Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 7867–7870

Synthesis of *N*-substituted 2,4-thiazolidinediones from oxazolidinethiones

Guadalupe Mendoza,[a] Hector Hernández,[a] Leticia Quintero,[a] Martha Sosa-Rivadeneyra,[a] Sylvain Bernès,[b,*] Estibaliz Sansinenea[b] and Aurelio Ortiz[a,*]

[a]*Centro de investigación de la Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla Pue. 72570, Mexico*
[b]*Instituto de Ciencias de la Benemérita Universidad Autónoma de Puebla, Puebla Pue. 72570, Mexico*

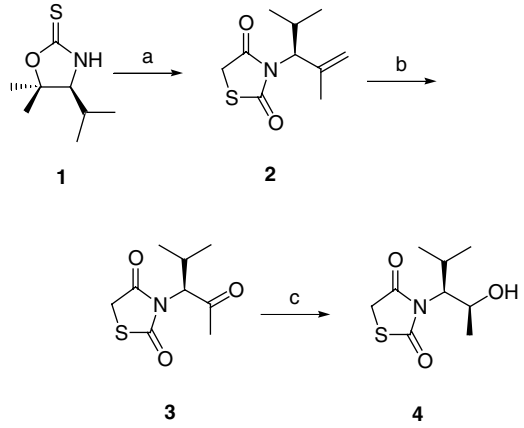
Received 10 August 2005; revised 14 September 2005; accepted 19 September 2005

Abstract—A novel reaction has been found between oxazolidinethione and bromoacetyl bromide to afford *N*-substituted 2,4-thiazolidinediones through an intramolecular nucleophilic substitution reaction. Interestingly a step of elimination was carried out in trisubstituted oxazolidinethiones forming a double bond.

Thiazolidinediones have been the subject of extensive researches because of their important antidiabetic activity.[1] Rosiglitazone and pioglitazone have become the most employed to this disease. The synthesis of the ring of thiazolidinedione has been performed from α-halo ester or α-halo nitrile by reaction with thiourea or potassium thiocyanate followed by acid hydrolysis.[2] Moreover, all derivatives have been synthesized like racemic mixture in relation with its stereogenic center at the C-5 position.

Knöevenagel condensation between aryl aldehyde and commercial 2,4-thiazolidinedione and subsequent olefinic bond reduction has been an efficient method to prepare many derivatives.[3]

In this letter we describe an interesting reaction observed during the attempted attachment of oxazolidinethiones to bromoacetyl bromide, employing *N*-acyl reaction conditions,[4] to provide *N*-substituted 2,4-thiazolidinediones. The chiral oxazolidinethione **1**[5] was treated with 1 equiv of NaH in CH_2Cl_2 at 0 °C and followed of a dropwise addition of bromoacetyl bromide at −78 °C to provide **2**[6] in 67% yield as a liquid compound $[\alpha]_D^{25}$ −45.9 (*c* 2, $CHCl_3$). Compound **2** was treated with an oxidant mixture of $NaIO_4$ (3 equiv) and OsO_4 catalytic in THF/H_2O, to provide the ketone **3** in 93% yield as a liquid compound $[\alpha]_D^{25}$ −138 (*c* 0.7, $CHCl_3$). Subsequent addition of the L-Selectride led to the formation of alcohol **4**[7] in 79% yield as a dense liquid $[\alpha]_D^{25}$ −19.5 (*c* 1.64, $CHCl_3$) with an excellent diastereoselectivity (98:2), as shown in Scheme 1.



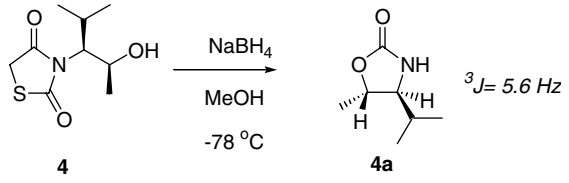
Scheme 1. Reagents and conditions: (a) NaH, 0 °C, $BrCOCH_2Br$, −78 °C CH_2Cl_2 (b) $NaIO_4$, OsO_4, THF/H_2O, (c) L-selectride, THF −78 °C.

Interestingly, the use of $NaBH_4$ (1 equiv) in the reduction reaction of **3** in THF at −70 °C resulted in the preferential formation of a diastereomeric mixture of

Keyword: Thiazolidinethiones.
* Corresponding authors. Tel.: +52 222 2295500 7297; fax: +52 222 2295551 (S.B.); tel.: +52 222 2295500 7518; fax: +52 222 2295584 (A.O.); e-mail addresses: sylvain_bernes@hotmail.com; jaortizm@siu.buap.mx

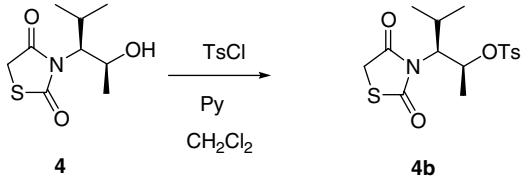
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.116

(4*S*,5*S*)-**4a** and (4*S*,5*R*)-4-isopropyl-5-methyl oxazolidinone **4a**′ in a ratio of (84:16).[8] They were obtained by reduction reaction of **3** and subsequent cyclization in situ. It was confirmed when oxazolidinone **4a** was achieved from **4**, using NaH, LDA, or $NaBH_4$. The last provided the best yield (96%) and the reaction was cleaner than the others. Absolute configuration of the newly formed stereogenic center in **4a** was confirmed by their vicinal coupling constant ($^3J = 5.6$ Hz),[9] as shown in Scheme 2.



Scheme 2.

Since **4** is a liquid, the assigned absolute configuration for this compound was confirmed by X-ray analysis of crystalline derivative **4b**, which was prepared through a functionalization of the hydroxyl group; **4b** was obtained in 60% as a yellowless solid (Scheme 3). (8*S*,12*S*)-**4b** presents a folded solid-state structure (Fig. 1), giving a characteristic intramolecular interaction between the thiazolidinedione and benzene ring belonging to the tosylate group (separation between centroids of ring less than 3.7 Å).[15]



Scheme 3.

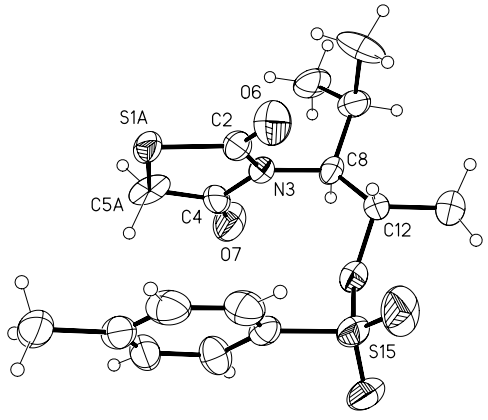
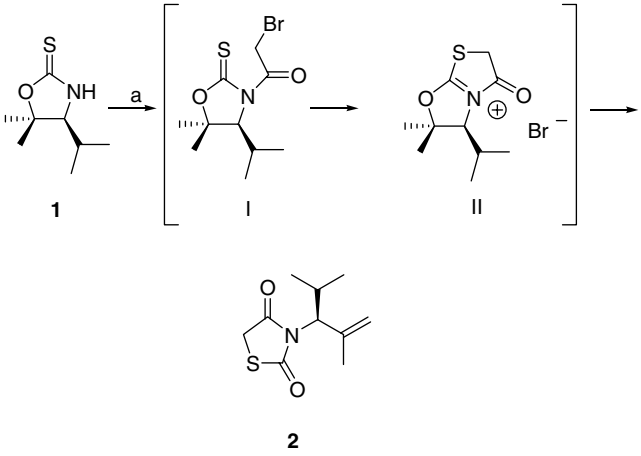


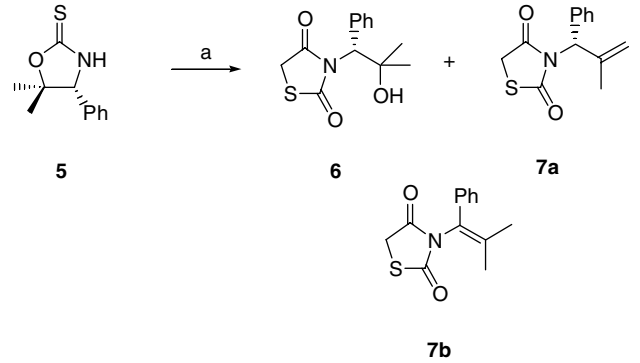
Figure 1. Molecular structure of adduct **4b**. Displacement ellipsoids are drawn at the 30% probability level for non-H atoms. Only one molecule of the asymmetric is represented, omitting the disordered atoms for clarity.

The obtention of **2** can be explained by previous formation of α-bromo-amide **I** in which is carried out an intramolecular nucleophilic substitution reaction between the sulfur atom (as nucleophile) and the bromine atom (as leaving group) to give the imonium **II**, as a plausible conjecture. Unexpected elimination reaction led to the formation of the double bond in **2** as shown in Scheme 4.



Scheme 4. Possible course of the reaction from **1** to **2**.

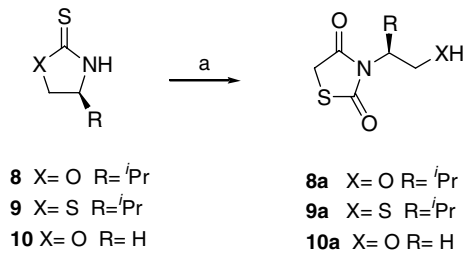
The intramolecular nucleophilic substitution reaction was investigated using (*R*)-4-phenyl-5,5-dimethyl oxazolidine-2-thione **5**, which was treated under the same reaction conditions described above to give three products after their purification by chromatographic column, alcohol **6**[10] and the olefins (**7a**, 59%, $[\alpha]_D^{25}$ −14.8, and **7b** 14%, $[\alpha]_D^{25}$ −7.0), all of them as liquid compounds as shown in Scheme 5.



Scheme 5. Reagents and conditions: (a) NaH, 0 °C $BrCOCH_2Br$, −78 °C, CH_2Cl_2.

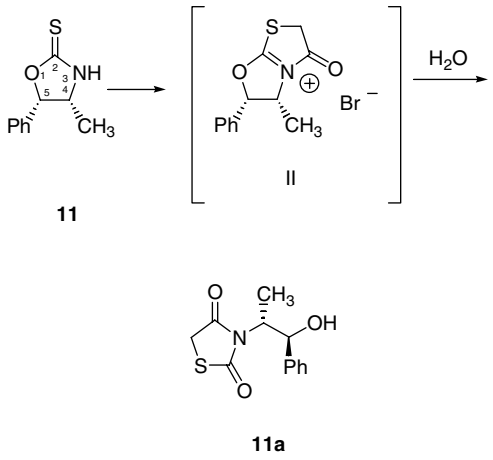
We examined the intramolecular nucleophilic substitution reaction with other derivatives using (*S*)-4-isopropyl oxazolidine-2-thione **8**,[11] (*S*)-4-isopropyl thiazolidine-2-thione **9**[11] and thiazolidine-2-thione **10**.[13] They were treated under the same reaction conditions described above to give the desired thiazolidinediones (**8a**, **9a**[14]) in 96% and 83% yields, respectively, and **10a** in 20% yield may be because of low solubility of **10** in

CH_2Cl_2, all of them as colorless liquid as shown in Scheme 6.



Scheme 6. Reagents and conditions: (a) NaH, 0 °C $BrCOCH_2Br$, −78 °C, CH_2Cl_2.

The *N*-substituted thiazolidinedione **11a** was prepared from the classical chiral oxazolidine-2-thione **11**[12] as described above to give **11a** in 93% yield as a white crystalline solid. The obtention of compounds (**8a**–**11a**) could be explained by the formation of α-bromo-amide **I** followed of **II**, and subsequent hydrolysis, where the molecule of H_2O attacks at the C-2 position of imonium **II**. Scheme 7.



Scheme 7. Possible course of the reaction shown for **11a**.

All ^1H and ^{13}C NMR spectrums of thiazolidinediones **4**, **6**, and (**8a**–**11a**) at 298 K showed a broad signal around at 4.0 and 33.0 ppm, respectively, for CH_2-5. Its physical properties are shown in Table 1.

Table 1. Physical properties of the thiazolidinediones

Compound	Mp (°C)	Yield (%)	$[\alpha]_D$ (*c*)[a]
4	liq.	49.2[b]	−19.5 (1.6)
6	liq.	19.9	+1.3 (1.5)
8a	liq.	96.0	+2.7 (2.3)
9a	liq	83.0	+33.7 (2.3)
10a	liq	20.0	
11a	140	93.0	−113.1 (2.0)

[a] Determined in $CHCl_3$ at 25 °C.
[b] Total yield.

In conclusion, we have found a new reaction that was carried out between oxazolidinethione or thiazolidinethione with bromoacetyl bromide to give *N*-substituted thiazolidinediones through the intramolecular nucleophilic substitution reaction. The trisubstituted oxazolidinethiones show an interesting reaction of elimination to form the double bonds in **2**, **7a**, and **7b**.

Acknowledgment

We thank VIEP (project) 37/G/NAT/05. The author H.H. acknowledges a grant from Promep.

References and notes

1. (a) Momose, Y.; Maekawa, T.; Yamano, T.; Kawada, M.; Odaka, H.; Ikeda, H.; Sohda, T. *J. Med. Chem.* **2002**, *45*, 1518–1534; (b) Wrobel, J.; Li, Z.; Dietrich, A.; McCaleb, M.; Mihan, B.; Sredy, J.; Sullivan, D. *J. Med. Chem.* **1998**, *41*, 1084–1091; (c) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1440–1445; (d) Bharatam, P. V.; Khanna, S. *J. Phys. Chem. A* **2004**, *108*, 3784–3788.
2. (a) Sohda, T.; Mizuno, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3563–3573; (b) Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3580–3600; (c) Sohda, T.; Mizuno, K.; Imamiya, E.; Tawada, H.; Meguro, K.; Kawamatsu, Y.; Yamamoto, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3601–3616.
3. Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994**, *37*, 3977–3985.
4. (a) Palomo, C.; Oiarbide, M.; Dias, F.; Ortiz, A.; Linden, A. *J. Am. Chem. Soc.* **2001**, *123*, 5602–5603; (b) Palomo, C.; Oiarbide, M.; Dias, F.; López, R.; Linden, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3307–3310.
5. Preparation of (*S*)-4-isopropyl-5,5-dimethyl-1,3-oxazolidinethione **1** is described in: Ortiz, A.; Quintero, L.; Hernández, H.; Maldonado, S.; Mendoza, G.; Bernès, S. *Tetrahedron Lett.* **2003**, *44*, 1129–1132.
6. Compound **2**: ^1H NMR (400 MHz, $CDCl_3$): δ 5.13 (1H, d, $J = 1.6$ Hz, CH=), 5.02 (1H, dq, $J = 1.6$, 1.2 Hz, CH=), 4.22 (1H, d, $J = 11.6$ Hz, CHN), 4.00 (2H, s, CH_2S), 2.85 (1H, m, $CH(CH_3)_2$), 1.74 (3H, s, CH_3), 0.93 (3H, d, $J = 6.4$ Hz, CH_3CH), 0.83 (3H, d, $J = 6.4$ Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) (HETCOR): δ 171.6 (2CO), 140.3 (C=), 117.2 (CH=), 67.2 (C–N), 33.3 (C–S), 25.4 ($CH(CH_3)_2$), 20.8 (CH_3), 20.6 (CH_3CH), 19.7 (CH_3CH);. IR (KBr): 1753.1, 1676.5, 1370.9, 1318.3, 1165.7, 1113.2, 904.8 cm^{-1}.
7. Compound **4**: ^1H NMR (400 MHz, $CDCl_3$) (COSY): δ 4.16 (1H, m, CHOH), 4.10 (1H, s, CHS), 4.00 (1H, s, CHS), 3.87 (1H, d, $J = 11.0$ Hz, CHN), 2.53 (1H, m, $CH(CH_3)_2$), 1.11 (3H, d, $J = 6.8$ Hz, CH_3CH), 1.08 (3H, d, $J = 6.8$ Hz CH_3CHO), 0.82 (3H, d, $J = 6.2$ Hz, CH_3CH); ^3C NMR (100 MHz, $CDCl_3$): δ 175.3 (C=O), 171.8 (C=O), 67.4 (C–O), 65.7 (C–N), 33.3 (CH_2S), 26.0 ($CH(CH_3)_2$), 20.8 (CH_3CHO), 19.8 (CH_3CH), 19.6 (CH_3CH); IR (KBr): 3468.3, 1747.0, 1663.6, 1386.2, 1333.0, 1163.2, 1108.8 cm^{-1}.
8. Ratio of the isomers was determined by ^1H and ^{13}C NMR.
9. To compound **11** its vicinal coupling constant ($^3J = 8.8$ *Hz*), where both protons are *syn*.

10. Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.52 (2H, m, Ph), 7.31–7.30 (3H, m, Ph), 5.17 (1H, s, CHN), 4.76 (1H, b, HO), 4.00 (1H, s, CH_2), 1.33 (3H, s, CH_3), 1.21 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4 (2CO), 136.0 (C*i*), 130.1 (C*m*), 128.5 (C*p*), 128.4 (C*o*), 71.8 (C–O), 68.6 (C–N), 33.5 (CH_2), 28.6 (CH_3), 28.4 (CH_3); IR (KBr): 3441.1, 2926.7, 1746.5, 1665.8, 1326.3, 1123.3, 700.5 cm^{-1}.
11. The oxazolidinethiones **5** and **7** were prepared from their respective amino alcohols as described in: (a) Li, G.; Othani, T.. *Heterocycles* **1997**, *45*, 2471–2474; (b) Li, G.; Tajima, H.; Ohtani, T. *J. Org. Chem.* **1997**, *62*, 4539–4540.
12. To compounds **6** and **8** was employed the method described in: Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604–6607.
13. Velázquez, F.; Olivo, H. F. *Curr. Org. Chem.* **2002**, *6*, 303–340.
14. Compound **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (2H, s, CH_2S), 3.86 (1H, ddd, $J = 12.0$, 10.4, 4.4 Hz, CHN), 3.14 (1H, ddd, $J = 13.6$, 11.6, 10.0 Hz CHS), 3.00 (1H, ddd, $J = 13.6$, 7.2, 4.8 Hz, CHS), 2.35 (1H, m, $CH(CH_3)_2$), 1.24 (1H, dd, $J = 10.0$, 7.2 Hz, SH), 1.02 (3H, d, $J = 6.4$ Hz, CH_3CH), 0.85 (3H, d, $J = 7.2$ Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (2CO), 64.7 (C–N), 33.1 (CH_2S), 29.6 (CH_2SH), 23.8 ($CH(CH_3)_2$), 20.4 (CH_3), 20.2 (CH_3); IR (KBr): 2924.9, 1748.9, 1671.1, 1336.7, 1157.7, 1116.9, 894.1 cm^{-1}.
15. *Crystal data for* **4b**: $C_{16}H_{21}NO_5S_2$, mp = 362 K, $M = 371.46$, colorless plate, $0.6 \times 0.4 \times 0.1$ mm^3, space group $P2_1$, cell parameters $a = 7.8146$ (18), $b = 27.540$ (6), $c = 8.6131$ (15) Å, $\beta = 101.056$ (19)°, $Z = 4$, $Z' = 2$, $D_c = 1.356$ g cm^{-3}. Five thousand and seventy nine reflections collected on a Bruker P4 diffractometer at room temperature, with the Mo-Kα radiation ($\lambda = 0.71073$ Å) in the range $2\theta = 4.82$–50.00°, of which 4213 are unique ($R_{int} = 0.0634$). Four hundred and eighty three variables refined: $R_1 = 0.0655$ [2746 data with $I > 2\sigma(I)$] and $wR_2 = 0.1816$ [all data].[16] The refinement is of rather poor quality, having to handle weak diffraction and a structure including a number of disordered sites. The asymmetric unit contains two independent molecules with identical configurations and related by a non-crystallographic inversion center. Absolute configuration was determined using anomalous scattering effects of S atoms, 936 Friedel pairs measured; Flack parameter, $\chi = 0.05(17)$.[17] Complete data have been deposited with the CCDC, reference 280598. Structure factors and raw files are available on request to authors.
16. Sheldrick, G. M. SHELXL97; University of Göttingen: Germany, 1997.
17. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881.