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Novel methods for the synthesis of 3-arylmethyl-4-thiazolidine carboxylic acid-2-thiones and their methyl esters

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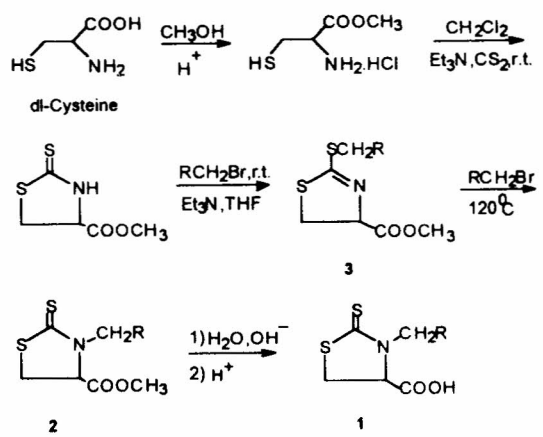
Reductive amination, using benzaldehyde derivatives and sodium borohydride, on L-cystine yields *N,N'*-di (arylmethyl) cystines **7a-c** which can be converted into *N, N'*-di(arylmethyl) cystine dimethyl esters **8a-c** by esterification. The reductive reaction by zinc, hydrochloric acid and methanol on the derivatives **7** and **8** yields the thiols **4a-c** and **5a-c**, respectively which on reaction with CS_2 or $EtOCS_2K$ are further converted into 3-arylmethyl-4-thiazolidine carboxylic acid-2-thiones **1a-c** and their methyl esters **2a-c**. Compounds **2a-c** are also produced by esterification of **1a-c**. Fewer reaction steps and higher yields are the advantages of these methods.

It has been clearly established that different types of 1,3-thiazolidine-2-thiones possess both biological and physiological activities[1]. Moreover, their optically active derivatives have recently been used in asymmetric synthesis quite extensively[2-9]. From among such compounds, here we focuss on a series of 3-arylmethyl-4-thiazolidine carboxylic acid-2-thiones **1** and their methyl esters **2** to be used in asymmetric synthesis.

3-Arylmethyl-4-thiazolidine carboxylic acid-2-thione methyl esters **2** were first prepared in 1988 by Nagao and his coworkers as a new series of aldose reductive inhibitors to be used for inhibiting diabetes[10]. These compounds were synthesized in four steps, starting from *dl*-cysteine. The key step in this method is the application of a Sykes type reaction which includes the rearrangement of RCH_2-group from *exo*-S atom to the N atom in *(rac)*-2-substituted thio-4-methoxycarbonyl-Δ^2 1,3-thiazolines **3**. A further alkaline hydrolysis stage is carried out in this procedure to yield the desired acids **1** (Scheme I). The R-group in Scheme I, includes a number of arylmethoxycarbonyl as well as those of the type –CH=CHOR'.

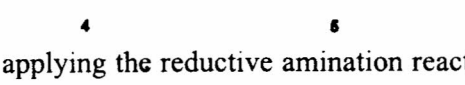
In view of the low overall yields achieved by the above method [33% for **2** (R = C_6H_5) and 28% for **2** (R = *p*-Cl–C_6H_4–)], we were compelled to search for a new method for the synthesis of these compounds having the substituent 3-arylmethyl. This paper aims of describe these novel methods in detail.



Scheme I

Result and Discussion

The expected key intermediates in these methods are the *N*-arylmethylcysteines **4** and their methyl esters **5**.



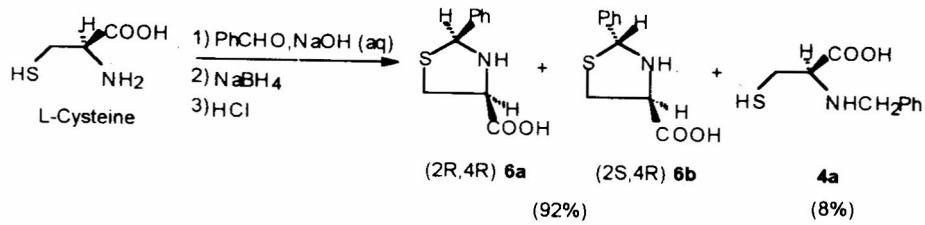
By applying the reductive amination reaction on L-cysteine and benzaldehyde, which yields the expected imine, and the subsequent *in situ* reduction of the imine by $NaBH_4$[11], we intended to produce **4a** (R=H). Due to interference caused by the –SH group, the major products from this

reaction, however, were obtained as a mixture of two diastereomers 2-phenyl-4-thiazolidine-carboxylic acids **6a** and **6b**[12]. The phenylmethylcysteine **4a** was obtained in this reaction only in about 8% yield (Scheme II).

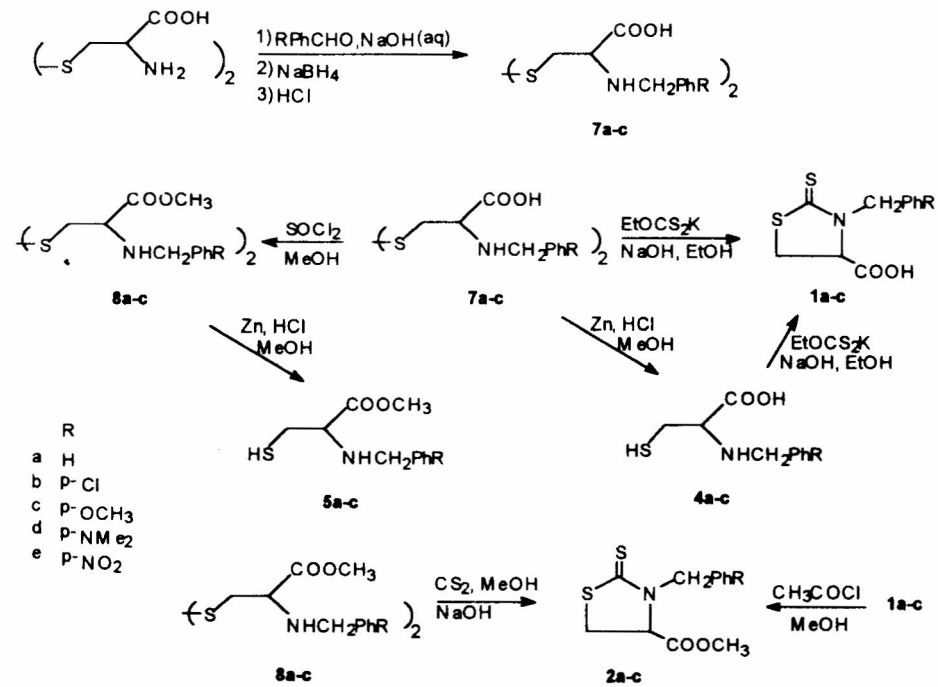
To eliminate the interference of SH group in this reaction, we decided to apply the oxidized form of the cysteine, i.e. cystine. Thus, by applying the reductive amination reaction using benzaldehyde and sodium borohydride on cystine at room temperature, *N,N*-di(arylmethyl) cystines **7a-c** were obtained in 70-83% yields. In the case of compound **7d** (R=*p*-NMe_2) the desired imine was not formed due to the strong electron donating effect of the dimethylamino substituent, and in the case of **7e** (R=*p*-NO_2), the resulting imine, due to the strong electron withdrawing effect of the NO_2 group, was too stable to be reduced by $NaBH_4$.

Esterification of the compounds **7a-c** by dry methanol and thionyl chloride at 45°C afforded *N,N'*-di(arylmethyl)cystine dimethyl esters **8a-c** (Scheme III) in 77-93% yields.

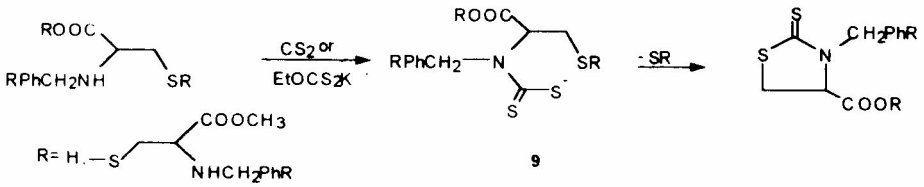
Reduction of the cystine derivatives **7a-c** and **8a-c** zinc powder, hydrochloric acid and methanol at 0°C gave the N-arylmethylcysteines **4a-c** and their methyl esters **5a-c** in 91-97% yields. The reaction of thiols **4a-c** with potassium ethylxanthate ($EtOCS_2K$) and NaOH in ethanol (95%) under reflux produced 3-arylmethyl-4-thiozolidine carboxylic acid-2-thiones **1a-c** in 67-70% yields. The reaction of thiols **5a-c** with carbon disulphide and sodium hydroxide in methanol (absolute) after a period of 20 hr at reflux resulted in the formation of 3-arylmethyl-4-methoxycarbonyl-1,3-thiazolidine-2-thiones **2a-c** in 69-83% yields. In the reaction of disulphides



Scheme II



Scheme III



Scheme IV

7a-c with potassium ethylxanthate and NaOH in ethanol (95%) the cyclization reaction also occurs[14] with the formation of the compounds **1a-c** in 78-82% yields. From the reaction of the disulphides **8a-c** with carbon disulphide and sodium hydroxide in methanol (absolute) compounds **2a-c** are formed in 53-66% yields.

Cyclization of the thiol or disulphide by carbon disulphide or its derivative, potassium ethylxanthate is probably accomplished by the formation of dithiocarbamate **9** as the primary intermediate which is in a later stage converted into the final product by an intramolecular substitution reaction (Scheme IV).

Another method applied for the synthesis of compounds **2a-c** was the esterification of acids **1a-c** by the reaction of methanol (dry) with acetyl chloride which produces esters **2a-c** (Scheme III) in 91-97% yields. Thus, the desired 3-arylmethyl-4-thiazolidine carboxylic acid-2-thiones **1a-c** are at best obtained through two stages with overall yields of 68% for **1a** (R = H), 57% for **1b** (R = *p*-Cl) and 56% for **1c** (R = *m*-OCH_3). Their methyl esters **2a-c** are obtained through three stages with overall yields of 63% for **2a** (R=H), 52% for **2b** (R=*p*-Cl) and 53% for **2c** (R=*m*–OCH_3).

The advantages of these methods are the fewer stages, higher overall yields, easier reaction conditions and cheaper raw materials.

Experimental Section

General. Melting points were determined on a Gallenkamp instrument and are uncorrected. IR spectra were run on a Shimadzu IR 435 spectrophotometer as KBr disks or as smears between salt plates. ^1H NMR spectra were recorded on a Varian-EM390 spectrometer, (chemical shifts are reported in δ, ppm with tetramethylsilane as an internal reference. Mass spectra were taken on a Varian Matt 711 double focusing mass spectrometer. All chemicals were purchased from Fluka Chemical Co., and were used as received unless otherwise specified.

General method for the synthesis of N,N'-(diarylmethyl)cystine 7. To a solution of L-cystine (11.7g, 48.7 mmoles) in NaOH solution (1*N*, 200 mL) was added benzaldehyde derivative (290 mmoles) and the mixture stirred for 3hr at room temperature. The *p*H of the reaction mixture was adjusted to 9.5 by adding HCl (20%) followed by the slow addition of $NaBH_4$ (3.9 g, 99.8 mmoles) maintaining the temperature below 30°C and stirring was continued for another 3hr. The reaction mixture was extracted first with CH_2Cl_2 (2×100 mL) and then with EtO_2 (1×100 mL). The *p*H of the solution was adjusted to 4 by adding HCl (20%). The solid, thus separated, was filtered, washed with water and acetone and dried *in vacuo*. The physical and spectral data of **7a-c** are given in Table I.

General method for the synthesis of *N,N'*-diarylmethylcystine dimethyl esters 8. To a stirred suspension of 10 mmoles of compound **7** in 120 mL of dry methanol was added thionyl chloride (40 mL) at −10°C under nitrogen atmosphere. After 15 min, the temperature was raised to 45°C and the reaction mixture stirred at this temperature for 12 hr. After concentration, 100 mL aq. $NaHCO_3$ was added and the solution extracted with $CHCl_3$ (3×100 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. This physical and spectral data of **8a-c** are given in Table I.

General method for the synthesis of *N*-arylmethylcysteines 4. To a stirred mixture of 5 mmoles of **7**, 2.5g zinc powder and 50 mL of dry methanol at 0°C and under N_2 atmosphere was gently added 12 mL of 30% hydrochloric acid. After stirring at 0°C for 45 min, the mixture was filtered and the filtrate concentrated under reduced pressure. To the cooled mixture, 20 mL water was added. By adding solid $NaHCO_3$, the *p*H was

Table I—Physical and spectral data of compounds **1a-c**, **2a-c**, **4a-c**,**5a-c**, **7a-c** and **8a-c**

Compd	Yield (%)	m.p., °C	Mol. formula	Found (%) (Calcd) C H N	^{1}H NMR (δ, ppm)
7a	83	169-172	$C_{20}H_{24}N_2O_4S_2$	57.1 5.7 6.6 (57.1 5.6 6.6)	2.8 (2H, m, –S–CH_2), 3.2 (1H, t, –N–CH–COONa), 3.55 (2H,m,–CH_2–phenyl), 4.6(D_2O, residue), 7.35 (5H, s, aromatic protons). (sodium salt). (solvent: D_2O)
7b	73	186-188 (decomp)	$C_{20}H_{22}Cl_2N_2O_4S_2$	49.2 4.6 5. (49.1 4.5 5.7)	2.75(2H, m, –S–CH_2), 3.15(1H, t, –N–CH–COONa), 3.47(2H, m, –Ch_2– aryl), 4.6(D_2O, residue), 7.2(4H, aromatic protons). (sodium salt) (solvent: D_2O)
7c	70	142-145 (decomp)	$C_{22}H_{28}N_2O_6S_2$	54.9 5.8 5.9 (55.0 5.9 5.8)	2.7(2H, m, –S–CH_2), 3.1(1H, t, –N–CH–COONa), 3.45(2H, m, –CH_2–aryl), 3.5(3H, s, CH_3O–), 4.6(D_2O, residue), 6.7(3H, m, aromatic protons), 7.1(1H, t, aromatic proton). (sodium salt). (solvent: D_2O)
8a	88	—	$C_{22}H_{32}N_2O_4S_2$	58.8 6.3 6.3 (58.9 6.3 6.2)	2.1(1H, br, exchangeable with D_2O, –NH–), 3.17 (2H, m, –S–CH_2–), 3.75(3H,m, aryl –CH_2–N–CH–COO–), 3.8 (3H, s, CH_3O–), 7.4(5H, s, aromatic protons) (solvent: $CDCl_3$)
8b	77	—	$C_{22}H_{26}Cl_2N_2O_4S_2$	51.6 5.1 5.5 (51.5 5.1 5.4)	2.2(1H, br, exchangeable with D_2O, NH), 3.0(2H, m, –S–CH_2), 3.75 (3H, m, –CH_2–N–CH–COO–), 3.8 (3H, s, CH_3O–), 7.4 (4H, s, aromatic protons) (solvent: $CDCl_3$)
8c	93	—	$C_{24}H_{32}N_2O_6S_2$	56.8 6.2 5.6 (56.7 6.3 5.5)	1.95(1H, br, exchangeable with D_2O, NH), 3.1(2H, m, –S–CH_2–), 3.74 (3H, m, –CH_2–N–CH–COO–), 3.76 (3H, s, CH_3O–aryl), 3.79 (3H, s, CH_3OOC–), 6.8(3H, m, aromatic protons), 7.25(1H, m, aromatic proton). (solvent: $CDCl_3$)
5a	97	68-70	$C_{11}H_{15}NO_2S$	58.7 6.8 6.2 (58.6 6.7 6.2)	3.14(2H, brs, –SH,–NH–), 3.5(2H, m, –S–CH_2–), 3.75 (1H, m, –N–CH–COO–), 3.8(3H, s, CH_3O–), 4.3(2H, m, –CH_2– phenyl), 7.48(5H, s, aromatic protons). (solvent: $CDCl_3$)
5b	92	—	$C_{11}H_{14}ClNO_2S$	50.7 5.4 5.5 (50.9 5.4 5.4)	2.92(2H, m, exchangeable with D_2O, NH), 3.6(6H, m), 4.2(2H, m, –CH_2–aryl), 7.42(4H, s, aromatic protons). (solvent: $CDCl_3$)
5c	91	—	$C_{12}H_{17}NO_3S$	56.6 6.8 5.6 (56.4 6.7 5.5)	2.95(2H, m,), 3.75(11H, m) 6.9(3H, m, aromatic protons 7.25(1H, t, aromatic proton) (solvent: $CDCl_3$)
4a	96	191-192 (dec)	$C_{10}H_{13}NO_2S$	56.7 6.1 6.7 (56.8 6.2 6.6)	2.65–4.2 (8H, brs, m), 7.2–7.6(4H, brs, aromatic protons). (solvent: DMSO–d_6)
4b	94	195-196 (dec)	$C_{10}H_{12}ClNO_2S$	48.8 4.8 5.7 (48.9 4.9 5.7)	2.67–4.17 (8H, brs, m), 7.2–7.6(4H, brs, aromatic protons). (solvent: DMSO–d_6)
4c	93	190-192 (dec)	$C_{11}H_{15}NO_3S$	54.8 6.2 5.7 (54.8 6.2 5.8)	2.7-4.2(11H,brs,m) 6.68–7.47(4H,m,aromatic protons). (solvent: DMSO–d_6
2a	(from **5a**); (from **8a**)	—	$C_{12}H_{13}NO_2S_2$	53.9 4.9 5.2 (54 4.9 5.2)	3.42 (2H, m, –S–CH_2), 3.78 (3H, s, CH_3O–), 4.3 (1H, d, J=15Hz, –C*H*–C_6H_5) 4.57(1H, dd, J_{ax}=3Hz, J_{bx}=9Hz, –C*H*–$COOCH_3$), 5.85(1H, d, J=15Hz, –C*H*–C_6H_5) (solvent: CCl_4)
2b	(from **5b**); (from **8b**)		$C_{12}H_{12}ClNO_2S_2$	47.9 4.1 4.7 (47.8 4.0 4.6)	3.48(2H, m, –S–CH_2), 3.78(3H, s, OCH_3), 4.3(1H, d, J=15Hz, –CH– aryl), 4.61(1H, dd, J_{ax}=3.5 Hz, J_{bx}=8.5Hz, –C*H*–$COOCH_3$), 5.78(1H, d, J=15Hz, –CH– aryl), 7.3(4H, s, aromatic protons). (solvent: CCl_4)
2c	(from **5c**); (from **8c**)	—	$C_{13}H_{15}NO_3S_2$	52.6 5.1 4.8 (52.5 5.1 4.7)	3.41(2H, m, –S–CH_2), 3.76(6H, s, OCH_3), 4.22(1H, d, J=15Hz, –CH– aryl), 4.58(1H, dd, J_{ax}=3Hz, J_{bx}=9Hz, –C*H*–$COOCH_3$), 5.83(1H, d, J=15Hz, –CH–aryl), 6.77(3H, m, aromatic protons), 7.21(1H, m, aromatic proton) (solvent: CCl_4)

Table I—Physical and spectral data of compounds **1a-c**, **2a-c**, **4a-c**,**5a-c**, **7a-c** and **8a-c**

Compd	Yield (%)	m.p., °C	Mol. formula	Found (%) (Calcd) C H N	^{1}H NMR (δ, ppm)
1a	(from **4a**); (from **7a**)	94-97	$C_{11}H_{11}NO_2S_2$	(52.2 4.3 5.5)	3.55(2H, m, –S–CH_2), 4.28(1H, d, *J*=15Hz, –C*H*–C_6H_5), 4.67(1H, dd, J_{ax}=3Hz, J_{bx}=9Hz, –C*H*–COOH), 5.93 (1H, d, *J*=15 Hz, –C*H*–C_6H_5), 7.32(5H,s,aromatic protons), 10.8(1H,brs,–COO*H*) (solvent: $CDCl_3$)
1b	(from **4b**); (from **7b**)	73-75	$C_{11}H_{10}ClNO_2S_2$	46.1 3.4 4.8 (46.2 3.5 4.8)	3.56(2H, m, –S–CH_2), 4.32(1H, d, *J*=15Hz, –CH–aryl), 4.68(1H, d, J_{ax}=3.5Hz, J_{bx}=8.5Hz, –C*H*–COOH), 5.86(1H, d, *J*–15Hz,–CH–aryl), 7.3(4H, s, aromatic protons), 8.56(1H, brs, –COO*H*). (solvent: $CDCl_3$)

adjusted to 4 and the product was separated by filtration. The physical and spectral data of **4a-c** are given in Table I.

General method for the synthesis of *N*-arylmethylcysteine methyl esters 5. At 0°C and under N_2 atmosphere. To a stirred mixture of 2.5 mmoles of **8**, 1.25g zinc powder and 20 mL of dry methanol at 0°C and under N_2 atmosphere was gently added 6 mL of 30% hydrochloric acid. After stirring at 0°C for 30 min, the reaction mixture was filtered and concentrated under reduced pressure. After adding 10 mL of saturated $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (3×30 mL), washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to yield **5**. The physical and spectral data of **5a-c** are given in Table I.

General method for the synthesis of 3-arylmethyl-4-thiazolidine carboxylic acid-2-thiones 1. A mixture of 5.5 mmoles NaOH, 6.5 mmoles of potassium ethylxanthate[15], 25 mL of ethanol (95%) and 5 mmoles of thiol **4** or 2.5 mmoles of disulphide **7** was refluxed for 21 hr under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure, 20 mL of H_2O added and the *p*H adjusted to 4-5 by adding 6*N* HCl. The mixture was extracted with CH_2Cl_2 (3×25 mL), washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to yield **1**. The physical and spectral data of **1a-c** are given in Table I.

General method for the synthesis of 3-arylmethyl-4-methoxycarbonyl-1,3-thiazolidine-2-thiones 2: Method-A. A mixture of 5.5 mmoles NaOH, 11.5 mmoles carbondisulphide, 19 mL MeOH and 5 mmoles thiol **5** or 2.5 mmoles disulphide **8** was refluxed for 21 hr under nitrogen atmosphere. The reaction mixture was concentrated and 15 mL of H_2O added to it. It was then extracted with CH_2Cl_2 (3×20 mL), washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to yield **2**. The physical and spectral data of **2a-c** is given in Table I.

Method-B. Under N_2 atmosphere, to an ice-cooled methanol (30 mL) was gently added 3 mL of acetyl chloride. After 15 min, a solution of 5 mmoles **1(a-c)** in 10 mL methanol was added. The reaction mixture was refluxed for 12 hr. After cooling to room temperature, saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with ether (3×20 mL) and the combined organic layers were washed with water (2×20 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* yielded **2a-c**. Their physical and spectral properties were identical with the products obtained above by the method-A: yield- **2a** (93%); **2b** (91%); **2c** (95%).

Acknowledgement

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