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Tetrahedron Letters 49 (2008) 1569–1572
Tetrahedron Letters

Stereomeric studies on the oxidation and alkylation of 4-thiazolidinones

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Received 11 November 2007; revised 24 December 2007; accepted 8 January 2008
Available online 12 January 2008

Abstract

Diastereoselectivity in the oxidation of different 4-thiazolidinones was discussed. Alkylation of these compounds with benzyl bromide was also studied. The stereoselectivity obtained was interpreted by the presence of the sulfoxide.
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Keywords: Reaction mechanism; Stereoselectivity; Sulfone; Sulfoxide

4-Thiazolidinones are important cores in the structures of biologically active compounds. In this sense, different 4-thiazolidinones with anti-inflammatory,[1] antibacterial,[2] or anticancer[3] activity have been reported. Their activity as calcium agonists[4] and HIV-RT inhibitors has also been described.[5] For this reason, the solid-phase[6] and solution[7] synthesis of 4-thiazolidinones has been widely described usually in a one-pot reaction involving an amine, an aldehyde, and an α-mercapto acid. If carbon 5 of the 4-thiazolidinone has to be substituted, the α-mercapto acid has to be previously synthesized[8] because only very few α-mercapto acids are commercially available. An alternative to the use of α-mercapto acids is via a Mannich reaction with formaldehyde and an amine.[9] Lastly, it is worth pointing out that sometimes the most potent compounds have the sulfide of the heterocycle oxidized into sulfoxide or even into sulfone.[3b]

Having this in mind, we decided to further investigate the oxidation of the sulfide of these compounds into sulfoxide and then to carry out the alkylation at carbon 5 of the heterocycle to obtain compounds with the general structure presented in Figure 1.

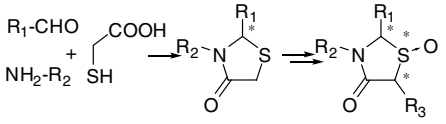

Fig. 1. Synthetic scheme for 4-thiazolidinones.

To identify the best conditions for this manipulation, a parallel strategy was used.[10]

Initially, five different 4-thiazolidinones (Fig. 2) were synthesized from five different aldehydes, benzylamine, and mercaptoacetic acid using a strategy modified from the one described in the literature.[7a] Yields and purities are outlined in Table 1. For **1**–**4**, the two enantiomers of each 4-thiazolidinone were obtained showing total absence of stereoselectivity (**5** does not present a chiral center).

Then, 4-thiazolidinone **1** was used as a model to find the best conditions for each reaction step as well as the best way to determine the stereoselectivity of the reactions.

First of all and taking as model **1**, a broad range of conditions were tested to find the best conditions for the oxidation into sulfoxide (Fig. 3). The best yield and total absence of overoxidation to sulfone were obtained when 1 equiv of AcOOH was used (Table 2, entry 11).

Next, a study of the diastereoselectivity for the 3-benzyl-2-(4-methoxyphenyl)thiazolidin-4-one-1-oxide (**6**) was car-

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doi:10.1016/j.tetlet.2008.01.038

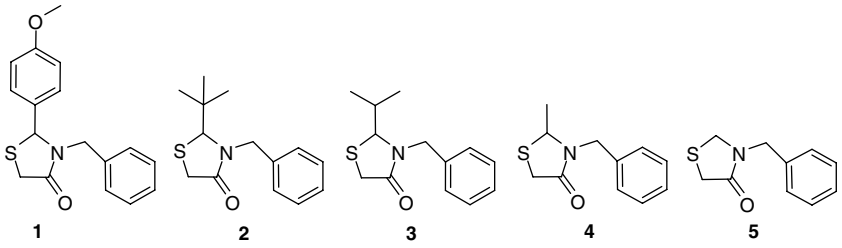

Fig. 2. 4-Thiazolidinones synthesized for this study.

Table 1
Purities and yields of the 4-thiazolidinones synthesized

4-Thiazolidinones	% Yield	% Purity[a]
1	89	97
2	92	99
3	78	94
4	95	99
5	48	96

[a] % Purity by HPLC at 210 nm.

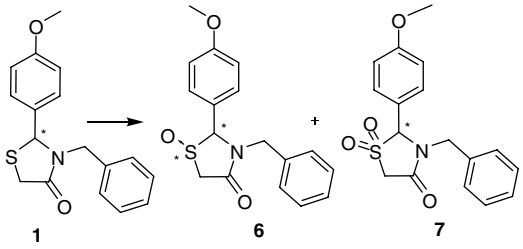

Fig. 3. sulfide oxidation of **1**.

Table 2
Conditions tested for the oxidation of **1** into sulfoxide

Entry	Oxidant (equiv)	Time (h)	**1**[a]	**6**[a]	**7**[a]
1	TBHP (1)	20	99	—	—
2	TBHP (5)	20	99	—	—
3	UHP (1)	20	97	3	—
4	UHP (5)	20	86	11	2
5	H_2O_2 (1)	20	79	21	—
6	H_2O_2 (5)	20	85	15	—
7	CHP (1)	20	51	48	—
8	CHP (5)	20	29	68	3
9	MCPBA (1)	20	37	63	—
10	MCPBA (5)	3.5	10	89	—
11	AcOOH (1)	3.5	—	99	—

[a] % Purity by HPLC at 210 nm.

ried out by HPLC with an X-Terra column and with the chiral column AD-H, observing a diastereomeric ratio, dr of 9:1 for the titled compound. The diastereomers of **6** were then separated by silica column and the major one was crystallized and analyzed by X-ray, obtaining a trans diastereoselectivity for this compound, as shown in Figure 4.

Next, the oxidation of the other 4-thiazolidinones was carried out under optimized conditions and each product was analyzed by HPLC to find the dr (except for the oxidation of **5** where 2 enantiomers were obtained). However,

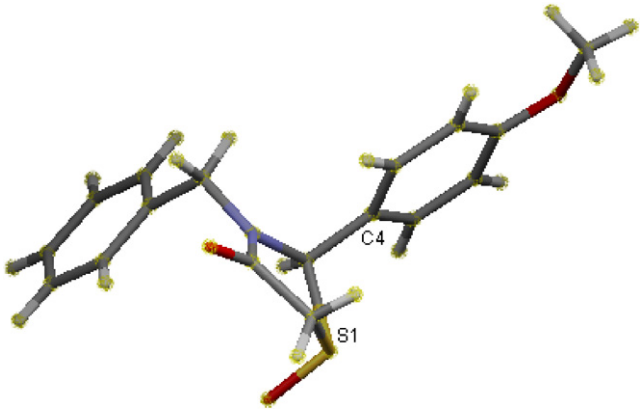

Fig. 4. X-ray structure of *trans*-3-benzyl-2-(4-methoxyphenyl)thiazolidin-4-one-1-oxide (*trans*-**6**).

after different trials with the chiral column AD-H and the X-Terra column, the conditions to separate both diastereomers were not found and the study was carried out by ^{1}H NMR. Table 3 shows that, as expected, the diastereoselectivity depends on the steric hindrance at carbon 2.

Finally, alkylation of 4-thiazolidinone-1-oxide at C-5 with benzyl bromide using various bases, various reaction times, and various temperatures was performed (Fig. 5).

Table 3
Diastereoselectivity of the oxidation of **2**–**4**

4-Thiazolidinones	4-Thiazolidinone-1-oxide[a]	Yield (%)	dr[b]
2	**8**	78	142:1
3	**9**	93	49:1
4	**10**	81	3:1

[a] Oxidation conditions: 1 equiv of AcOH during 3.5 h in DCM.
[b] As determined by ^{1}H NMR.

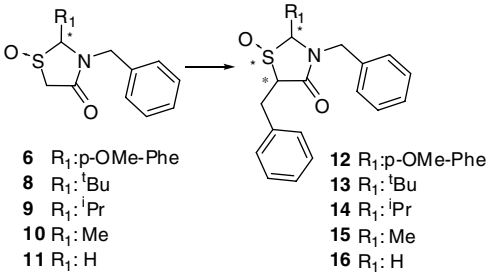

Fig. 5. Alkylation of the 4-thiazolidinones-1-oxide **6**–**11**.

Table 4 shows that the best results for the alkylation of **6** were obtained by using NaH as a base for 4 h at 4 °C (Table 4, entry 11) in THF.

Once the best alkylating conditions were determined, the diastereoselectivity of the reaction was investigated. Since the separation of the 8 possible stereoisomers of **12** was not possible using HPLC, the alkylation of the *trans*-3-benzyl-2-(4-methoxyphenyl)thiazolidin-4-one-1-oxide (*trans*-**6**) was carried out instead, rendering 4 different stereoisomers only. After the reaction, the dr was calculated by HPLC obtaining a dr of 19:1. Furthermore, both diastereomers were separated by silica column and the major diastereomer was crystallized and analyzed by X-ray spectroscopy, which indicated that the substituent of carbon 5 and the sulfoxide were in a cis conformation (Fig. 6).

Table 4
Optimized alkylation of **6**

Entry	Base	Base equiv	Temperature (°C)	Time (h)	% **6**[a]	% **12**[a]	% Bisalkylated prod[a]
1	LHMDS	1.05	−78	6	89	—	—
2	LHMDS	1.1	−60	3	88	7	—
3	LHMDS	1.05	rt	24	32	28	—
4	LDA	1.1	−78	3	91	—	—
5	LDA	1.1	−30	4	87	4	—
6	LDA	1.1	4	24	56	17	—
7	LDA	1.1	rt	48	23	73	7
8	^{n}BuLi	1.05	−60	3	80	18	—
9	NaH	1.05	0	4	41	3	—
10	NaH	1.05	10	4	10	61	21
11	NaH	1.00	4	4	2	87	8

[a] % Purity by HPLC at 210 nm.

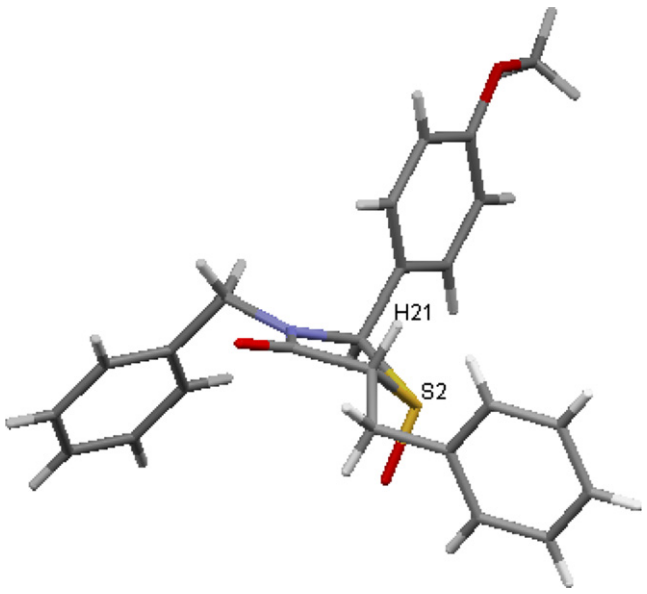

Fig. 6. X-ray structure of the major enantiomer of **12** after alkylation of *trans*-**6**.

Table 5
Yields and purities of the alkylation of **8**–**11**

Entry	4-Thiazolidinone-1-oxide[a]	5-Benzyl-4-thiazolidinone-1-oxide	% Yield	% Purity[b]
1	**8**	**13**	60	88
2	**9**	**14**	22	98
3	**10**	**15**	59	97
4	**11**	**16**	34	81

[a] Reaction conditions: 1 equiv of NaH, 1.1 equiv of benzyl bromide, 4 h, at 4 °C.
[b] % Purity by HPLC at 210 nm.

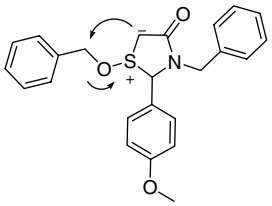

Fig. 7. Key intermediate in the alkylation step of **6**.

Finally, the same conditions used for the alkylation of **6** (1 equiv of NaH, 1.1 equiv of benzyl bromide, 4 h at 4 °C) were applied to the other racemic 4-thiazolidinone-1-oxides (**8**–**11**) to give **13**–**16** (Fig. 5). Table 5 shows yields and purities obtained for these reactions.

It was only possible to separate diastereomers of **16** showing a dr of 6:1. Comparing with the selectivity obtained during the alkylation of **6**, this result indicates that the selectivity is induced by the sulfoxide group and depends on the steric hindrance at carbon 2. To confirm this, sulfone **7** of the model compound **1** was first synthesized[11]and then alkylated[12] obtaining a dr of 2:1, which confirms the importance of having a sulfoxide for good diastereoselectivity in the alkylation process.

These results match with those reported in the literature for the oxidation and alkylation of a thiazoloisoquinoline[13] and allow us to postulate that the sulfoxide attacks the benzyl group before the nucleophile (carbon 5) does (Fig. 7), allowing the cis orientation between the sulfoxide and the benzylic group.

Acknowledgments

This work was partially supported by funds from CICYT (CTQ2006-03794/BQU), Almirall Laboratories, and the Barcelona Science Park. A.C. thanks Almirall Laboratories for providing a predoctoral fellowship. We also wish to thank Dr. Rick Roberts for his help on the synthesis of 4-thiazolidinones and Dr. Rodolfo Lavilla for the discussion on the alkylation mechanism.

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11. The synthesis of **7** was carried out using 1.5 equiv of $KMnO_4$ in a solution of H_2O/AcOH (1:1) for 2 h giving the titled compound with a yield of 72%.
12. The alkylation was carried out using 1.1 equiv of LDA and 1.1 equiv of benzyl bromide in THF for 24 h at room temperature. The 5-benzyl-2-(4-methoxyphenyl)thiazolidin-4-one-1,1-dioxide was obtained with a yield of 70%.
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