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SYNTHESIS OF 3-ARYLMETHYL-4-THIAZOLIDINE-CARBOXYLIC ACID-2-ONES AND 2-THIONES

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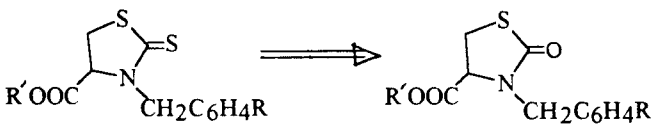
Abstract

Barium salts of dibenzylidene cystines **8a-c** were obtained from the reaction of L-cystine with benzaldehyde or its derivatives in the presence of barium hydroxide. Their reduction with zinc and hydrochloric acid in methanol yielded the N-arylmethylcysteines **9a-c**. These can, in turn, be converted by esterification into the methyl esters **10 a-c**. Reaction of N, N'-carbonyl diimidazole (Im_2CO) or N, N'-thiocarbonyl diimidazole (Im_2CS) with thiols **9a-c** and **10a-c** gave 3-arylmethy-4-thiazolidine-carboxylic acid-2-ones **3a-c** or 2-thiones **1a-c** and their methyl esters **4a-c** and **2a-c** respectively. From the reaction of P_4S_{10} with 3-arylmethyl 4-thiazolidine-carboxylic acid-2-ones **3a-c** and **4a-c** the derivatives of 2-thiones **2a-c** and **1a-c** were obtained as well.

Introduction

Pursuant to the synthesis of 3-arylmethyl-4-thiazolidine carboxylic acid-2-thiones **1** and their methyl esters **2** [1a, b] it seems that the 2-one derivatives of compounds 1 and **2**, i.e., 3-arylmethyl- 4 - thiazolidine carboxylic acid- 2 - ones **3** and their methyl esters **4** are suitable compounds for the synthesis of **1** and **2** derivatives (Scheme 1).



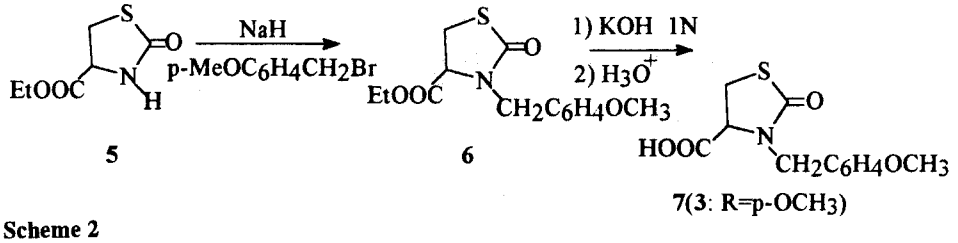
R'=H **1**
R'=CH3 **2**

R'=H **3**
R'=CH3 **4**

Scheme 1

Thiazolidine-2-ones are derivatives of thiazolidines which belong to a major group of heterocyclic compounds. These compounds possess many biological properties and physiological activities and over the past years many reports exist in the chemical literature on the new methods for their synthesis [2]. One of the oldest methods for their synthesis is the use of their 2-thione derivatives. In this method the thiocarbonyl group is converted into carbonyl by such reagents as potassium permanganate [3], mercuric oxide in acetic acid [4], basic hydrogen peroxide [5-7], and hydrogen peroxide in acetic acid [8]. The most common method, however, is the cyclization reaction of the derivatives of thioethanol amine with phosgene [9]. Due to the acute toxicity of phosgene, in some cases, other reagents like urea [10] diphenyl carbonate [11] and phenyl chloroformate [12] have also been used. But the less hazardous substitutes for phosgene is the N,N'-carbonyl diimidazole (Im_2CO) which has been used in the production of 4-thiazolidine carboxylic acid-2-ones and their methyl esters [13-14]. The only method so far applied for the synthesis of the compounds **3** and **4** is the benzylation of the 4-thiazolidine-carboxylic acid-2-ones ethylester **5** in the presence of a strong base (NaH) and p-methoxy-benzyl bromide which produces 3-(4-methoxybenzyl)-4-thiazolidine carboxylic acid-2-one ethyl ester **6** in 79% yield. The alkaline hydrolysis of **6** produces acid **7** in 95% yield [15] (Scheme 2).

Keywords: Dibenzylidene cystine; L-cystine; Thiazolidine



5 6 7(3: R=p-OCH3)

Scheme 2

In this article, a new method is presented for the synthesis of thiazolidine-2-ones (2-thiones) in which the 3-aryl methyl substituent is introduced into the starting material before the ring closer. Thus, the benzyl bromide derivatives required for benzylation are replaced by benzaldehyde derivatives [16]. Furthermore, by using the P_4S_{10}, the thiazolidine-2-ones **3** and **4** could be converted into the thiazolidine-2-thiones **1** and **2** in satisfactory yields.

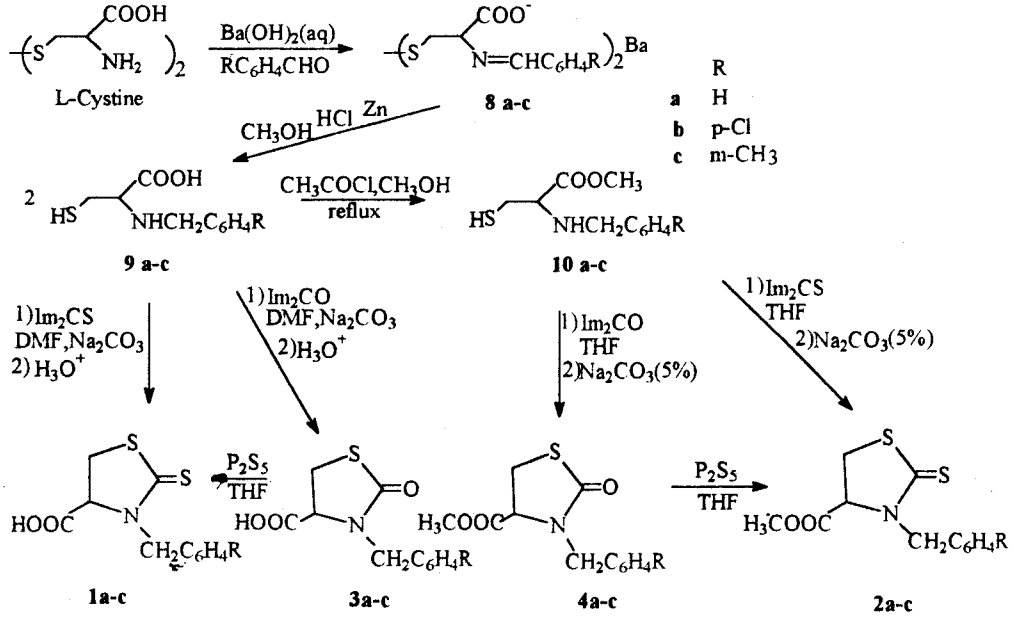
Results and Discussion

At room temperature, the disubstituted benzylidene cystine barium salt **8a-c** [17] are obtained from the reaction of L-cystine with benzaldehyde derivatives in barium hydroxide solution in 66-92% yields. The reduction of the diimines **8a-c** by zinc and hydrochloric acid in methanol at 0°C conveniently produces the N-aryl methyl-cysteine [1b] **9a-c** in 57-77% yields. Esterification of **9a-c** derivatives by methanol and acetyl chloride yields the N-aryl methylcysteine methyl esters [1b] **10a-c** in 89-92% yields (Scheme 3).

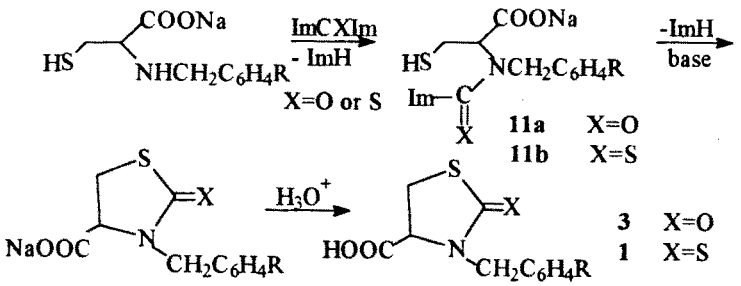
The reaction of **9a-c** with Im_2CO and sodium carbonate in dimethyl formamide (DMF) at room temperature produces **3a-c** derivatives in 78-84% yields. Similarly, the replacement of Im_2CS for Im_2CO produces the **1a-c** derivatives in 75-82% yields (Scheme 3). A possible mechanism of these reactions is shown in Scheme 4.

The reaction of **10a-c** derivatives with Im_2CO in THF at reflux produces an intermediate which is probably the N-(imidazolyl-1-carbonyl) **12a**. Sodium carbonate solution 5% affected the intramolecular cyclization reaction leading to the production of **4a-c** derivatives in 73-81% yields. Similarly, reaction of Im_2CS with **10a-c** derivatives gives the intermediate N-(imidazolyl-1-thiocarbonyl) **12b** which, under alkaline conditions, produces **2a-c** derivatives in 75-78% yields (Scheme 3,5).

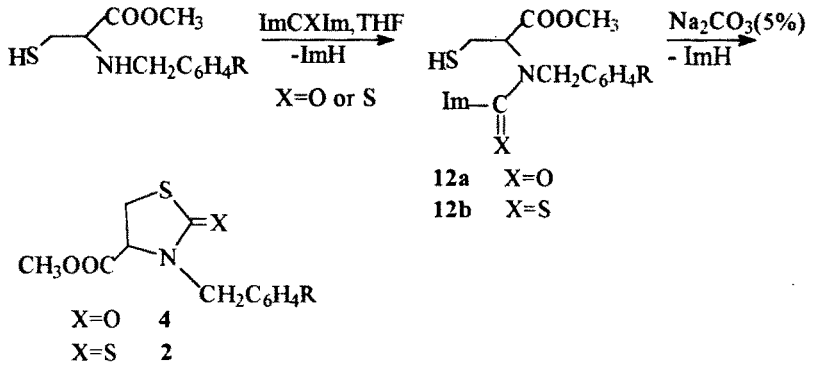
Furthermore, the esterification of derivatives **3a-c** with methanol and acetyl chloride yields compounds **4a-c** in 92-96% yields [18] (Scheme 3). Another method applied for the synthesis of **1a-c** and **2a-c** derivatives is the reaction of P_4S_{10} with **3a-c** and **4a-c**. (Scheme 3).



Scheme 3



Scheme 4



Scheme 5

Experimental Section

General

Melting points were determined with a Gallenkamp instrument and were uncorrected. Infrared (IR) spectra were run on a Shimadzu IR 435 Spectrophotometer as KBr disks or as smears between salt plates. The ^{1}H-NMR spectra were recorded on a Varian-EM 390 Spectrometer. Chemical shifts were reported in values in ppm with tetramethylsilane as on internal standard. Mass spectra were taken with a Varian Matt 711 double focusing mass spectrometer.

General Synthetic Method for Disubstituted Benzylidene Cystine

Barium salts (**8**) 4g. (16.3 mmol, 98%) of L-cystine is dissolved in 100 ml of 0.4 molar barium hydroxide solution and mixed mechanically. To the solution, benzaldehyde or benzaldehyde derivative (65 mmol) was added and stirred for 2.5 hrs. The reaction mixture was then filtered and the precipitate was washed with ether (3×10 ml), water (100 ml) and acetone, (2×50 ml). It was then vacuum-dried.

Dibenzylidene Cystine Barium Salt (8a)

Yellow powder (92%); m.p. 197-199°C (decomp.). Anal. Calcd. for $C_{20}H_{18}N_2O_4S_2Ba$: C, 43.5%; H, 3.3%; N, 5.1% Found: C, 43.3%; H, 3.2%; N, 5.1% IR: 1380, 1407, 1458, 1585, 1640 cm^{-1}.

Bis (4-chlorobenzylidene) Cystine Barium Salt (8b)

White powder (66%); m.p. 195-198°C (decomp). Anal. Calcd. for $C_{20}H_{16}Cl_2N_2O_4S_2Ba$: C, 38.7%; H, 2.6%; N, 4.5%. Found: C, 38.6%, H.2.7%; N, 4.5%. IR: 1400, 1480, 1585 and 1640 cm^{-1}.

Bis (3-methoxybenzylidene) Cystine Barium Salt (8c)

Yellow powder (82%); m.p. 182-184°C (decomp.) Anal. Calcd. for $C_{22}H_{22}N_2O_6S_2Ba$: C, 43.2%; H, 3.6%, N, 4.6%. Found: C, 43%; H, 3.7%; N, 4.7%. IR: 1260, 1315, 1400, 1460, 1480, 1585, 1640 cm^{-1}.

General Synthetic Method for N-Arylmethyl Cysteines (9)

At 0°C, to a mixture of **8** (10 mmoles) and zinc powder (5.8 g) in methanol (100 ml) under nitrogen atmosphere was slowly added concentrated hydrochloric acid (24 ml). After the addition of the acid was complete, the reaction mixture was stirred for 1hr at 0°C. After filtration, the methanol was removed under reduced pressure. Water (20

ml) was added and the pH was then raised to 5 by adding saturated aqueous $NaHCO_3$. The precipitate was filtered and washed first with water then acetone. It was finally vacuum dried.

N-benzylcysteine (9a)

White powder (57%) m.p. 191-192°C (decomp.) Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.8%; H, 6.2%; N, 6.6%. Found: C, 56,6%; H, 6.2%; N, 6.7% MS (CI) m/z 212 $(M+1)^+$.

N-(4-chlorobenzyl) cysteine (9b)

White powder (77%) m.p. 195-197°C (decomp.) Anal. Calcd. for $C_{10}H_{12}ClNO_2S$: C, 48.9%; H, 4.9%; N, 5.7%. Found: C, 48.8%; H, 4.9%; N, 5.6% MS (CI) m/z 246 $(M+1)^+$.

N-(3-methoxybenzyl) cysteine (9c)

White powder (62%) m.p. 189-192°C (decomp.) Anal. Calcd. for $C_{11}H_{15}NO_3S$: C, 54.7%; H, 6.3%; N, 5.8%. Found: C, 54.8%; H, 6.3%; N, 5.9% MS (CI) m/z 242$(M+1)^+$.

General Synthetic Method for N-Arylmethyl Cysteine Methyl Esters (10)

Under N_2 gas, 1 ml of acetyl chloride was added to 15 ml of dry methanol at 0°C. After 2 min, 2 mmoles of 9 was added to the solution and it was refluxed for 18 hrs. The reaction mixture was concentrated under reduced pressure, 10 ml sat. aqueous $NaHCO_3$ was added and extracted with CH_2Cl_2 (2×15ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated.

N-benzylcysteine methyl ester (10a)

White solid (89%) m.p. 68-71°C. Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.6%; H,6.7%; N, 6.2%. Found: C, 58,5%; H, 6.8%; N, 6.2% MS (CI) m/z 226 $(M+1)^+$. IR: 1215, 1420, 1440, 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.14 (2H, brs), 3.5 (2H,m), 3.75 (1H, m), 3.8 (3H,s), 4.3(2H,m), 7.48 (5H,s).

N-(4-chlorobenzyl) cysteine methyl ester (10b)

Colorless oil (92%); Anal. Calcd. for $C_{11}H_{14}ClNO_2S$: C, 50.9%; H,5.4%; N,5.39%. Found: C, 50.8%; H, 5.4%; N, 5.5%. MS (CI) m/z 260 $(M+1)^+$. IR: 1085, 1180, 1220, 1340, 1425, 1440, 1490 and 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.92 (2H, m), 3.6 (6H,m), 4.2 (2H, m), 7.42 (4H,s).

N-(3-methoxybenzyl) cysteine methyl ester (10c)

Colorless oil (90%); Anal. Calcd. for $C_{12}H_{17}NO_3S$: C, 56.4%; H,6.7%; N,5.5%. Found: C, 56.6%; H, 6.8%; N, 5.4%. MS (CI) m/z 256 $(M+1)^+$. IR: 1260, 1435, 1455, 1490, 1600 and 1720 cm^{-1}. ^1HNMR ($CDCl_3$): δ 2.95 (2H, m), 3.75 (11H,m), 6.9 (3H, m), 7.25 (1H,t).

General Synthetic Method for 3-Arylmethyl-4-Thiazolidinecarboxylic Acid-2-Ones (3)

To a mixture of 9 (2 mmoles), 0.36 g (98%, 2.2 mmol) of N, N-carbonyl diimidazole and 0.32 g (3 mmol) of Na_2CO_3, 12 ml of dry DMF was added. The solution was stirred for 12 hrs at room temperature. After this period, the pH of the reaction mixture was adjusted to 5 by adding aqueous HCl (6M) and then extracted with ether (3× 10 ml). The combined extracts were washed with brine, dried ($MgSO_4$)and concentrated.

3-Benzyl-4-thiazolidinecarboxylic acid-2-one (3a)

Colorless needles (80%); m.p. 110-112°C. Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.7%; H,4.7%; N,5.9%. Found: C, 55.9%; H, 4.8%; N, 5.9%. MS m/z 237 (M^+). IR: 1400, 1440, 1675, 1735 and 2400-3200 (br) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.46 (2H, m), 4.0 (1H, d, J=15Hz), 4.18 (1H, dd, J_{ax}=3.5Hz, J_{bx}=8.5Hz), 5.2 (1H,d, J=15Hz), 7.35 (5H,s), 10.42 (1H, brs).

3-(4-chlorobenzyl)-4-thiazolidinecarboxylic acid-2-one (3b)

Yellow solid (78%); m.p. 65-67°C. Anal. Calcd. for $C_{11}H_{10}ClNO_3S$: C, 48.6%; H,3.7%; N,5.2%. Found: C, 48.4%; H, 3.8%; N, 5.1%. MS m/z 271 (M^+). IR: 1400, 1440, 1495, 1680, 1735 and 2400-3500 (br) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.52 (2H, m), 4.07 (1H, d, J=15Hz), 4.22 (1H, dd, J_{ax}=3Hz, J_{bx}=9Hz), 5.18 (1H,d, J=15Hz), 5.9 (1H,brs), 7.22, 7.4 (each 2H, AB type, J=9Hz).

3-(3-methoxybenzyl)-4-thiazolidinecarboxylic acid-2-one (3c)

Brown viscous oil (84%). Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.9%; H,4.9%; N,5.2%. Found: C, 54.1%; H, 4.8%; N, 5.2%. MS m/z 267 (M^+). IR: 1400, 1435, 1495, 1680, 1735 and 2600-3450 (br) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.51 (2H, m), 3.78 (3H,S), 4.06 (1H, d, J=15Hz), 4.28 (1H, dd, J_{ax}=3Hz, J_{bx}=9Hz), 5.22 (1H,d, J=15Hz), 6.83 (3H, d, J=6.5Hz), 7.35(1H, t, J=6.5 Hz), 10.3(1H,brs).

General Synthetic Method for 3-Arylmethyl-4-Methoxycarbonyl-1, 3- Thiazolidine-2-Ones (4)

Method A: A mixture of 2 mmoles of **10**, 0.35 g (2.1 mmol, 98%) of N, N'-carbonyl diimidazole and 6 ml dry THF was stirred for an hour at room temperature under nitrogen atmosphere and then was refluxed for 12 hrs. 2.5 ml of 5% aqueous Na_2CO_3 was added to the reaction mixture and stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure and extracted with Et_2O (3×10ml). The combined extracts were washed with brine, and then water, dried ($MgSO_4$)

and concentrated.

3- Benzyl-4-methoxycarbonyl-1,3-thiazolidine-2-one (4a)

Yellow oil (81%); Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.4%; H,5.2%; N,5.6%. Found: C, 57.3%; H, 5.2%; N, 5.6%. MS m/z 251 (M^+). IR: 1395, 1430, 1496, 1675, 1740 and 2950 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.43 (2H, m), 3.8 (3H,s), 4.04 (1H, d, J=15 Hz), 4.2 (1H, dd, J_{ax}=3.5Hz, J_{bx}=8.5Hz), 5.18 (1H,d, J=15Hz), 7.37 (5H,s).

3-(4-chlorobenzyl)-4-methoxycarbonyl-1,3-thiazolidine-2-one (4b)

White needles (73%); m.p. 65-67°C. Anal. Calcd. for $C_{12}H_{12}ClNO_3S$: C, 50.4%; H,4.2%; N,4.9%. Found: C, 50.5%; H, 4.1%; MS m/z 285 (M^+). IR: 1395, 1430, 1500, 1675, 1740 and 2950 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.4 (2H, m), 3.75 (3H,s), 4.02 (1H, d, J=15 Hz), 4.15 (1H, dd, J_{ax}=3Hz, J_{bx}=9Hz), 5.05 (1H,d, J=15Hz), 7.12, 7.28(each 2H, AB type, J=9Hz).

3-(3-Methoxybenzyl)-4-methoxycarbonyl-1,3-thiazolidine-2-one (4c)

Yellow oil (78%). Anal. Calcd. for $C_{13}H_{15}NO_4S$: C, 55.5%; H,5.3%; N,5%. Found: C, 55.3%; H, 5.3%; N, 4.9%. MS m/z 281 (M^+). IR: 1400, 1430, 1495, 1680, 1740, 2950 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.38 (2H, m), 3.75 (6H,s), 3.9 (1H, d, J=15 Hz), 4.15 (1H, dd, J_{ax}=3Hz, J_{bx}=9Hz), 5.0 (1H,d, J=15Hz), 6.72 (3H, d, J=6.5Hz), 7.2 (1H, t, J=6.5Hz).

Method B: To 1 mmole ice-cooled solution of **3** in 8 ml of dry methanol under nitrogen atmosphere, 0.6 ml of acetyl chloride was slowly added. After 15 min at 0°C, the solution was refluxed for 1.5 hr. The solution was concentrated by rotary evaporator and then 2 ml sat. aqueous $NaHCO_3$ was added and extracted with Et_2O (3×6 ml). The combined extracts were washed first with brine (3×5ml), then with water (5ml), dried ($MgSO_4$) and concentrated. In this method the compounds **4a-c** were obtained in 96, 93 and 92% respectively.

General Synthetic Methods for 3-Arylmethyl-4-Thiazolidinecarboxylic Acid-2-Thiones (1)

Method A: To a mixture of 2 mmoles of **9**, 0.4 g (2.2 mmol, 97%) of N, N'-thiocarbonyl diimidazole and 0.32 g (3 mmol) Na_2CO_3, 12 ml of dry dimethyl formamide was added. The solution was stirred at room temperature for 12 hrs. Water was added (8ml), and the pH was adjusted to 5 by adding 6M aqueous HCl solution. The reaction mixture was extracted and washed with brine (5×10ml) and water (3×10ml), dried ($MgSO_4$) and concentrated.

3-Benzyl-4-thiazolidinecarboxylic acid-2-thione (1a)

Pale brown solid (79%); m.p. 94-97°C. Anal. Calcd. for $C_{11}H_{11}NO_2S_2$: C, 52.1%; H,4.4%; N,5.5%. Found: C, 53.5%; H, 4.4%; N, 5.6%. MS m/z 253 (M^+). IR: 1350, 1410, 1455, 1460, 1500, 1710, 2400-3300 (brs) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.55 (2H, m), 4.28 (1H, d, J=15 Hz), 4.67 (1H, dd, J_{ax}=3Hz, J_{bx}=9Hz), 5.93 (1H,d, J=15Hz), 7.32(5H, s), 10.8(1H, brs).

3-(4-chlorobenzyl)-4-thiazolidinecarboxylic acid-2-thione (1b)

Yellow solid (75%); m.p.73-75°C. Anal. Calcd. for $C_{11}H_{10}NO_2S_2$: C, 45.9%; H,3.5%; N,4.9%. Found: C, 46.1%; H, 3.4%; N, 4.8%. MS m/z 287 (M^+). IR: 1403, 1420, 1455, 1490, 1725, 2380-3280 (brs) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.56 (2H, m), 4.32 (1H, d, J=15 Hz), 4.68 (1 dd, J_{ax}=3.5Hz, J_{bx}=8.5Hz), 5.86 (1H,d, J=15Hz), 7.3(4H, s), 8.56(1H, brs).

3-(3-Methoxybenzyl)-4-thiazolidinecarboxylic acid-2-thione (1c)

Pale brown needles (82%); m.p.128-130°C. Anal. Calcd. for $C_{12}H_{13}NO_3S_2$: C, 50.9%; H,4.6%; N,4.9%. Found: C, 50.6%; H, 4.5%; N,4.8% MS m/z 283 (M^+). IR: 1493, 1585, 1605, 1735 and 2750-3280 (brs) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.47 (2H, m), 3.76 (3H,s), 4.22 (1H, d, J=15 Hz), 4.68 (1H, dd, J_{ax}=3Hz, J_{bx}=9Hz) m 5.89 (1H,d, J=15Hz), 6.86 (3H,m), 7.3 (1H,m), 10.6(1H, brs).

Method B: To a solution of vigorously stirred **3** (2 mmoles) in 10 ml dry THF under nitrogen and while at 35°C, 0.9 g (2mmol, 98%) of diphosphorous pentasulfide (P_4S_{10}) was slowly added. Stirring at the same temperature was continued overnight. The mixture was filtered on a celite bed and the deposits on the filter were washed with 15 ml of THF. The filtrate was concentrated and purified by column chromatography on silica gel. The compounds **1a-c** with physical and spectral properties identical to those achieved in Method A were obtained in yields 71,69 and 73% respectively.

General Synthetic Methods for 3-Arylmethyl-4-Methoxycarbonyl-1, 3-Thiazolidine-2- Thiones (2)

Method A: A mixture of 2 mmoles of **10**, 0.39 g (2.1 mmol, 97%) of N, N'-thiocarbonyl diimidazole and 6 ml of dry THF was stirred at room temperature for an hour (under N_2) and then refluxed for 12 hrs. The reaction mixture was concentrated under reduced pressure. (2.5 ml) of sat. aqueous $NaHCO_3$ (3ml) was added and further stirred for 1.5 hr at room temperature. Water (3ml) was added and the mixture was extracted with Et_2O (3×5ml). The combined organic extracts were washed with brine (3×5 ml), dried ($MgSO_4$) and concentrated.

3-Benzyl-4-methoxycarbonyl-1,3-thiazolidine-2-thiones (2a)

Brown oil (78%). Anal. Calcd. for $C_{12}H_{13}NO_2S_2$: C, 54%; H,4.9%; N,5.2%. Found: C, 53.9%; H, 4.9%; N, 5.2%. MS m/z 267 (M^+). IR: 1420, 1447, 1495, 1740 cm^{-1}. ^1H NMR (CCl_4): δ 3.42 (2H, m), 3.78 (3H,s), 4.3 (1H, d, J=15 Hz), 4.57 (1H, dd, J_{ax}=3Hz, J_{bx}=9Hz), 5.85 (1H,d, J=15Hz), 7.32(5H, s).

3-(4-chlorobenzyl)-4-Methoxycarbonyl-1,3-thiazolidine-2-thiones (2b)

Brown oil (68%). Anal. Calcd. for $C_{12}H_{12}ClNO_2S_2$: C, 47.8%; H,4%; N,4.6%. Found: C,47.7%; H, 4.1%; N, 4.7%. MS m/z 301 (M^+). IR:1400, 1448, 1492, 1740 cm^{-1}. ^1H NMR (CCl_4): δ 3.48 (2H, m), 3.78 (3H,s), 4.3 (1H, d, J=15 Hz), 4.61 (1H, dd, J_{ax}=3.5Hz, J_{bx}=8.5Hz), 5.78 (1H,d, J=15Hz), 7.3 (4H, s).

3-(3-Methoxybenzyl)-4-methoxycarbonyl-1,3-thiazolidine-2-thione (2c)

Yellow oil (75%). Anal. Calcd. for $C_{13}H_{15}NO_3S_2$: C, 52.5%; H,5.1%; N,4.7%. Found: C, 52.4%; H, 5.1%;N, 4.8%; MS m/z 297(M^+). IR: 1490, 1600, 1740 cm^{-1}. ^1HNMR ($CDCl_4$): δ 3.41 (2H, m), 3.76 (6H,s), 4.22 (1H, d, J=15 Hz), 4.58 (1H, dd, J_{ax}=3Hz, J_{bx}=9Hz), 5.83 (1H,d, J=15Hz), 6.77 (3H, m), 7.2(1H, m).

Method B: To a solution of 2 mmoles of **4** in 10 ml of dry THF under nitrogen, and while vigorously stirred at 35°C, 0.9 g (2 mmol, 98%) of diphosphorous pentasulfide (P_4S_{10}) was slowly added. Stirring at the same temperature was continued overnight. The mixture was filtered on a celite bed. The filtrate was concentrated. The filter cake was washed with CH_2Cl_2 (3×10 ml). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ (3x5ml). The aqueous phase was extracted with CH_2Cl_2 (2×5 ml). The organic phase was dried ($MgSO_4$) and concentrated. The product was purified by column chromatography on silica gel. The derivatives **2a-c** with physical and spectral properties identical to those achieved in Method A were obtained in yields of 84,81 and 87% respectively.

References

1. Nagao, Y., Fujita, E. and Takagi, S. *Chem. Pharm. Bull.* 36, 495-508, (1988); Ghiaci, M; Tabrizi, R.; *Indian J. of Chem. Soc.* Section B. (accepted).
2. Singh, S.P.; Parmar, S.S.; Raman, K. Stenberg, B.I. *Chem. Rev.*, **81**, 175-203, (1981).
3. Takeda, J. *J.Pharm. Soc. Jpn.*, **422**, 281, (1917).
4. Erlenmeyer, H. *Helv. Chim. Acta*, **30**, 1336-8, (1947).
5. Cook, A.H. *J. Chem. Soc.*, 1947-54, (1950).
6. Kashida, Y. *J. Pharm. Soc. Jpn.* 73, 953-8, (1953).
7. Cook, A.H. *J. Chem. Soc.*, 2367-70, (1949).
8. Gaul, R.J. *J.Org. Chem.*, **26**, 5103-6, (1961).
9. Kubodera, N., Nagano, H., Takagi, M. and Matsunaga, I. *Heterocycles*, **18**, 251-63, (1982).
10. Fujimoto, E. and Shimizu, T. *Jpn. Patent*, (1978); *Chem. Abstr.* **90**, 121582h, (1979).
11. Szabadkai, I. *et al. Eur. Patent. Chem. Abstr.*, **112**, 77171 v, (1990).
12. Boettcher, B. and Meister, A. *Methods Enzymol.*, **113**, 458-60, (1985); *Chem. Abstr.* **103**, 211822c, (1985).
13. Komives, T. *Org. Prep. Proced. Int.*, **21**, 251-3, (1989).
14. d' Ischia, M. Prota, G. *Synthetic Commun.*, **17**, 1577-85, (1987).
15. Smith, A.B., Leahy, J.W., Noda, I., Remiszewski, S.W., Liverton, N.J. and Zibuck, R. *J. Am. Chem. Soc.* **114**, 2995-3007, (1992).
16. Soai, K. and Ishizaki, M. *Heterocycles*, **22**, 2827-28, (1984).
17. Bergmann, M. and Zervas, L. *Z. Physiol. Chem.*, **152**, 282-99, (1926).
18. Koskinen. Ari, M.P. and Ghiaci, M. *Tetrahedron Lett.*, **31**, 3209-12, (1990).