2$: C; 61.12, H; 4.49, N; 8.91. Found: C; 60.95, H; 4.39, N; 8.79.

Pummerer Reaction of 4

Reaction in the presence of DBU. After a solution of **4a** (145 mg, 0.53 mmol) and DBU (161 mg, 1.06 mmol) in $CHCl_3$ (10 mL) had been stirred for 0.5 hr at room temperature, $(CF_3CO)_2O$ (1.10 g, 5.3 mmol) was added. The resultant mixture was then stirred for 1.5 hr and poured onto ice–water. The mixture was then washed with an aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated. The so-obtained residue was chromatographed on a column of Florisil with hexane as eluent to give 80 mg (67%) of **5a**. Under similar conditions, **4b** afforded a 15:1 mixture of **5b** and **5b**′ in 32% yield.

Reaction in the absence of DBU. A mixture of **4a** (40.2 mg, 0.15 mmol) and $(CF_3CO)_2O$ (315 mg, 1.5 mmol) in $CHCl_3$ (4 mL) was heated under reflux for 6 hr. The mixture was then treated as described above to give a 5:2 mixture of **5a** and **5a**′ in 61% yield. The Pummerer reaction of **4a** at room temperature for 24 hr gave a 1:1 mixture of **5a** and **5a**′ in 20% yield. Pummerer reaction of **4b** at room temperature for 2 hr gave a 5:2 mixture of **5b** and **5b**′ in 11% yield.

Structural assignments of **5a**, **5a**′, **5b**, and **5b**′ were based on the comparison of spectroscopic data with those of authentic samples.

References

[1] Recent papers. (a) Ishii, A., Yamashita, R., Saito M. and Nakayama, J., *J. Org. Chem.*, **68**, 1555 (2003). (b) Ono, Y., Sugihara, Y., Ishii, A. and Nakayama, J., *Bull. Chem. Soc. Jpn*, **76**, 613 (2003). (c) Nakayama, J., Furuya, T., Ishii, A., Sakamoto, A., Otani, T. and Sugihara, Y., *Bull. Chem. Soc. Jpn*, **76**, 619 (2003). (d) Otani, T., Takayama, J., Sugihara, Y., Ishii, A. and Nakayama, J., *J. Am. Chem. Soc.*, **125**, 8255 (2003). (e) Takayama, J., Fukuda, S., Sugihara, Y., Ishii, A. and Nakayama, J., *Tetrahedron Lett.*, **44**, 5159 (2003). (f) Tanaka, S., Sugihara, Y., Sakamoto, A., Ishii, A. and Nakayama, J., *J. Am. Chem. Soc.*, **125**, 9024 (2003). (g) Ono, Y., Sugihara, Y., Ishii, A. and Nakayama, J., *J. Am. Chem. Soc.*, **125**, 12114 (2003). (h) Takayama, J., Sugihara, Y., Ishii, A. and Nakayama, J., *Tetrahedron Lett.*, **44**, 7893 (2003).

[2] Matsuda, T. and Takada, Y., *Phosphous Sulfur*, **1**, 75 (1976).

[3] Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Zakrzewski, V. G., Montgomery, J. A., Jr., Stratmann, R. E., Burant, J. C., Dapprich, S., Millam, J. M., Daniels, A. D., Kudin, K. N., Strain, M. C., Farkas, O., Tomasi, J., Barone, V., Cossi, M., Cammi, R., Mennucci, B., Pomelli, C., Adamo, C., Clifford, S., Ochterski, J., Petersson, G. A., Ayala, P. Y., Cui, Q., Morokuma, K., Malick, D. K., Rabuck, A. D., Raghavachari, K., Foresman, J. B., Cioslowski, J., Ortiz, J. V., Baboul, A. G., Stefanov, B. B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Gomperts, R., Martin, R. L., Fox, D. J., Keith, T., Al-Laham, M. A.,

Peng, C. Y., Nanayakkara, A., Gonzalez, C., Challacombe, M., Gill, P. M. W., Johnson, B. G., Chen, W., Wong, M. W., Andres, J. L., Head-Gordon, M., Replogle, E. S. and Pople, J. A., *Gaussian 98 (Revision A.7)* (Gaussian, Inc., Pittsburgh, PA, 1998).

[4] (a) Sataty, I., *J. Heterocycl. Chem.*, **7**, 431 (1970). (b) Nakayama, J., Konishi, T., Ishii, A. and Hoshino, M., *Bull. Chem. Soc. Jpn*, **62**, 2608 (1989).

[5] (a) Asinger, F., Thiel, M., Peschel, G. and Meincke, K.-H., *Liebigs Ann. Chem.*, **619**, 145 (1858). (b) Bock, H., Rittmeyer, R. and Stein, U., *Chem. Ber.*, **119**, 3766 (1986). (c) Nakayama, J., Choi, K. S., Yamaoka, S. and Hoshino, M., *Heterocycles*, **29**, 391 (1989).

[6] Meijer, J., Vermeer, P., Verkruijsse, H. D. and Brandsma, L., *Recl. Trav. Chim. Pays-Bas*, **92**, 1326 (1973).

[7] (a) Nakayama, J., Masui, N., Sugihara, Y. and Ishii, A., *Bull. Chem. Soc. Jpn*, **71**, 1181 (1998) (and references cited therein). (b) Gasper, P. P., Harrison, J. F. and Herold, B. J., In: Kirmse, W. (Ed.), *Carbene Chemistry* (Academic Press, New York and London, 1971), 2nd ed., Chap. 9, pp. 375.

[8] Kirmse, W., *Eur. J. Org. Chem.*, 2193 (2002).

[9] Barker, H. R. and Barkenbus, C., *J. Am. Chem. Soc.*, **58**, 262 (1936).

[10] Nakayama, J., Motoyama, H., Machida, H., Shimomura, S. and Hoshino, M., *Heterocycles*, **22**, 1527 (1984).