Synthesis of Novel 1,3,4-Oxadiazinane-2-thiones Derived from (1*R*,2*S*)-Ephedrine, (1*S*,2*S*)-Pseudoephedrine and (1*R*,2*S*)-Norephedrine

Shawn R. Hitchcock,* George P. Nora, David M. Casper, Joseph D. Wiman, Jeromy T. Bentley, Carrie Stafford and Michael D. Squire

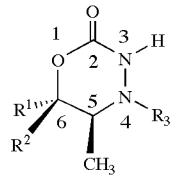
Department of Chemistry, Illinois State University, Normal, IL 61790-4160

Received April 30, 2002

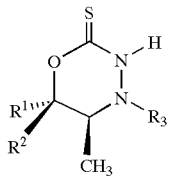
A several novel 1,3,4-oxadiazinan-2-thiones have been synthesized by the cyclization of β-hydrazino-alcohols with either carbon disulfide or 1,1'-thiocarbonyldiimidazole (TCDI).

J. Heterocyclic Chem., **39**, 1113 (2002).

In the course of our synthetic and conformational studies [1,2] of 1,3,4-oxadiazinan-2-ones **1**, we became interested in developing the corresponding thione derivatives **2** (Figure 1). This interest was stimulated by the success of chiral, non-racemic oxazolidin-2-thiones **3** in asymmetric aldol reactions [3-7]. In fact, Crimmins and coworkers have employed *N*-acyloxazolidin-2-thiones in the total synthesis of Callystatin A [8]. Thus, oxazolidin-2-thiones have proven to be useful tools in organic synthesis.



1,3,4-Oxadiazinan-2-one (**1**)



1,3,4-Oxadiazinan-2-thione (**2**)

Figure 1. 1,3,4-Oxadiazinan-2-ones and 2-thiones.

In regard to the 1,3,4-oxadiazinan-2-ones, their application in asymmetric reactions have only recently been exploited by Husson [9-11] and these studies do not mention the closely related 1,3,4-oxadiazinane-2-thiones. Our overall research program is focused on the synthesis, conformational analysis and asymmetric application of these heterocycles. Ultimately, we seek to employ 1,3,4-oxadiazinan-2-ones and 2-thiones in asymmetric aldol reactions. The comparative reactivity of these heterocycles in such reactions is unknown in terms of the impact of the 2-position, *i.e.*, C=O *vs.* C=S (Figure 2). It is possible that the reactivities of the oxadiazinan-2-ones and 2-thiones may parallel the observed behavior of the oxazolidin-2-ones and 2-thiones but this question cannot be address without first addressing the synthesis of the 1,3,4-oxadiazinane-2-thiones. The thione derivatives, to our knowledge, have not been prepared previously and their synthesis would allow further studies in conformational analysis and asymmetric applications. Herein we report on the synthesis of chiral, non-racemic 1,3,4-oxadiazinane-2-thiones derived from ephedrine and its derivatives.

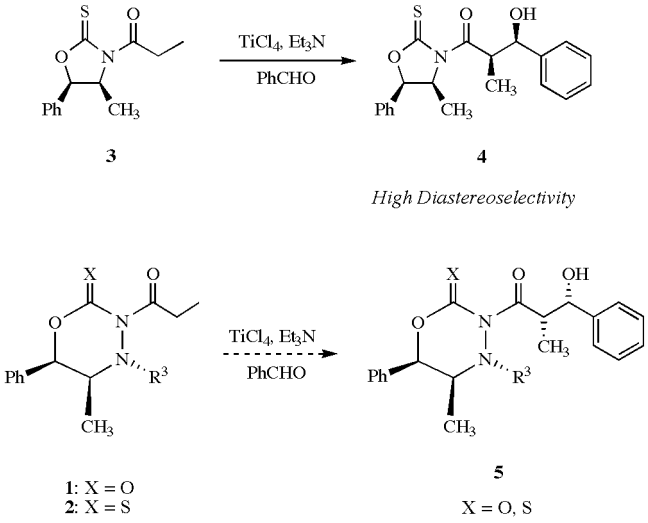
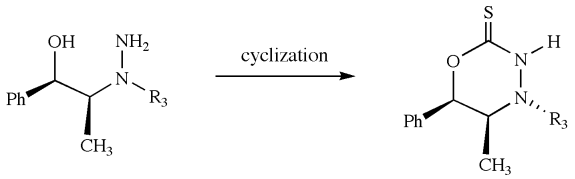


Figure 2. Synthetic applications of oxazolidine-2-thiones.

A variety of methodologies were explored for the purpose of synthesizing the thione derivatives. Le Corre and coworkers [12] have studied the formation of oxazolidine-2-thiones *via* cyclization of β-amino-alcohols with carbon disulfide. Their studies suggested that it might be possible to conduct a similar cyclization with enantiomerically pure β-*hydrazino*-alcohols to afford 1,3,4-oxadiazinane-2-thiones with retention of stereochemistry [13].

The reaction of the ephedrine derived **6a** [14] with carbon disulfide and potassium hydroxide afforded the thione heterocycle **2a** in 40% yield. The reaction of the β-hydrazino-alcohol **6a** with thiophosgene and sodium hydride yielded a complex mixture of products that complicated isolation of the target material; presumably these materials represented incomplete cyclization and oligomerization. Due to the poor yield efficiency and high toxicity of thiophosgene, we opted to pursue a more benign reagent. We were gratified to learn that **6a** could be converted to the heterocycle by treatment with 1,1'-thiocarbonyldiimidazole (TCDI) [15-17] in the presence of *p*-toluenesulfonic acid in 79% yield (Scheme 1).

Scheme 1



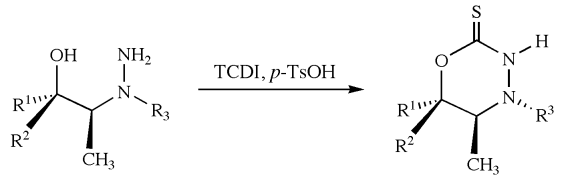
6a **2a**

CS_2, KOH;Cl_2C=S; Im_2C=S, *p*-TsOH

Cyclization of β-hydrazino-alcohol **6a**.

β-Hydrazino-alcohols derived from (1*S*,2*S*)-pseudoephedrine **6b** [14] and (1*R*,2*S*)-norephedrine **6c-e** [18] were also cyclized using the optimized TCDI methodology (Scheme 2). This process afforded the desired heterocycles **6b-e** in fair to good yields.

Scheme 2



6b-e **2b-e**

b: R_1 = Ph; R_2 = H; R_3 = CH_3
c: R_1 = H; R_2 = Ph; R_3 = $CH_2CH_2CH_3$
d: R_1 = H; R_2 = Ph; R_3 = $CH_2C(CH_3)_3$
e: R_1 = H; R_2 = Ph; R_3 = $CH_2CH_2OCH_3$

Cyclization of β-hydrazino-alcohols **6b-e**.

The collected spectroscopic and analytical data for **6a-e** were consistent with the assigned structures of the 1,3,4-oxadiazinane-2-thiones. The ^{1}H NMR spectra for thiones **6a-e** were similar to the ^{1}H NMR spectra of the 1,3,4-oxadiazinan-2-ones that were prepared previously [1,2] with the only significant difference being the chemical shift of the amide proton of the N_3-nitrogen ($\delta_{avg} \approx 6.2$ ppm for 2-ones *vs.* $\delta_{avg} \approx 8.5$ ppm for 2-thiones).

In terms of their conformational preference these compounds may well exists as twist boat conformers similar to those observed in the case of the 1,3,4-oxadiazinan-2-ones derived from ephedrine and pseudoephedrine [1]. Research is underway to study their conformational behavior and to exploit the use of these novel heterocycles in asymmetric applications such as the aldol addition reaction.

EXPERIMENTAL

General Remarks.

Tetrahydrofuran (THF) was distilled from a potassium/sodium alloy containing benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Flash chromatography was conducted with silica gel (32-63 mesh). All ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a Varian spectrometer in $CDCl_3$ operating at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (*J* values) are listed in hertz (Hz). Infrared spectra are reported in reciprocal centimeters (cm^{-1}). Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Low resolution gas chromatography was performed on a Hewlett-Packard Instrument (G1800A/GCD) with an ionization voltage of 70 eV; peaks are reported as *m/z* (% intensity relative to the base peak). Elemental analyses were conducted by either Galbraith Laboratories, Inc. Knoxville, TN or by the Microanalytical Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign.

Carbon Disulfide Procedure for the Synthesis of (5*S*,6*R*)-4,5-Dimethyl-6-phenyl-1,3,4-oxadiazinane-2-thione (**2a**).

In a flame-dried, nitrogen purged 1000 mL round bottom flask was placed β-hydrazino-alcohol **6a** (5.45 g, 30.0 mmol), THF (10 mL) and carbon disulfide (150 mL) and a 5 *M* aqueous solution of potassium hydroxide (30 mL, 150 mmol). The reaction was heated to reflux temperature and allowed to stir for 12 hours. The reaction was cooled to room temperature and quenched by the addition of an aqueous solution of sodium bicarbonate (75 mL). The reaction mixture was then extracted with ethyl acetate (75 mL). The organic layer was washed with a saturated aqueous solution of brine (75 mL). The solvents were removed by rotary evaporation to afford a yellow solid. This material was purified by recrystallization from hexanes and ethyl acetate to yield the target product in 40% yield (2.62 g); $[\alpha]_D^{23}$ +85.24° (*c* 1.05, methanol); Mp = 159-160 °C; ^{1}H NMR ($CDCl_3$): δ 0.91 (d, 3H, *J* = 7.0 Hz), 2.87 (s, 3H), 3.22 (dq, 1H, *J* = 7.0, 2.9 Hz), 5.57 (d, 1H, *J* = 2.93 Hz), 7.32-7.43 (m, 5H), 8.60 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 11.8, 46.1, 57.2, 75.5, 125.7, 128.6, 128.9, 135.4, 181.5. IR (KBr): 3126, 2986, 1176. EI-MS (*m/z*, relative intensity): 146 (51), 117 (100), 91 (60).

Anal. Calc'd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60; S, 14.42. Found: C, 59.19; H, 6.42; N, 12.47; S, 14.30.

General Procedure for the Synthesis of 1,3,4-Oxadiazinane-2-thiones.

In a flame-dried, nitrogen purged 250 mL round bottom flask was placed β-hydrazino-alcohol (2.00 g, 11.1 mmol) and THF (50 mL). To this solution was added *p*-toluenesulfonic acid monohydrate (2.32 g, 12.2 mmol) and 1,1'-thiocarbonyldiimidizole (2.18 g, 12.2 mmol). After the addition was completed the resulting mixture was heated to reflux. The reaction mixture was cooled to room temperature after 3 hours and an aqueous saturated solution of sodium bicarbonate (50 mL) was added. The resulting mixture was then extracted with EtOAc (3 x 50 mL) washed with a saturated aqueous solution of brine (50 mL), dried (Na_2SO_4) followed by the removal of solvent by rotary evaporation.

(5*S*,6*R*)-4,5-Dimethyl-6-phenyl-1,3,4-oxadiazinane-2-thione (**2a**).

This process yielded a yellow oil, which was purified by column chromatography on silica gel (EtOAc/hexanes, 2:3, R_f = 0.26, column dimensions = 12.5 x 5 cm) to yield the title compound (79%) as a white solid; $[\alpha]_D^{25}$ +78.90° (*c* 1.03, methanol); Mp = 162-163 °C; ^{1}H NMR ($CDCl_3$): δ 0.91 (d, 3H, *J* = 7.0 Hz), 2.87 (s, 3H), 3.22 (dq, 1H, *J* = 7.0, 2.9 Hz), 5.57 (d, 1H, *J* = 2.93 Hz), 7.32-7.43 (m, 5H), 8.60 (bs, 1H).

(5*S*,6*S*)-4,5-Dimethyl-6-phenyl-1,3,4-oxadiazinane-2-thione (**2b**).

This process yielded a yellow oil, which was purified by column chromatography on silica gel (EtOAc/hexanes,1:1, R_f = 0.77 (EtOAc), column dimensions = 12.5 x 5 cm) to yield a yellow solid which was recrystallized by the addition of CH_2Cl_2 and hexanes to afford **2b** (69%) as a white solid; $[\alpha]_D^{25}$ +9.62° (*c* 1.02, methanol); Mp = 176-177 °C; ^{1}H NMR ($CDCl_3$): δ 0.98 (d, 3H, *J* = 6.6 Hz), 2.43 (s, 3H), 3.24 (q, 1H, *J* = 6.6 Hz), 5.14 (d, 1H, *J* = 9.2 Hz), 7.31-7.41 (m, 5H), 9.77 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 40.3, 58.1, 81.5, 127.5, 129.1, 129.6, 135.6, 182.0. IR (KBr): 3155, 2978, 1154; EI-MS (*m/z*, relative intensity):117 (100), 91 (34), 77 (23).

Anal. Calc'd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60; S, 14.42. Found: C, 59.18; H, 6.38; N, 12.46; S, 14.22.

(5*S*,6*R*)-5-Methyl-6-phenyl-4-propyl-1,3,4-oxadiazine-2-thione (**2c**).

This process yielded a yellow oil which was purified by column chromatography on silica gel (EtOAc/hexane, 1:1, R_f = 0.70, column dimensions = 12.5 x 5 cm) to yield the title compound (36%) as a white solid; $[\alpha]_D^{25}$ +123.46° (*c* 1.01, methanol); Mp = 120-121 °C; ^{1}H NMR ($CDCl_3$): δ 0.91 (d, 3H, *J* = 6.6 Hz), 1.01 (t, 3H, *J* = 7.3 Hz), 1.62-1.75 (m, 2H), 2.78-2.85 (m, 1H), 3.06-3.12 (m, 1H), 3.30-3.36 (m, 1H) 5.59 (s, 1H), 7.32-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 11.7, 11.9, 20.2, 55.9, 60.7, 76.2, 125.6, 128.5, 128.9, 135.6, 182.2. IR (KBr): 3221, 2976, 1164 cm^{-1}; EI-MS (m/z, relative intensity): 232 (22), 77 (93), 56 (100).

Anal. Calc'd for $C_{13}H_{18}N_2OS$: C: 62.37; H, 7.25; N, 11.19. Found: C, 62.06; H, 7.16; N, 11.03.

(5*S*,6*R*)-5-Methyl-4-(2,2-dimethylpropyl)-6-phenyl-1,3,4-oxadiazinane-2-thione (**2d**).

Cyclization of β-hydrazino-alcohol **6d** yielded a yellow oil which was purified by column chromatography on silica gel (EtOAc/hexane, 1:1, R_f = 0.44, column dimensions = 15 x 5 cm) to yield **2d** (77 %) as a colorless oil. This oil was further purified by recrystallization from the minimum amount of ethyl acetate and hexanes and to afford the title compound as a crystalline white solid. $[\alpha]_D^{25}$ +89.39° (*c* 1.03, methanol); Mp = 124-125 °C; ^{1}H NMR ($CDCl_3$): δ 0.90 (d, 3H, *J* = 6.6 Hz), 0.99 (m, 1H), 2.72 (d, 1H, *J* = 13.9 Hz), 2.93 (d, 1H, *J* = 13.9 Hz), 3.18 (dq, 1H, *J* = 6.9, 2.9 Hz), 5.51 (d, 1H, *J* = 2.6 Hz), 7.31-7.42 (m, 5H), 9.55 (bs, 1H); ^{13}C ($CDCl_3$): δ 11.7, 27.6, 32.8, 58.9, 72.6, 76.8, 125.3, 128.3, 128.6, 135.3, 181.5. IR (neat): 3134, 2979, 1192; EI-MS (m/z, relative intensity): 132 (49), 117 (100), 105 (68).

Anal. Calc'd for $C_{15}H_{22}N_2OS$: C, 64.71; H, 7.96; N, 10.06; S, 11.52. Found: C, 64.93; H, 8.19; N, 10.13; S, 11.79.

(5*S*,6*R*)-5-Methyl-4-(2-methoxyethyl)-6-phenyl-1,3,4-oxadiazinane-2-thione (**2e**).

This process yielded a yellow oil that was purified by column chromatography on silica gel (EtOAc/hexanes, 4:1, R_f = 0.62, column dimensions = 15 x 5 cm) to yield **2e** (88 %) as an oil which was recrystallized from ethyl acetate and hexanesl $[\alpha]_D^{25}$-148.89° (*c* 1.02, methanol); Mp = 100-102 °C; ^{1}H NMR ($CDCl_3$): δ 0.92 (d, 3H, *J* = 6.6 Hz), 3.06-3.24 (m, 2H), 3.43 (s, 3H), 3.69 (m, 2H), 5.55 (d, 1H, *J* = 2.9 Hz), 7.32-7.42 (m, 5H), 8.88 (bs, 1H); ^{13}C ($CDCl_3$): δ 10.9, 54.9, 56.8, 58.6, 69.8, 75.8, 124.9, 127.7, 128.0, 134.9, 180.1. IR (KBr): 3142, 2986, 1187 cm^{-1}.

Anal. Calc'd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52; S, 12.04. Found: C, 58.50; H, 6.70; N, 10.39; S, 12.50.

Acknowledgements.

We gratefully acknowledge financial support from the department of chemistry of Illinois State University (ISU) and the University Research Grant (URG) program sponsored by ISU. We also acknowledge continued support from Merck & Co, Inc.

REFERENCES AND NOTES

[1] S. R. Hitchcock, G. P. Nora, D. M. Casper, M. D. Squire, C. D. Maroules, G. M. Ferrence; L. F. Szczepura and J. M. Standard, *Tetrahedron* **57**, 9789 (2001).

[2] D. M. Casper, G. P. Nora, J. R. Blackburn, J. T. Bentley, D. C. Taylor and S. R. Hitchcock, *J. Heterocyclic Chem.,* In press.

[3] M. T. Crimmins, B. W. King, E. A. Tabet and K. Chaudhary, *J. Org. Chem.* **66**, 894 (2001).

[4] M. T. Crimmins, B. W. King and E. A. Tabet, *J. Am. Chem. Soc.* **119**, 7883 (1997).

[5] Y. Nagao, S. Yamada, T. Kumagai, M. Ochiai and E. Fujita, *J. Chem. Soc., Chem. Comm.* **20**, 1418 (1985).

[6] D.-W. Su, Y.-C. Wang and T.-H.Yan, *Tetrahedron Lett.* **40**, 4197 (1999).

[7] E. Fujita and Y. Nagao, *Adv. Hetereocyclic Chem.* **45**, 1 (1989).

[8] M. T. Crimmins and B. W. King, *J. Am. Chem. Soc.* **120**, 9084 (1998).

[9] F. Roussi, A. Chauveau, M. Bonin, L. Micouin and H. Husson, *Synthesis* 1170 (2000).

[10] F. Roussi, M. Bonin, A. Chiaroni, L. Micouin, C. Riche and H. Husson, *Tetrahedron Lett.*, **40**, 3727 (1999).

[11] F. Roussi, M. Bonin, A. Chiaroni, L. Micouin, C. Riche and H. Husson, *Tetrahedron Lett.*, **39**, 8081 (1998).

[12] D. Delaunay, L. Toupet and M. Le Corre, *J. Org. Chem.*, **60**, 6604, (1995) and references sited therein.

[13] M. Moreno-Mañas and I. Padras, *J. Heterocyclic Chem.*, **30**, 1235, (1993).

[14] For the synthesis of β-hydrazino-alcohols **6a** and **6b**, see ref. [1].

[15] M. Mulvihill, D. V. Nguyen, B. S. MacDougall, D. G. Weaver and W. D. Mathis, *Synthesis*, **13**, 1965 (2001).

[16] F. Benedini, G. Bertolini, F. Ferrario, R. Guidani and A. Sala, *J. Heterocyclic Chem.*, **31**, 1598 (1994).

[17] K. Funaki, K. Takeda and E. Yoshii, *Tetrahedron Lett.*, **23**, 3069 (1982).

[18] For the synthesis of β-hydrazino-alcohols **6c**-**e**, see ref. [2].