Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6217–6220

One-pot synthesis of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones from valine, arenealdehydes and mercaptoacetic acid

Wilson Cunico,* Claudia R. B. Gomes, Maria de Lourdes G. Ferreira, Liliane R. Capri, Marcio Soares and Solange M. S. V. Wardell

FioCruz—Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos, FarManguinhos. R. Sizenando Nabuco, 100, Manguinhos, 21041-250 Rio de Janeiro, RJ, Brazil

Received 14 March 2007; revised 15 June 2007; accepted 18 June 2007
Available online 24 June 2007

Abstract—A three-component one-pot synthesis of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones from valine, arenealdehydes and mercaptoacetic acid with good yields is reported. Characterization of products was generally achieved by NMR techniques and specifically for 2-isopropyl-3-(4-nitrobenzyl)-1,3-thiazolidin-4-one by X-ray crystallography.

Thiazolidinones and their derivatives are an important group of heterocyclic compounds, having valuable biological activities in the areas of medicine and agriculture.[1] They have found uses, for example, as insecticides, tuberculostatic,[2] anti-inflammatory[3] and antiviral agents.[4] In recent years, 4-thiazolidinones and 4-oxazolidinones are among the most extensively investigated compounds. While oxazolidinones have emerged as a new class of antibiotic agents, for example, lizezolid,[5,6] 1,3-thiazolidin-4-ones have found utility as anti-HIV agents.[4] The biological activity of 1,3-thiazolidin-4-ones is reported to be associated with their ability to assume a 'butterfly-like' conformation. This provides a binding mode similar to that provided by other non-nucleosides reverse transcriptase inhibitors (NNRTIs).[7]

The main synthetic routes to 1,3-thiazolidin-4-ones involve three components (an aldehyde, an amine and mercaptoacetic acid), either in a one- or a two-step process.[1] The reactions proceed by initial formation of an imine, which undergoes attack by the sulfur nucleophile, followed by intramolecular cyclization on elimination of water. The most common protocol to remove the water is by azeotropic distillation, but use of chemical drying agents (scavengers) such as DCC has been demonstrated.[8]

The reaction of a (L)-valine ester hydrochloride, an aldehyde and mercaptoacetic acid was reported to produce 3-methyl-[2-alkyl(aryl)-4-oxathiazolinin-3-yl]-butanoic acids, **1** (Fig. 1), in a two-step process, after hydrolysis.[9] Such reactions have also been carried out using microwave radiation.[10] Recently, we attempted to synthesize similar heterocycles directly from (L)-valine in a one-step reaction; however, our products were not the expected compounds **1**, but instead were the non-chiral 2-aryl-3-benzyl-1,3-thiazolidin-4-ones **2** (Fig. 1).[11]

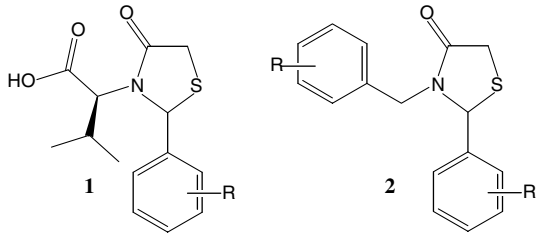
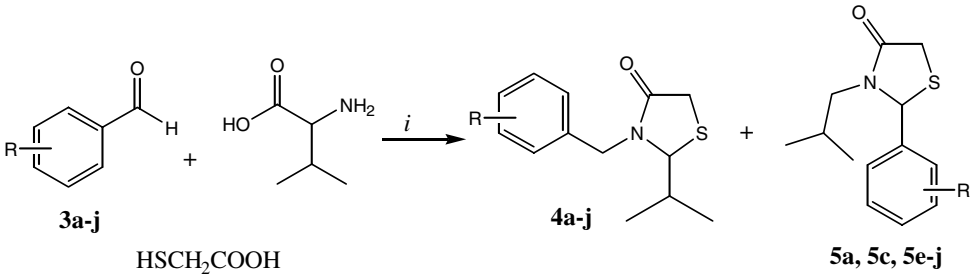


Figure 1. 3-Methyl-2-(2-aryl-4-oxothiazolinin-3-yl)butanoic acids **1** and 2-aryl-3-benzyl-1,3-thiazolidin-4-ones **2**.

Keywords: 4-Thiazolidinone; Heterocycles; Valine; One-pot reaction; Cycloaddition.
* Corresponding author. Tel.: +55 2139772463; e-mail: wjcunico@far.fiocruz.br

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.06.101



Scheme 1. Reagents and conditions: (i) toluene, 110 °C, 16 h, Dean-Stark.

We have subsequently investigated this reaction in more detail and observed the formation of different and new 1,3-thiazolidinone compounds when the reactions are carried out in 1:1:3 mole ratio of valine–arenealdehyde–mercaptoacetic acid in order to minimize the formation of heterocycle type **2** (Scheme 1).

Refluxing a mixture of 4-nitrobenzaldehyde **3d**, valine and mercaptoacetic acid in toluene for 16 h, with azeotropic removal of water, led to the formation of two new thiazolidinone compounds, 2-isopropyl-3-(4-nitrobenzyl)-1,3-thiazolidin-4-one **4d** (92%) and 2-(4-nitrophenyl)-3-isobutyl-1,3-thiazolidin-4-one **5d** (3%) (Table 1, entry 4), as well as 2-(4-nitrophenyl)-1,3-oxathiol-4-one ring (5%), the latter formed from reaction of mercaptoacetic acid solely with 4-nitrobenzaldehyde.[11,12] The same result was found when 2-nitrobenzaldehyde **3b** was used as a precursor (entry 2).

Similar results were obtained using the same ratio of reagents in a two-step procedure, in which mercaptoacetic acid was added to a pre-refluxed (4 h) mixture of 4-nitrobenzaldehyde **3d** and valine in toluene, with further heating for 12 h. When the reaction was carried out at low temperature, large quantities of the starting materials were recovered, as well as a low yield of 2-(4-nitrophenyl)-1,3-oxathiol-4-one.[12]

To gain further insight into the reaction, other substituted arenealdehydes were used. Thus from 4-methoxybenzaldehyde **3j**, the products obtained were 2-(4-methoxyphenyl)-3-isobutyl-1,3-thiazolidin-4-one **5j**, (40% yield) and only 27% of 2-isopropyl-3-(4-methoxybenzyl)-1,3-thiazolidin-4-one **4j** (Table 1, entry 10). We also identified the presence of 2-(4-methoxyphenyl)-1,3-oxathiol-4-one and 2-(4-methoxyphenyl)-3-(4-methoxybenzyl)-1,3-thiazolidin-4-ones (heterocycle type **2**) in small concentrations. Corresponding products were obtained with other substituted arenealdehydes, with the **4**:**5** product ratios dependent on the particular substituent, see Table 1.

Separation of each **4**/**5** product pair was difficult due to retention times in chromatography. Thus, only limited quantities of very pure compounds were obtained. However, these quantities were sufficient for general characterization by 1D and 2D NMR techniques, and in the case of compound **4d** by single crystal X-ray crystallography.

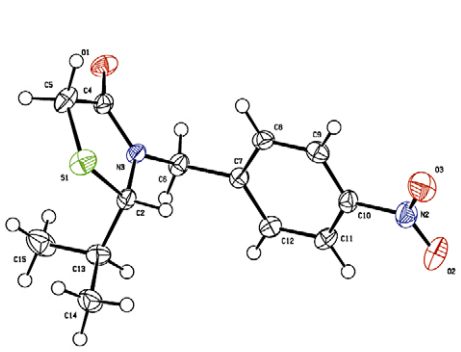
The atom arrangements with selected geometric parameters are shown in Figure 2.[14] The 2-isopropyl-3-(4-nitrobenzyl)-1,3-thiazolidin-4-one **4d** is best described as having a twisted conformation [on S1–C2] from the Cremer and Pople puckering analysis.[15] The overall molecule is far from planar with the angle between the best planes of the thiazolidin-4-one and phenyl rings being 75.25 (0.05)°. No classical hydrogen bonds are found in the structure.

A possible mechanism is outlined in Scheme 2. Initial reaction of valine with arenealdehyde produces **imine I**, which at the reflux temperature is decarboxylated to an equilibriating pair of imines, **II** and **III**. When the

Table 1. Yields, melting points and GC-analysis of compounds **4** and **5**

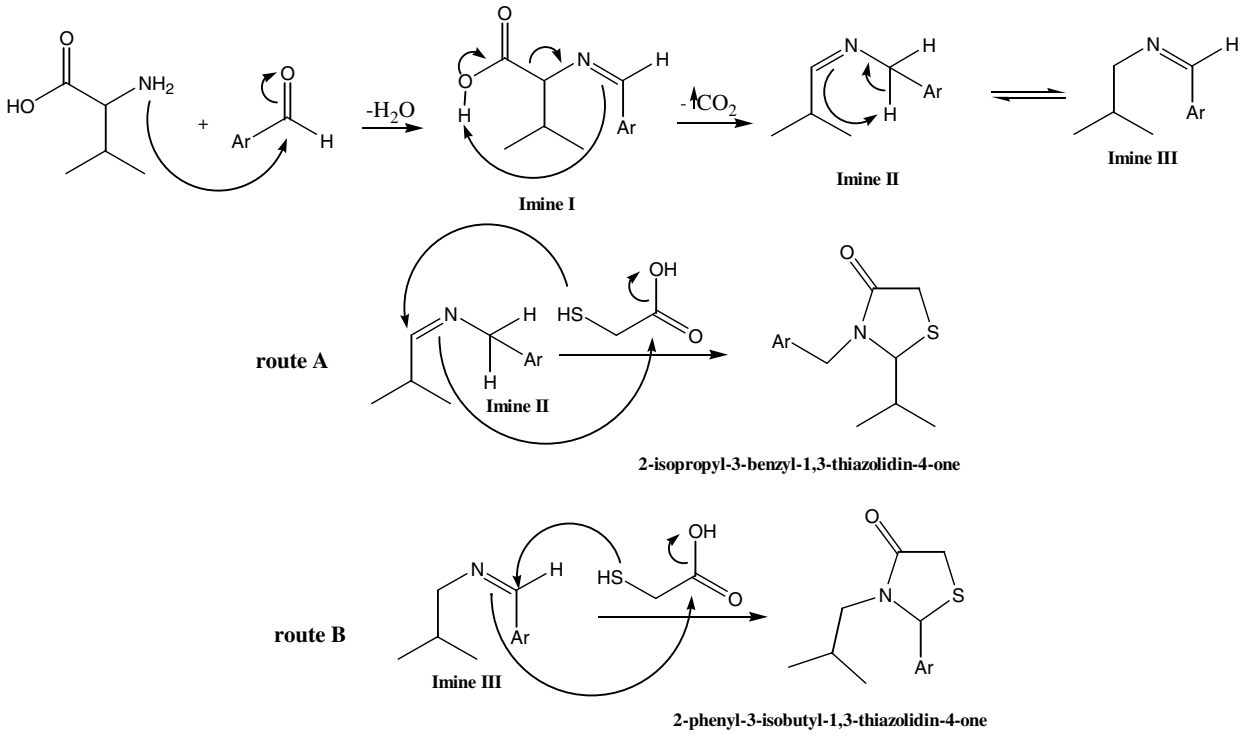
Entry		R	Mp[a] (°C)		Yield (%) mixture[b]	GC-analysis[13]	
			4	**5**		**4**	**5**
1	**a**	H	90–92	Oil	76	35	27
2	**b**	2-NO_2	116–118	Oil	83	77	—
3	**c**	3-NO_2	110–112	Oil	68	73	12
4	**d**	4-NO_2	119–121	Oil	89	92	3
5	**e**	2-F	96–97	Oil	74	65	12
6	**f**	3-F	80–82	Oil	71	40	25
7	**g**	4-F	90–92	Oil	76	34	32
8	**h**	2-OMe	100–101	Oil	64	27	36
9	**i**	3-OMe	120–123	Oil	69	34	28
10	**j**	4-OMe	115–117	Oil	72	27	40

[a] Melting points are uncorrected.
[b] Isolated mixture.



C2-S1	= 1.8323(19)
S1-C5	= 1.804(2)
C5-C4	= 1.514(3)
C4-N3	= 1.352(2)
N3-C2	= 1.457(2)
S1-C5-C4	= 107.97(14)
C5-C4-N3	= 111.70(17)
C4-N3-C2	= 119.3(2)
N3-C2-S1	= 104.61(12)
C2-S1-C5	= 93.50(9)

Figure 2. Molecular structure and selected geometric parameters, (Å, °), for compound **4d**. Ellipsoids, for non-hydrogen atoms, are drawn at the 50% probability level: H atoms are drawn as arbitrary spheres.



Scheme 2. Mechanism of the formation of thiazolidinones **4** and **5**.

mercaptoacetic acid reacts with **imine II**, thiazolidinones of type **4** are formed (route A), whereas reaction with **imine III** produces the type **5** thiazolidinones (route B).

In conclusion, novel thiazolidinones heterocycles were formed from valine, arenealdehydes and mercaptoacetic acid in good yields. The strong withdrawing group, NO_2, present on benzaldehydes, promotes the selective formation of heterocycle **4** in good yields, whereas the methoxy and fluoro groups do not show good selectivity. The study of this reaction with different amino acids is ongoing.

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Buchi Melting Point B-545 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer (^{1}H at 400.14 MHz and ^{13}C at 100.61 MHz) and on a Bruker Avance 500 spectrometer (^{1}H at 500.13 MHz and ^{13}C at 125.75 MHz) in $CDCl_3$ containing TMS as an internal standard. HPLC analyses were performed on a LACHROM—Hitachi (injector: L-7250; detector: L-7455; pump: L-7100). GC/MS analyses were performed on a GC: 6890N Network GC System Agilent; MS: 5973N Mass detector; Injector: 7683 Series injector.

General procedure: A mixture of valine (5 mmol), arenealdehyde (5 mmol) and mercaptoacetic acid (15 mmol) in toluene (50 ml) was heated at 130 °C with a Dean-Stark trap until the reaction was complete, as shown

by GC (about 16 h). The organic layer was separated, washed with saturated $NaHCO_3$ (3×100 ml), dried with $MgSO_4$ and concentrated to give an oil. The oil was purified by column chromatography on silica gel using hexane–ethyl acetate as eluent (9:1) to give a mixture of compounds **4** and **5**. The mixture of **4** and **5** (60 mg) was dissolved in 12 ml of water–acetonitrile (4:6) and injected in 1.0 ml aliquots into the HPLC preparative column (SHIM-PACK C_8 Shimadzu, 250 mm × 20 mm).

Acknowledgements

The authors thank FarManguinhos for the financial support of the research and thank the EPSRC X-ray Crystallographic Service, University of Southampton, England, for the data collections.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.101.

References and notes

1. Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175.
2. Kuçukguzel, G.; Kocatepe, A.; De Clercq, E.; Sahin, F.; Gulluce, M. *Eur. J. Med. Chem.* **2006**, *41*, 353.
3. Look, G. C.; Schullek, J. R.; Holmes, C. P.; Chinn, J. P.; Gordon, E. M.; Gallop, M. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 707.
4. (a) Barreca, M. L.; Balzarini, J.; Chimirri, A.; De Clercq, E.; De Luca, L.; Holtje, H. D.; Holtje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zapallà, M. *J. Med. Chem.* **2002**, *45*, 5410; (b) Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zapallà, M. *Il Farmaco* **2004**, *59*, 33; (c) Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zapallà, M. *Antiviral Res.* **2004**, *63*, 79; (d) Rawal, R. K.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. *Bioorg. Med. Chem.* **2005**, *13*, 6771.
5. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, M. N.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Troops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
6. de Souza, M. V. N. *Recent Patents Anti-Infective Drug Discovery* **2006**, *1*, 33.
7. Barreca, M. L.; Carotti, A.; Carrieri, A.; Chimirri, A.; Monforte, A. M.; Pellegrini Calace, M. L.; Rao, A. *Bioorg. Med. Chem.* **1997**, *7*, 2283.
8. Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619.
9. Homes, C. P.; Chinn, J. P.; Look, C. G.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328.
10. Gudurudu, V.; Nguyen, V.; Dalton, J. T.; Miller, D. D. *Synlett* **2004**, 2357.
11. Cunico, W.; Capri, L. R.; Gomes, C. R. B.; Sizilio, R. H.; Wardell, S. M. S. V. *Synthesis* **2006**, 3405.
12. Satsumabayashi, S.; Irioka, S.; Kudo, H.; Tsujimoto, K.; Motoki, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 913.
13. GC-14B Shimadzu, HP-1 (Crosslinked Methyl Siloxane): Film thickness: 0.25 mm; length: 30 m; phase ratio: 320; Column ID: 0.32 mm. Program: $T_0 = 50$ °C; $t_0 = 2.0$ min; rate 16.0 °C/min; $T_f = 250$ °C; $t_f = 10.0$ min; Inj. = 250 °C; Det. = 270 °C.
14. X-ray crystal data for **4d**: CCDC 634756; empirical formula $C_{13}H_{16}N_2O_3S$; formula weight 280.34; $T = 120(2)$ K; $\lambda =$ 0.71073 Å; crystal system = monocyclic; space group $P21/c$; unit cell dimensions: $a =$ 9.7764(5) Å, $\alpha = 90°$, $b = 14.0489(7)$ Å, $\beta = 115.079(3)°$, $c = 10.8292(4)$ Å, $\delta = 90°$; $V = 1347.14(11)$ Å^3; $z = 4$; $D = 1.347.14$ g/cm^{-3}; $\mu = 0.246$ mm^{-1}; theta range for data collection 3.57–27.47°; reflections collected 18,239; independent reflections 3078 [R(int) = 0.0598]; refinement method full-matrix least-squares on F^{-2}; $R_1 = 0.0480$, $wR_2 = 0.1076$ [$I > 2\sigma(I)$]. Structure solution and refinement were achieved using SHELX97 and SHELXL97 (Sheldrick, G.M. SHELXS97 and SHELXL97, University of Göttingen, Germany, 1997).
15. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *197*, 354.