The Use of Curtius Rearrangement in the Synthesis of 4-Aminothiazolidines

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Abstract: The amine group of the L-cysteine was protected as (4*R*)-1,3-thiazolidines-4-carboxylic acids **2a–b** and was used for the synthesis of functionalized 1,3-diamines by the way of Curtius reaction. An optimization of this methodology was made using the acylation in situ of the amine group of the thiazolidines and the activation of the carboxylic acid, after Curtius rearrangement yielded the ureas **7a,b** and **8a** and amine derivatives **6a,b**. The Curtius reaction occurred without racemization, preserving the chemical and pharmacological importance of these products.

Key words: cysteine, Curtius rearrangement, amino acids

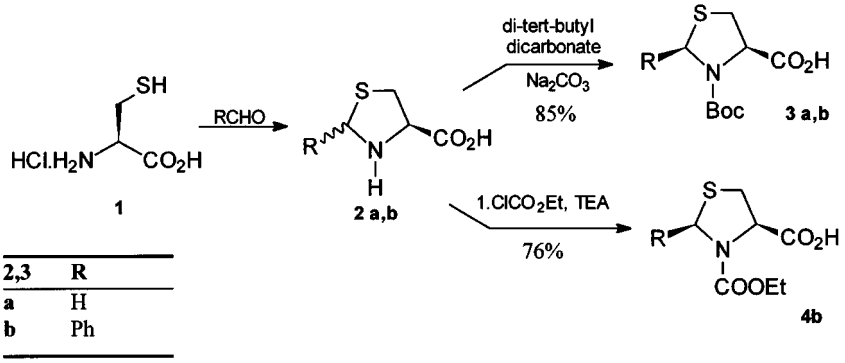
We have exploited the versatility of the nitrogen fragments such as enamino ketones and esters[1,2] in the construction of heterocyclic compounds containing nitrogen atoms.[3,4] In this context and as a part of our research project we required α- or β-functionalized amines as precursors to obtain enamino compounds with defined stereochemistry. These characteristics are present in the fragments of the amino acids such as cysteine, an amino acid similar to β-sulfanylalkylamine which provides both the nitrogen and sulfur atoms, important for building heterocyclic compounds such as thiazolidines and derivatives. The chirality of this amino acid offers the advantage of introducing asymmetry into the heterocyclic systems. The thiazolidine ring system plays an important role in organic synthesis because antimicrobial substances such as penicillins, cephalosporins, narcodicins, thienamicyn and other compounds that have physiological activities have been prepared from thiazolidines.[5,6]

The differential protection of amino acids with side chains containing functional groups can involve difficult and tedious manipulations. A number of papers dealing with the reaction of cysteine with aqueous formaldehyde and benzaldehyde have been published[7,8] and others describe similar studies using organic solvents instead of water as the reaction medium.[9] In this work we report the strategies for simultaneous protection of amino acids and further transformation of acid to azides, amine or ureas in one step.

The transformation of a carboxylic acid into a free or protected amino group constitutes a synthetically important reaction which can be achieved by employing a large variety of reagents and experimental conditions.[10] The Curtius rearrangement here appeared to be the most suitable owing to its efficiency and stereospecificity.

The protection step involves the cyclization of L-cysteine **1** with aldehydes to build thiazolidines-4-carboxylic acids **2a,b**. When using benzaldehyde, a new chiral center at the C-2 position of the thiazolidine ring is generated to give a mixture of two diastereoisomers (45:55) (Scheme 1). The mechanism involves the opening of the ring, the closure and the epimerization of the C-2, according to the results reported previously.[11] The protection of the nitrogen of the thiazolidine with ethoxycarbonyl and *tert*-butyloxycarbonyl (Boc) groups prevents the opening/closure of the ring and allows the isolation of the pure diastereoisomers **3b** and **4b**. The relative stereochemistry of these compounds were established by ^{1}H NMR spectral data, through the sum of the coupling constants. The geminal protons (CH_2) with CH represent the ABX system of the thiazolidine ring,[12] which can be related to the structure of the 2-substituted thiazolidine-4-carboxylic acid derivatives. According to the results reported by Szilágyi,[11] the sum of these coupling constants for the *cis* isomers is greater than the sum of the *trans* isomer.

In our attempt to prepare 4-amino-1,3-thiazolidine derivatives we developed a convenient strategy using two



2,3	R
a	H
b	Ph

Scheme 1

equivalents of ethyl chloroformate in order to protect the nitrogen atom and activate the carboxy group of C-4 thiazolidine. The addition of sodium azide to mixed anhydrides afforded acyl azide intermediates **5a,b** (Scheme 2). Their conversion into desired derivatives depends on reaction conditions.

When the Curtius rearrangements of **5a,b** were carried out in a benzene/water 9:1 emulsion, the symmetrical ureas **7a,b** were obtained in good yields. If the acyl azides were treated in non aqueous conditions (anhydrous benzene) and subsequently refluxed with anhydrous *tert*-butyl alcohol the (4*S*)-4-[amine-(Boc)]thiazolidines derivatives were obtained. The compounds **6b** and **7b** have the defined configuration at C-2 (2*R*), due to the N-protection step. This high reactivity of isocyanates was utilized in the reaction with (*R*)-phenylethylamine in order to afford the asymmetrical urea **8a** (Scheme 2). The spectroscopic data of structures **2–4** and **6–8** are reported in the Table. IR and elemental analysis are reported in the experimental section.

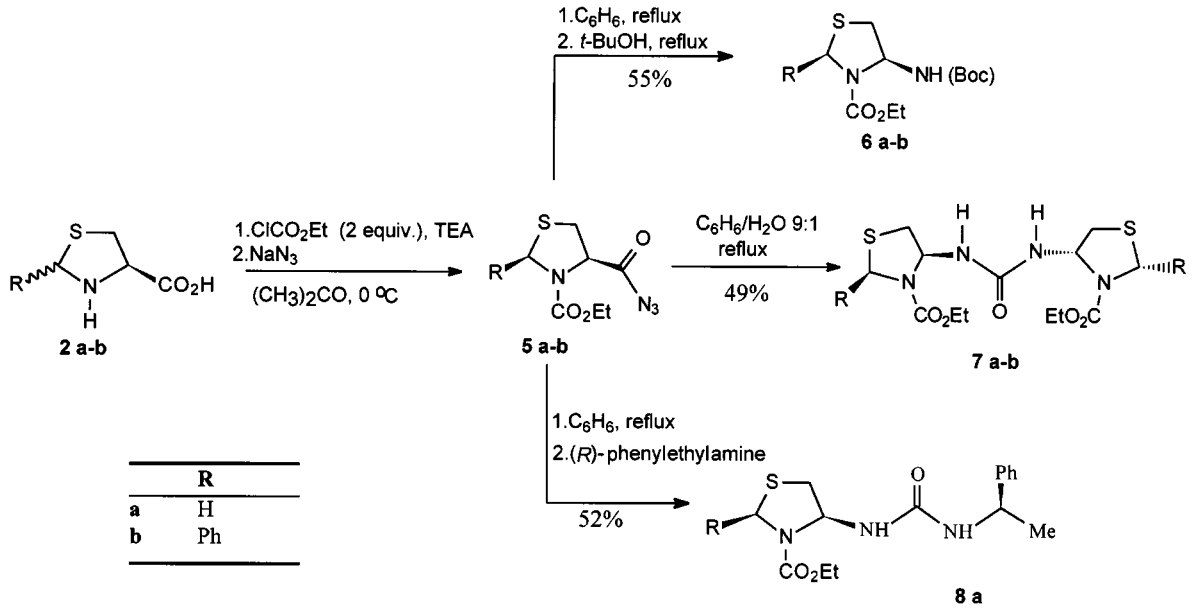
Ureas and amine derivatives analogues to the compounds **6**, **7** were prepared in good yields using our methodology from the (4*R*)-3-(Boc)-4-carboxylic acids **3a,b**. The spectroscopic data relevant to products obtained are in agreement with their structures.

The compounds obtained from the Curtius rearrangement in this work were isolated without any evidence of racem-

Table Thiazolidines and Thiazolidines Derivatives Prepared[a]

Product	Yield[b] (%)	mp (°C)	^{1}H NMR ($CDCl_3$) δ, *J*(Hz)	^{13}C NMR($CDCl_3$) δ
2b[c,d]	90	>166 (dec)	Isomer A: 3.08 (*dd*,1H, J_{ab}=10.00, J_{ax}=8.40), 3.38 (dd,1H, J_{ba}=10.00, *J*=7.20), 3.90 (dd,1H, *J*=8.40, *J*=7.20), 5.50 (s,1H), 7.30–7.51(m,5H, arom.) Isomer B: 3.14 (dd,1H, *J*=10.40, *J*=4.80), 3.30 (dd,1H, *J*=10,40, *J*=7.0) 4.24 (dd,1H, *J*=7.20, *J*=4.80) 5.68 (*s*,1H,) 7.30–7.51 (m, 5H, arom.)	38.0, (38.5), 64.9, (65.5), 71.1, (71.8), 126.9, 127.3, 128.2, 128.5, 127.6, (128.3) ,138.9, (141.2), 172.3, (173.0).
3a[e]	86	131–132	(s,9H), 3.27 (*m*,2H), 4.44 (*d*,1H, *J*=8.80), 4.62 (*d*,1H, *J*=8.80), 4.81 (sl,1H), 9.37 (sl,1H,OH)	28.1, 32.9(34.3), 48.2(48.9), 61.3, 81.7, 153.1(153.7), 175.1(176.0)
3b[e]	85	>179(dec)	1.23 (s,9H), 3.26 (m,2H, J_{ax} + J_{bx} = 12.40), 4.69 (t,1H,J_{ax} + J_{bx} = 12.40), 5.96 (s,1H), 7.20 (m, 3H, Ph) 7.55 (m,2H, Ph)	27.2, 32.4, 63.5, 65.6, 80.1, 125.7, 126.4, 127.2, 140.9, 152.4, 171.3
4b	76	oil	1.11 (t,3H, *J*=7.00), 3.35 (d,2H, *J*=6.40), 4.11 (q, 2H, *J*=7.00), 4.94 (t,1H, J_{ax} + J_{bx} =12.80), 6.12 (s,1H), 7.58–7.23 (m,5H, Ph.), 9.34 (br, 1H, OH)	14.2, 32.7, 62.5, 64.3, 66.6, 126.5, 127.8, 128.3, 140.2, 154.9, 174.7
6a	55	116–119	1.86 (t,3H,*J*=7.20), 1.46 (s,9H), 2.90 (d,1H, J_{ba}=11.60),3.17 (dd,1H, J_{ab}=11.60, J_{ax}=4.80), 4.17 (q,2H, *J*=7.20), 4.43 (s,2H), 5.31(sl,1H,NH), 5.97 (m,1H)	14.4, 28.2, 38.6, 47.5, 61.9, 65.9, 79.9, 153.5, 153.8
6b[e]	51	oil	1.24 (t,3H, *J*=7.00), 1.48 (s,9H,), 2.92 (dd,1H, J_{ba} =11.80, J_{bx} = 1.80), 3.20 (dd,1H, J_{ab}=11.80, J_{ax}=4.80), 4.10 (q,2H, *J*=7.00), 5.31(br, 1H, NH), 6.03 (s,1H), 6.26 (m,1H), 7.27–7.36 (m,5H,Ph.)	14.3, 28.3, 38.4, 62.1, 65.2, 68.6, 80.2, 126.0, 127.9, 128.5, 140.0, 153.9
7a	48	179–181	1.22 (t,3H,*J*=7.10), 2.88 (d,1H, J_{ba}=11.50), 3.17 (dd,1H, J_{ab}= 11.50, J_{ax}= 4.40), 4.11 (q,2H, *J*=7.10), 4.33 (d,1H, *J*=8.80), 4.49 (d,1H, *J*=8.80), 6.04 (br,1H)	13.8, 36.9, 46.5, 61.5, 67.0, 153.5, 155.0
7b	41	177–180	1.01 (t,3H, *J*=7.20), 2.93 (d,1H,J_{ba}=11.80), 3.29 (dd,1H, J_{ab} =11.80, J_{ax}=5.0), 3.86 (q,2H, *J*=7.20), 5.97 (*s*,1H,), 6.22 (br,1H,CH), 7.22–7.46 (m,5H,Ph)	14.1, 38.2, 62.1, 65.7, 69.2, 126.5, 127.9, 128.3, 139.9, 154.6, 156.0
8a[c]	52	193–195	1.18 (t,3H, *J*=7.00), 1.30 (d,3H, *J*=6.80), 2.78 (d,1H, J_{ab}=11.40) 3.12 (dd,1H, J_{ab}=11.40 , J_{ax}=4.80), 4.06 (q,2H, *J*=7.00), 4.29 (d,1H, *J*=8.80), 4.42 (d,1H, *J*=8.80), 4.74 (m,1H,NH), 5.91(t,1H, J_{ax} + J_{bx}=11.80), 6.43 (m,1H), 7.19–7.30 (m,5H,Ph.)	14.4, 23.3, 37.6, 46.9, 48.4, 61.2, 65.7, 125.5, 126.5, 128.2, 145.3, 153.1,155.6

[a] All compounds gave satisfactory elemental analyses: C ± 0.16, H ± 0.08, N ± 0.14.
[b] yield of pure isolated product.
[c] NMR spectrum in DMSO-d_6.
[d] Obtained as a 45:55 A/B diastereoisomeric mixture.
[e] NMR ^{1}H spectrum adquired at 50°C.



Scheme 2

ization or epimerization. These results showed the versatility of this methodology in convenience and yield as well as in number of steps.

Solvents were purified according to standard procedures.[13] Mps were determined with a Microquímica APF-301 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 and DPX 400 spectrometers in DMSO-d_6 and $CDCl_3$/TMS. Elemental analyses were carried out on a Foss Hareaus Vario CHN-standard analyser. IR spectra were recorded on Perkin-Elmer 1310 and Bruker IFS 28. Capillary GC analyses were performed in a Carlo Erba Mega Series 5400 chromatograph equipped with a split/splitless injector and FID detector.

(4*R*)-1,3-Thiazolidine-4-carboxylic Acid (2a)

L-Cysteine hydrochloride (**1**) (19.0 mmol, 3.0 g) was dissolved in H_2O (100 mL) and commercial 37% formaldehyde (2.5 mL, 28.5 mmol) was added. The mixture was allowed to stand overnight (15h) at r.t. Then, pyridine (2.5 mL) was added which resulted in the formation of a precipitate. EtOH (5 mL) was added and the mixture was stirred and filtered. The product was recrystallized from H_2O to give **2** (2.15g, 85%) as long colorless needles, which melt with decomposition at 207–211 °C.

IR (KBr): ν = 3463, 3044, 2344, 1631 cm^{-1}.

$C_4H_7NO_2S$	Calc.	C	36.08	H	5.30	N	10.52
(133.2)	Found		35.70		5.38		10.67

(4*R*)-2-Phenyl-1,3-thiazolidine-4-carboxylic Acid (2b)

L-Cysteine hydrochloride (12.7 mmol, 2.0g) and sodium acetate (14 mmol) were dissolved in H_2O (17 mL). To this solution was added (12.72 mmol, 1.35g) of benzaldehyde and dissolved in EtOH (18 mL). On shaking vigorously precipitation occurred. After refrigeration overnight the product was separated by filtration, washed with EtOH (10 mL) to give **2b** (2.38g, 90%); mp 166–171 °C.

IR (KBr): ν = 2962, 2744, 2614, 2466, 1570 cm^{-1}.

$C_{10}H_{11}NO_2S$	Calc.	C	57.40	H	5.30	N	6.70
(209.3)	Found		57.37		5.46		6.71

(4*R*)-3-(Boc)-1,3-thiazolidine-4-carboxylic Acid (3a,b)

To a stirred solution of thiazolidine (10 mmol) in dioxane (20 mL), H_2O (10 mL) and Na_2CO_3 1M (10 mL) cooled in an ice-water bath was added di-*tert*-butyl dicarbonate (11 mmol, 2.4 g), the stirring was continued at r.t. for 20 h. The solution was concentrated in vacuo to about 10 to 15 ml and cooled in an ice–water bath covered with EtOAc (30 mL) and acidified with a dilute solution of $KHSO_4$ until pH 2–3. The aqueous phase was extracted with EtOAc (3x15 mL). The organic layer was washed with H_2O (2x30 mL), dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was recrystallized with EtOAc/hexane, yielded **3a** (2.0g, 86%); m.p 131–32ºC and **3b** (2*R*,4*R*) isomer (85%); mp 177–180 °C.

IR (KBr): ν = 3018, 2936, 1750, 1637 cm^{-1}.

3a: $C_9H_{15}NO_4S$	Calc.	C	46.34	H	6.49	N	6.01
(233.3)	Found		46.56		6.54		5.97

IR (KBr): ν = 2980, 1740, 1660, 1640 cm^{-1}.

3b:(2*R*,4*R*) $C_{15}H_{19}NO_4S$	Calc.	C	58.23	H	6.19	N	4.53
(309.4)	Found		58.43		6.14		4.51

(2*R*,4*R*)-3-(Ethoxycarbonyl)-2-phenyl-1,3-thiazolidine-4-carboxylic Acid (4b)

To a suspension of **2b** (5 mmol, 1.05 g) in acetone (10 mL) cooled to 0 °C (ice-salt bath) was added TEA (9.56 mmol, 1.74 mL). The mixture was stirred at r.t. for 15 min. To this mixture at 0 °C was added dropwise ethyl chloroformate (12.9 mmol, 1.16 mL). The solution was stirred at r.t. for 2 h and the solvent was removed in vacuo. The residue was treated with H_2O (25mL) and then with HCl 10% until pH 3 and extracted with EtOAc. The organic layer was washed with H_2O, dried (Na_2SO_4) and the solvent was removed in vacuo yielded **4b** (76%) as a thick oil.

IR (KBr): ν = 3450, 2933, 1701 cm^{-1}.

Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-1,3-thiazolidine-3-carboxylates (6a,b)

To a suspension of **2a** (10 mmol, 1.33g) or **2b**(10 mmol, 2.09g) in H_2O (2 mL) and acetone (20 mL) cooled to 0°C (ice–salt bath) was added a solution of TEA (23.6 mmol, 2.38g) in acetone (15 mL). While maintaining the temperature at 0 °C a solution of ethyl chloroformate (25.6 mmol, 2.90g) in acetone (10 mL) was added slowly. The solution was stirred at 0 °C for 45 min. and then a solution of sodium azide (15 mmol, 1.0g) in H_2O (3 mL) was added dropwise. The mixture was stirred at 0 °C for 5 h, poured into an excess of ice water and extracted with Et_2O (3x30 mL). The combined Et_2O extracts were dried with (Na_2SO_4). the solvent was removed in vacuo and the residue (acyl azide) was dissolved in dried benzene (20 mL). The benzene solution was refluxed for 5 h and the solvent was removed in vacuo. The residue was dissolved in anhyd *tert*-butanol and refluxed for 40 h. The solvent was removed and the residue was purified by column chromatography on silica gel (Aldrich, 70–230 mesh) using 1% $CHCl_3$/MeOH as eluent.

6a: yield (1.51g, 55%); mp 116–19ºC.

IR (KBr): ν = 3329, 2977, 1720, 1682, 1517 cm^{-1}

$C_{11}H_{20}N_2O_4S$	Calc	C	47.81	H	7.29	N	10.14
(276.4)	Found		47.79		7.16		10.13

6b (2*R*,4*S*) isomer yield (1.80g, 51%) as a oil

IR (KBr): ν = 3339, 3062, 1693, 1601 cm^{-1}.

***N*,*N*'-Di[(4*S*)-3-(ethoxycarbonyl)-4-thiazolidinyl]ureas (7a,b)**

To a suspension of **2a** and **2b** (10 mmol) in H_2O (2 mL) and acetone (20 mL) cooled to 0 °C (ice–salt bath) was added a solution of TEA (23.6 mmol, 2.38g) in acetone (15 mL). While maintaining the temperature at 0 °C a solution of ethyl chloroformate (25.6 mmol, 2.90g) in acetone (10 mL) was added slowly. The solution was stirred at 0 °C for 45 min. and then a solution of sodium azide (15 mmol, 1.0g) in H_2O (3 mL) was added dropwise. The mixture was stirred at 0 °C for 5 h, poured into an excess of ice water and extracted with Et_2O (3x30 mL). The combined Et_2O extracts were dried (Na_2SO_4), the solvent was removed in vacuo and the residue (acyl azide) was dissolved in benzene/H_2O 9:1 (20 mL). The solution was refluxed for 20 h and the solvent was remove in vacuo, afforded a solid residue that was recrystallized in CH_2Cl_2/Et_2O, **7a** (1.82g, 48%); mp 179–181ºC and **7b** (2*R*,4*S*) isomer (2.18g 41%); mp 177–180ºC**.**

IR (KBr): ν = 3320, 2970, 1700, 1630, 1560 cm^{-1}.

7a $C_{13}H_{22}O_5N_4S_2$	Calc.	C	41.26	H	5.86	N	14.80
(378.5)	Found		41.39		5.88		15.30

7b: (2*R*,4*S*) isomer

IR (KBr): ν = 3340, 2970, 1700, 1645 cm^{-1}.

$C_{25}H_{30}O_5N_4S_2$	Calc.	C	56.59	H	5.70	N	10.56
(530.7)	Found		56.60		5.73		10.38

***N*-[(1*R*)-1-phenylethyl]-*N*'-[(4*S*)-3-(ethoxycarbonyl)-4-thiazolidinyl]urea (8a)**

To a suspension of **2a** (10 mmol, 1.33g) or **2b**(10 mmol, 2.09g) in H_2O (2 mL) and acetone (20 mL) cooled to 0 °C (ice–salt bath) was added a solution of TEA (23.6 mmol, 2.38g) in acetone (15 mL). While maintaining the temperature at 0 °C a solution of ethyl chloroformate (25.6 mmol, 2.90g) in acetone (10 mL) was added slowly. The solution was stirred at 0 °C for 45 min. and then a solution of sodium azide (15 mmol, 1.0g) in H_2O (3 mL) was added dropwise. The mixture was stirred at 0 °C for 5 h, poured into an excess of ice water and extracted with Et_2O (3x30 mL). The combined Et_2O extracts were dried (Na_2SO_4), the solvent was removed in vacuo and the residue (acyl azide) was dissolved in anhyd benzene (20 mL). The benzene solution was refluxed for 5 h and (*R*)-phenylethylamine (10 mmol, 1,20g) was added, occurring the formation of a white solid that was recrystallized by ethyl alcohol afforded **8a** (1.68g, 52%); mp 193–95ºC.

IR (KBr): ν = 3341, 3302, 1711, 1632, 1559 cm^{-1}.

$C_{15}H_{21}N_3O_3S$	Calc.	C	55.71	H	6.54	N	12.99
(323.4)	Found		55.41		6.38		13.20

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