Desulfurization–Oxygenation of Chiral 1,3-Thiazolidine-2-thiones and 1,3-Oxazolidine-2-thiones Using Propylene Oxide and Microwave Irradiation

Leticia Minor-Villar,[a] Rodolfo Tello-Aburto,[b] Horacio F. Olivo,[b] Aydee Fuentes,[a] Moises Romero-Ortega*[a]

[a] Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México, Toluca, México
Fax +52(722)2173890; E-mail: mromeroo@uaemex.mx

[b] Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, IA 52242, USA

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Abstract: An efficient method for the desulfurization–oxygenation of 1,3-thiazolidine-2-thiones and 1,3-oxazolidine-2-thiones using propylene oxide and employing microwave irradiation is described. This strategy of oxygenation of the thiocarbonyl group provides an attractive methodology to prepare chiral 1,3-thiazolidin-2-ones and 1,3-oxazolidin-2-ones from the corresponding precursors in good yields.

Key words: thiazolidinethiones, oxazolidinethiones, thiazolidinones, propylene oxide, chiral auxiliaries.

Chiral auxiliary based processes have a prominent position among the most reliable strategies for accessing a stereoisomer in enantiomerically pure form.[1] Chiral auxiliaries such as oxazolidin-2-ones **1**,[2] thiazolidine-2-thiones **2**,[3] and oxazolidine-2-thiones **3**[4] (Figure 1) have become a superb tool for the stereoselective construction of carbon–carbon bonds and have reached tremendous success. Nevertheless, the diastereoselectivity imparted by boron enolates of *N*-acetyl oxazolidin-2-ones is low.[5] However, the problem has been solved by employing its sulfur analogues.[6] Additionally, the use of oxazolidin-2-ones **1** has also attracted attention because of their antimicrobial activity as antibiotics.[7] There are a few oxazolidinones currently in clinical trials.[8]

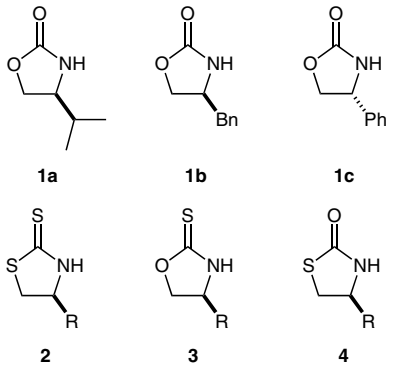

Figure 1

Nagao reported that tin enolates of *N*-acyl-1,3-thiazolidine-2-thiones could participate in highly stereoselective aldol processes.[6] Further reports have shown that both chlorotitanium enolates of 1,3-thiazolidine-2-thiones **2** and 1,3-oxazolidine-2-thiones **3** (Figure 1) provide excellent levels of diastereoselectivity in aldol reactions.[9] For example, the *syn*-Evans and *syn*-non-Evans propionate aldol sulfur adducts can be accessed depending on the amount of Lewis acid and base used and they have the remarkable advantage of easier removal of the auxiliary after completion of the chiral induction.[10] Such a feature has great merits in the synthesis of complicated and fragile molecules containing different functionalities.

Recently, we encountered some problems in the purification of the *N*-enoyl imide derivatives during our work on the 1,4-addition of organocuprates to *N*-enoyl thiazolidinethiones and oxazolidinethiones.[11] This problem was attributed to the high nucleophilicity of the sulfur atom present in the thiocarbonyl group reacting intramolecularly with the unsaturation during chromatography. Palomo described the rearrangement of the sulfur atom in the thiocarbonyl of *N*-enoyl oxazolidinethiones when Lewis acids are present.[12] This rearrangement was employed for the preparation of β-mercapto carbonyl derivatives. Eventually, we solved the purification problem by adding some triethylamine to the eluent during flash column chromatography or avoiding the chromatographic step by a simple recrystallization.

It has been reported that thiocarbonyl compounds undergo desulfurization to generate the corresponding carbonyl compounds when treated with a variety of oxidizing reagents.[13] During the course of our studies, a method was reported for the syntheses of chiral 1,3-thiazolidin-2-ones **4** from 1,3-thiazolidine-2-thiones **2**.[14] 4-Substituted thiazolidinethiones were treated with bromoethanol in ethanol with sodium ethoxide as a base. The yields of the products were in the range of 45% (R = Me) to 85% (R = Ph). Another method appeared in the patent literature, where 4-benzylthiazolidinethione was transformed to the corresponding thiazolidinone utilizing propylene oxide and trifluoroacetic acid. However, the yield of the thiazolidinone was extremely low (2.5%).[15a] Calo et al. reported very good yields for the preparation of 4-isopropylthiazolidinone (**4a**; 87%) and 4-methylthiazolidinone (**4d**; 91%) utilizing also trifluoroacetic acid and 1-butene oxide.[15b] Also, the 4-phenylthiazolidinone has been reported to be obtained in 38–67% yields utilizing aqueous hydrogen peroxide and sodium hydroxide at room temperature for two hours.[16] There are a few other

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reports on the conversion of thiazolidine-2-thiones to thiazolidin-2-ones, but they are not related to chiral auxiliaries.[17] White and Kawasaki also prepared a 1,3-thiazolidin-2-one as found in a marine sponge metabolite latrunculin A.[18] In this context, we decided to investigate a practical method to prepare chiral 1,3-thiazolidin-2-ones **4** auxiliaries based on the desulfurization–oxygenation reaction of 1,3-thiazolidine-2-thiones **2** avoiding the use of highly corrosive trifluoroacetic acid.

We selected chiral thiazolidinethiones **2a**–**e** and oxazolidinethiones **3a**–**e** because they are the most widely used auxiliaries to accomplish the highest asymmetric inductions and because their syntheses are accomplished in two steps following known procedures. Reduction of the corresponding amino acid to the amino alcohol[19] and exposure of the amino alcohol to carbon disulfide in KOH delivered thiazolidinethiones **2a**–**d** in excellent yields.[20] Thiazolidinethione **2e** was prepared from the corresponding *trans*-1-amino-2-indanol according to our procedure.[3d] We found that stirring thiazolidinethiones **2a**–**e** with propylene oxide in a sealed tube immersed in an oil bath at 100 °C delivered after 48 hours the corresponding thiazolidin-2-ones **4a**–**e** in good yields 71–86% (Table 1). Reducing the reaction time delivered the products in lower yields.

The methodology was extended for the desulfurization–oxygenation of chiral oxazolidine-2-thiones **3a**–**e** to oxazolidin-2-ones **1a**–**e**. Chiral oxazolidine-2-thiones **3a**–**e** were prepared from the corresponding amino alcohols using carbon disulfide in the presence of potassium carbonate and hydrogen peroxide.[21] These chiral auxiliaries reacted equally well with propylene oxide under thermal conditions for 48 hours to give the corresponding 1,3-oxazolidin-2-ones **1a**–**e** in good yields (80–92%; Table 2).

We found that propylene oxide is a general reagent for this transformation and the use of N-unsubstituted 1,3-thiazolidine-2-thione **2** was critical for the successful exchange of the thiocarbonyl for a carbonyl group. When *N*-acetyl derivative of thiazolidinethione **2e** was subjected to the same desulfurization reaction conditions with propylene oxide, no product was observed. All four chiral auxiliaries can be easily distinguished by the chemical shift of their carbonyl or thiocarbonyl carbon atom in ^{13}C NMR (Figure 2).

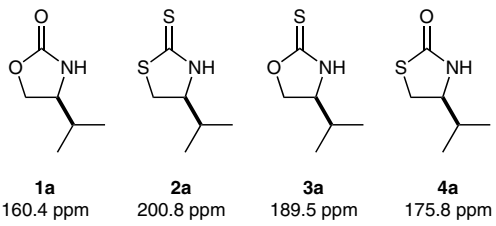
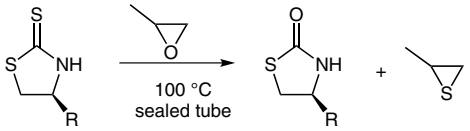


Figure 2 Chemical shifts in ^{13}C NMR

Although the process occurred in a general and good to very good yielding fashion with all the investigated 1,3-thiazolidine-2-thiones **2a**–**e** and 1,3-oxazolidine-2-thiones **3a**–**e** under conventional thermal conditions, the reaction time required for the reaction to complete could be long (48 h). In this context, the use of high-power microwave irradiation offers a complementary technology to improve the efficiency of energy transfer to the reaction mixture. In the last two decades fast microwave heating has been shown to accelerate a large number of organic transformations.[22] In this respect, the desulfurization–oxygenation process was investigated in chloroform using sealed vessels and microwave heating. The reaction time was set to 60 minutes and the temperature at 150 °C. The investigated substrates **2c**, **2d**, **3b**, **3c** and **3e**, were smoothly transformed in very good yields to thiazolidin-2-ones **4c**, **4d** and oxazolidin-2-ones **1b**, **1c** and **1e**, respectively, under the microwave-assisted method (Table 3). The reaction workup consisted simply in evaporation of the solvent and 2-methylthiirane.[23]

Table 1 Desulfurization–Oxygenation of 1,3-Thiazolidine-2-thiones



2a–e **4a–e**

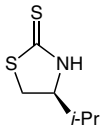
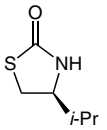
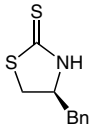
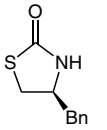
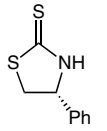
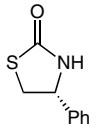
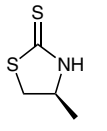
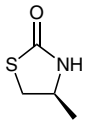
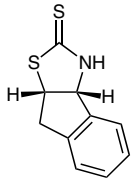
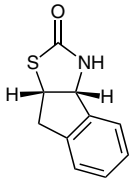
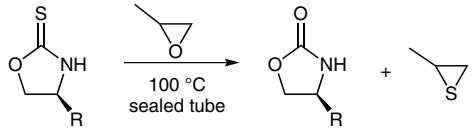
Entry	Substrate	Product	Yield (%)
1	 **2a**	 **4a**	71
2	 **2b**	 **4b**	86
3	 **2c**	 **4c**	78
4	 **2d**	 **4d**	80
5	 **2e**	 **4e**	76

Table 2 Desulfurization–Oxygenation of 1,3-Oxazolidine-2-thiones



3a–e **1a–e**

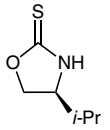
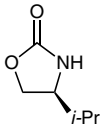
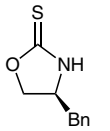
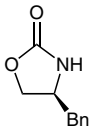
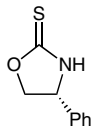
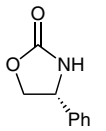
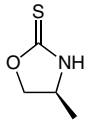
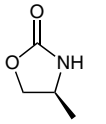
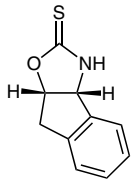
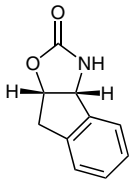
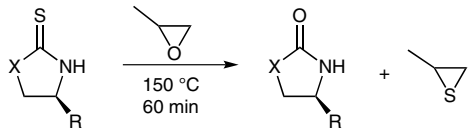
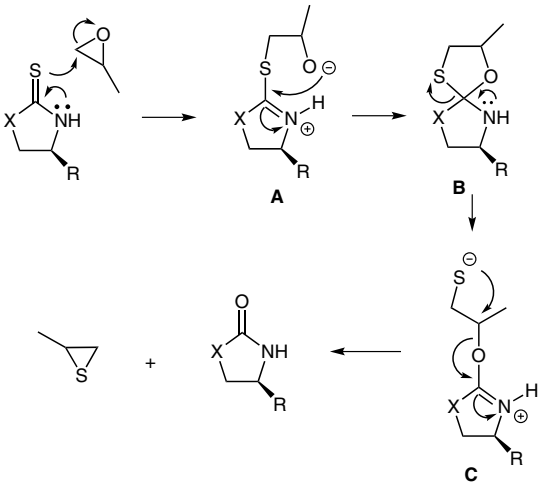
Entry	Substrate	Product	Yield (%)
1	 **3a**	 **1a**	80
2	 **3b**	 **1b**	87
3	 **3c**	 **1c**	92
4	 **3d**	 **1d**	84
5	 **3e**	 **1e**	83

Table 3 Desulfurization–Oxygenation using Microwave Irradiation



Entry	Substrate	Product	Yield (%)
1	**2c**	**4c**	85
2	**2d**	**4d**	88
3	**3b**	**1b**	90
4	**3c**	**1c**	94
5	**3e**	**1e**	89

We believe that the desulfurization–oxygenation reaction of 1,3-thiazolidine-2-thiones **2** and 1,3-oxazolidine-2-thiones **3** using propylene oxide, involves three reactive intermediates (Scheme 1). The nucleophilic sulfur atom attacks the oxirane, opening the ring, forming an iminium ion A. Intramolecular attack of the alkoxide ion to the iminium A generates the tetraheteroatom spiro intermediate B. This high-energy intermediate undergoes ring opening via iminium intermediate C to deliver propylene episulfide and the desired 1,3-thiazolidin-2-one or the 1,3-oxazolidin-2-one. When a reaction was carried out in a sealed NMR tube under thermal conditions, the ^{1}H NMR signals for the propylene episulfide could be observed in the spectra.



Scheme 1 Mechanism of the desulfurization–oxygenation reaction

In summary, we have developed a simple and highly efficient synthetic route to prepare both 1,3-thiazolidin-2-ones **4** and 1,3-oxazolidin-2-ones **1** via a desulfurization–oxygenation process, using commercially available and inexpensive propylene oxide. This methodology is particularly attractive using microwave conditions for brevity and efficiency. The influence of endocyclic sulfur atom on the reactivity of the non-racemic 1,3-thiazolidin-2-ones **4** and their application in asymmetric synthesis are under investigation.

Acknowledgment

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(23) **General Procedure for the Synthesis of 1,3-Thiazolidin-2-ones 4 and 1,3-Oxazolidin-2-ones 1 under Thermal Conditions**: A solution of thiazolidine-2-thione **2** or oxazolidine-2-thione **3** (1.0 mmol) in propylene oxide (2.5 mL) was heated in a sealed tube at 100 °C under nitrogen during 48 h. The reaction mixture was then allowed to cool to r.t. and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography eluting with hexanes–EtOAc (4:1) for the 1,3-thiazolidin-2-ones and hexanes–EtOAc (3:2) for the 1,3-oxazolidin-2-ones to give analytically pure products **4** and **1**.
General Procedure for the Synthesis of 1,3-Thiazolidin-2-ones 4 and 1,3-Oxazolidin-2-ones 1 using Microwave Irradiation: To a solution of thiazolidine-2-thione **2** or oxazolidine-2-thione **3** (1.0 mmol) in $CHCl_3$ (1.5 mL) was added propylene oxide (1.5 mL) in a 10-mL vessel with a screw cap under a nitrogen blanket. The reaction mixture was heated at 150 °C (hold time 60 min, ramp time 1–2 min). After cooling (cool down, 50 °C, 2 min), the reaction mixture was allowed to cool to r.t. and the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography eluting with hexanes–EtOAc (4:1) for 1,3-thiazolidin-2-ones and hexanes–EtOAc (3:2) for 1,3-oxazolidin-2-ones to give analytically pure products **4** and **1**, respectively.
(4*S*)-Isopropyl-1,3-thiazolidin-2-one (4a): was obtained as a white solid after purification by flash column chromatography; mp 75–76 °C (CH_2Cl_2–hexanes); $[\alpha]^{24}_D$ +19.2 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96 (br, 1 H), 3.60–3.68 (dt, *J* = 7.8, 15.3 Hz, 1 H), 3.35 (dd, *J* = 7.5, 10.9 Hz, 1 H), 3.16 (dd, *J* = 8.2, 10.9 Hz, 1 H), 1.77–1.89 (m, 1 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 61.4, 32.5, 32.4, 18.7, 18.1. HRMS: *m*/*z* calcd for $C_6H_{11}NOS$: 145.0556; found: 145.0562.
(4*S*)-4-Benzyl-1,3-thiazolidin-2-one (4b): was obtained as a white solid after purification by flash column chromatography; mp 69–70 °C (CH_2Cl_2–hexanes); $[\alpha]^{25}_D$ –9.6 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.36 (m, 3 H), 7.16–7.20 (m, 2 H), 6.01 (br, 1 H), 4.07 (m, 1 H), 3.43 (dd, *J* = 7.2, 11.1 Hz, 1 H), 3.17 (dd, *J* = 6.3, 11.1 Hz, 1 H), 2.93 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8, 136.4, 129.0, 128.9, 127.1, 56.5, 40.9, 34.3. HRMS: *m*/*z* calcd for $C_{10}H_{11}NOS$: 193.0556; found: 193.0555.
(4*R*)-Phenyl-1,3-thiazolidin-2-one (4c): was obtained as a white solid after purification by flash column chromatography; mp 162–164 °C (CH_2Cl_2–hexanes); $[\alpha]^{24}_D$ –86.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (br, 1 H), 7.32–7.39 (m, 5 H), 4.94 (td, *J* = 0.9, 7.5 Hz, 1 H), 3.68 (dd, *J* = 7.5, 11.0 Hz, 1 H), 3.26 (dd, *J* = 7.7, 11.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 139.9, 128.3, 127.8, 125.5, 58.4, 37.0. HRMS: *m*/*z* calcd for C_9H_9NOS: 179.0399; found: 179.0390.
(4*R*)-Methyl-1,3-thiazolidin-2-one (4d): was obtained as a white solid after purification by flash column chromatography; mp 40–42 °C (CH_2Cl_2–hexanes); $[\alpha]^{24}_D$ +12.80 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70 (br, 1 H), 3.99–4.06 (m, 1 H), 3.47 (dd, *J* = 7.2, 10.8 Hz, 1 H), 3.04 (dd, *J* = 7.2, 10.8 Hz, 1 H), 1.34 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.4, 51.2, 36.5, 20.5.
(4*R*,5*S*)-Indano[1,2-*d*]-1,3-thiazolidine-2-one (4e): was

obtained as a white solid after purification by flash column chromatography; mp 195–196 °C (CH_2Cl_2–hexanes); $[\alpha]^{23}_D$ +3.2 (*c* = 0.5 $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$–DMSO): δ = 8.21 (br, 1 H), 7.37–7.39 (m, 1 H), 7.24–7.31 (m, 3 H), 5.17 (d, *J* = 7.5 Hz, 1 H), 4.67 (td, *J* = 3.0, 7.5 Hz, 1 H), 3.48 (dd, *J* = 7.5, 17.0 Hz, 1 H), 3.20 (dd, *J* = 3.0, 17.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$–DMSO): δ = 173.1, 140.3, 139.4, 128.2, 126.9, 124.5, 124.3, 63.0, 46.7. HRMS: *m*/*z* calcd for $C_{10}H_9NOS$: 191.0399; found: 191.0393.