New aspects of the formation of 2-substituted thiazolidine-4-carboxylic acids and their thiohydantoin derivatives

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Abstract

Aromatic aldehydes reacted readily with (*R*)-cysteine in boiling acidified methanol to give diastereomeric mixtures of the corresponding 2-(aryl substituted) thiazolidine-4-carboxylic acids. 4-Nitrobenzaldehyde under similar conditions afforded one isomer of 2-(4-nitrophenyl)-thiazolidine-4-carboxylic acid, which epimerized in the NMR solvents into a diastereomeric mixture. 2-Nitrobenzaldehyde reacted with (*R*)-cysteine to afford 3,5-bis-(2-nitrophenyl)-tetrahydro-1*H*-thiazolo[3,4-*c*]oxazol-1-one as the sole product, which collapsed in the NMR solvent into a diastereomeric mixture of the thiazolidine-4-carboxylic acids. The thiazolidine derivatives reacted smoothly with phenyl isothiocyanate to give single isomers of the corresponding thiohydantoins.

Keywords: Thiazolidine-4-carboxylic acids, thiohydantoins, cyclization, epimerization

Introduction

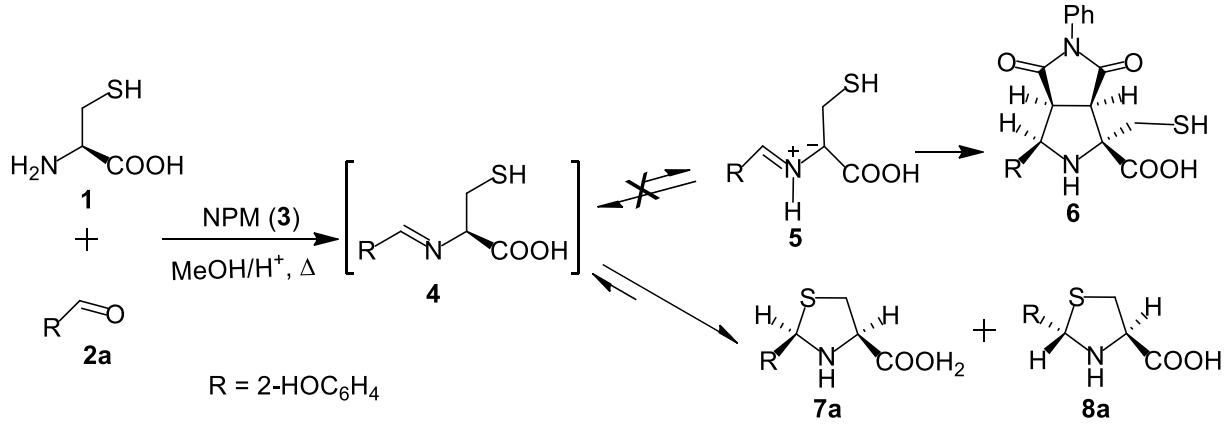
Penicillins are the class of antibiotic drugs contain a β-lactam nucleus fused to thiazolidine-4-carboxylic acid derivatives (TCDs).[1] The thiazolidine-4-carboxylic acid core used in biology as a pseudo-/thio-proline or bioisostere of proline to improve the desired biological or physical properties of a compound without making significant changes in the chemical structure.[2-7] TCDs exhibit a broad spectrum of anticancer activities[8-12] against, e.g. liver,[13,14] breast,[13-15] colon,[13,16] prostate,[17] endometrial[13] and melanoma[17] cell lines. In the same vein, TCDs are used as, e.g. antimalarial,[18,19] selective Na^+/Ca^{2+} exchange inhibitors,[20] immunostimulating agents,[21] tyrosinase inhibitors,[22] influenza A neuraminidase inhibitors,[23] antitubercular,[24] HIV-1 protease inhibitors[2,25] and ACE inhibitors.[26] Furthermore, TCDs were introduced as versatile scaffolds in the syntheses of natural products, i.e. (+)-biotin,[27,28] (+)-lyngbyabellin M,[29] (+)-hyalodendrin,[30] prepiscibactin[31] and dehydroluciferin.[32] Glutathione is a tripeptide works as a cellular protective agent and cannot

be used as a drug because it does not enter the living cells.[33] The vital amino acid building block in the *in vivo* synthesis of glutathione is (*R*)-cysteine, which cannot be supplemented directly due to toxicity and instability problems.[33,34] TCDs work as (*R*)-cysteine prodrugs[33,35] which metabolize intracellularly to release (*R*)-cysteine to stimulate glutathione synthesis. Straightforward formation of TCDs opens the door for this process to be used for detection of cysteine amino acid and *N*-terminal cysteines[36] and also for estimation/binding of aldehydes.[37]

The aim of this work is to use acidified methanol as a solvent in the preparation of some TCDs and to shed some light on the mechanism of their formation, and their conversion into the corresponding diastereospecific thiohydantoins.

Results and Discussion

The reaction of (*R*)-cysteine (**1**), salicylaldehyde (**2a**) and *N*-phenylmaleimide (**3**) (NPM, a reactive dipolarophile) in acidified methanol under reflux failed to give the expected cycloadduct **6**,[38] and instead gave a 98% yield of the well known (2*RS*)-(2-hydroxyphenyl)thiazolidine-(4*R*)-carboxylic acids (**7a**) and (**8a**) in a 1.5:1 ratio, respectively. It is worth mentioning that using acidified methanol gave a better yield and an opposite diastereomeric ratio compared to the previously reported results[39] (Table, entry a). This result encouraged us to study the diastereoselectivity in the formation of 2-(substituted)thiazolidine-4-carboxylic acids by using our conditions.

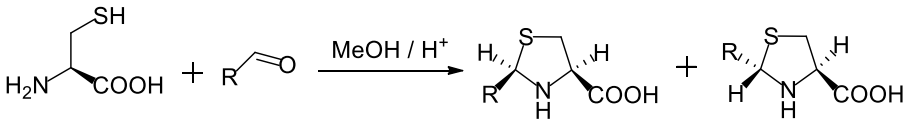


Scheme 1. The competition between cycloaddition and cyclization.

It seems that the Schiff's base **4** undergoes cyclization in such case much faster than the generation of azomethine ylide **5** and this could be mainly attributed to the bigger size and softer nature of the sulfur atom. The reaction starts by the formation of imine **4** which suffers an intramolecular nucleophilic attack by the thiol group from either side to furnish a diastereomeric mixture of 2-(substituted)thiazolidine-4-carboxylic acids.[40,41] The isomerization at C-4 of the thiazolidine *via* deprotonation/protonation is ruled out based on spectroscopic data (*vide infra*). It

is believed that, under our conditions, the generation of azomethine ylide has not been formed and hence the chirality at C-4 remained unchanged. Heating under reflux a mixture of (*R*)-cysteine (**1**) and formaldehyde (**2b**) in acidified aqueous methanol (MeOH/H_2O/AcOH 1:1: drops) gave an 84% yield of thiazolidine-(4*R*)-carboxylic acid (**7b**) (Entry b).

Table. Formation of 2-(substituted)thiazolidine-4-carboxylic acids



1 **2** **7** **8**

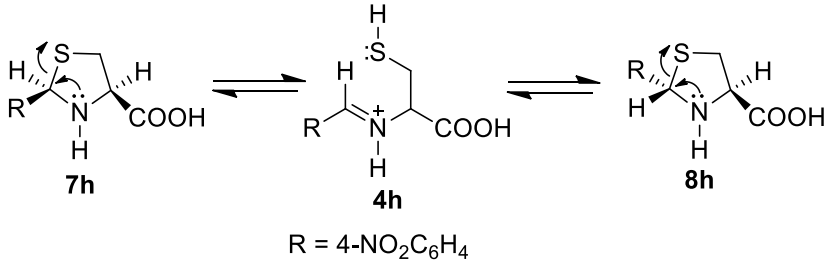
Entry	R	Yield (Lit.)	Ratio **7**:**8**[i] (Lit.)[ii]
a	2-HOC_6H_4	98[38] (78)[39]	1.5:1[38] (1:2.3)[39]
b	H	84 (82,[39] 98[42])	-
c	Ph	88 (89,[43] 71[42])	2:1 (2.3:1,[43] 1:1.2[42])
d	4-HOC_6H_4	89 (86,[42] 91[39])	3:1 (1:1.1,[42] 1:1.9[39])
e	2-$MeOC_6H_4$	75 (65,[43] 83[39])	2:1 (1:1.5,[43] 1:2.7[39])
f	4-ClC_6H_4	93 (75,[43] 73[39])	1.4:1 (19:1,[43] 1:1.9[39])
g	3-$NO_2C_6H_4$	92 (80[39])	2:1 (1:1[39])
h	4-$NO_2C_6H_4$	89 (90,[42] 80[43])	100:0[iii] (1.9:1,[42] 1:19[43])

[1]H-NMR spectra were recorded in: (*i*) $CDCl_3$/TFA, (*ii*) DMSO-d_6, (*iii*) $CDCl_3$/CD_3OD

Furthermore, refluxing an equimolar mixture of (*R*)-cysteine (**1**) and benzaldehyde (**2c**) as the carbonyl component in acidified methanol gave an 88% yield of 2-phenylthiazolidine-4-carboxylic acid (**7c**) and (**8c**) as an isomeric mixture in a 2:1 ratio, respectively (Entry c). The pure configuration of both diastereomers **7c** and **8c** was assigned on the basis of the experimental NOE data which supported the relationship between the substituents at C-2 and C-4 to be *cis*-**7c** and *trans*-**8c**. Thus, in the case of **7c**, irradiation of 2-H gave 3.8 and 3.7% enhancement for 4-H and 5-Ha protons, respectively. Also, irradiation of 4-H showed 3.1 and 1.4% enhancement of 2-H and 5-Ha protons, respectively. However, in the case of **8c**, irradiation of 2-H and 4-H protons gave no effect across the ring.

Aryl aldehydes **2d-g** reacted with (*R*)-cysteine (**1**) under the same conditions to produce diastereomeric mixtures of 2-substituted thiazolidine-4-carboxylic acids **7d-g** and **8d-g** in 75-93% yield (Entries d-g). It is worth noting that the diastereomeric ratio depends on the NMR solvent. Thus, the [1]H-NMR spectrum of the isomeric mixture **7f** and **8f** in $CDCl_3$/CD_3OD showed a 2.5:1 ratio, respectively, whereas in $CDCl_3$/TFA, the isomeric ratio of **7f** and **8f** was 1.4:1, respectively. This result also confirmed that the epimerization process at C-2 is solvent and pH dependent.[44,45] The recorded NOE data of **7f** and **8f**, yet again, supported the *cis*-relationship in the case of the major isomer **7f** and *trans*-relationship of the minor isomer **8f** (see experimental).

Surprisingly, the use of 4-nitrobenzaldehyde (**2h**) as the carbonyl component lead to the formation of 2-(4-nitrophenyl)thiazolidine-4-carboxylic acid (**7h**) as the only product in an 89% yield (Entry h). The stereochemistry of **7h** was established on the basis of its spectral data (see experimental and chart 1a). Standing compound **7h** in the NMR solvent ($CDCl_3/CD_3OD$) for 20min, 7h and 24h at room temperature gave an isomeric mixture of **7h** and **8h** in 21:1, 3:1 and 1.4:1 ratios, respectively (Chart 1b-1d). Extending the time for 48h (Chart 1e) under the same conditions afforded a 1:1 ratio and no further change was noticed even after one week. It is believed that the obtained isomer **7h** in solution would be in equilibrium with Schiff's base **4h**, which suffers a nucleophilic attack by the thiol group from the opposite side to give the other cyclization product **8h** (Scheme 2). Repeating the ^{1}H-NMR experiment for compound **7h** in a different solvent ($CDCl_3$/TFA) showed immediately an isomeric mixture of **7h** and **8h** in a 2:1 ratio, respectively. It is obvious that the presence of TFA accelerates the epimerization rate, and the unshared pair of electrons on the thiazolidine nitrogen drives the epimerization process.



Scheme 2. Epimerization of **7h** into **8h** *via* ring opening and recyclization.

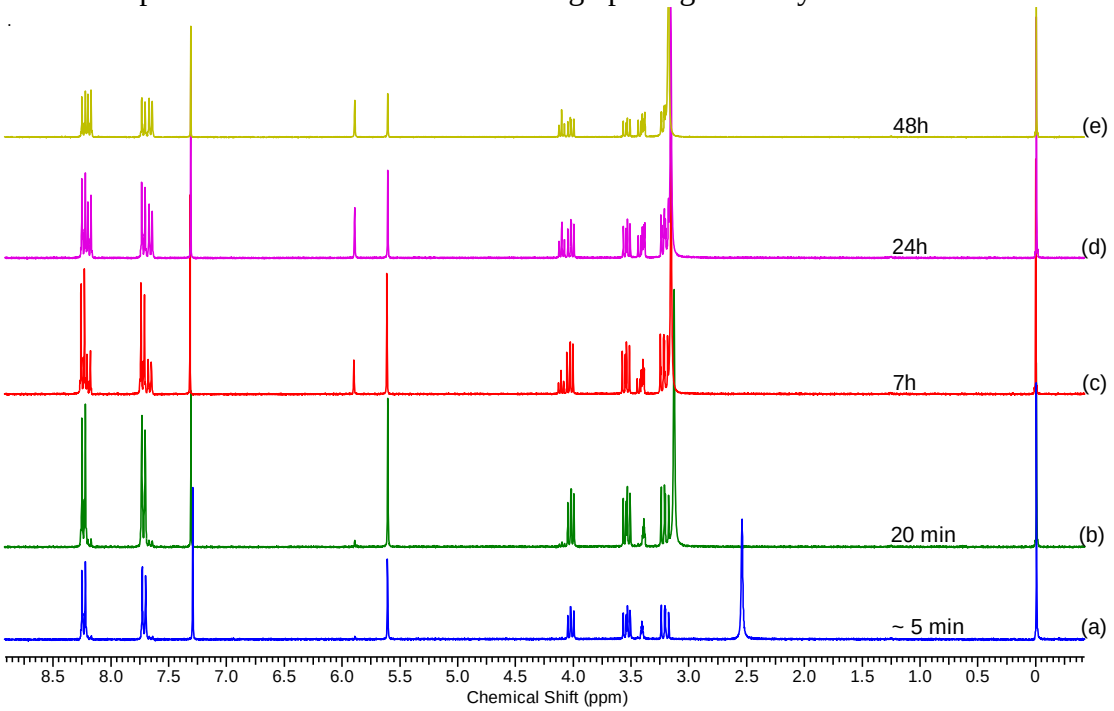
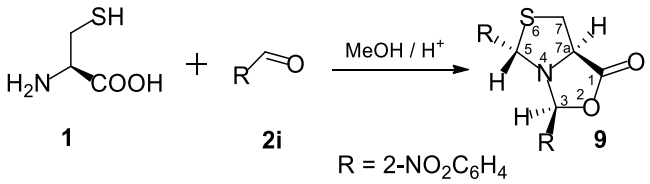


Chart 1. ^{1}H-NMR ($CDCl_3/CD_3OD$) experiments illustrating the epimerization of **7h.**

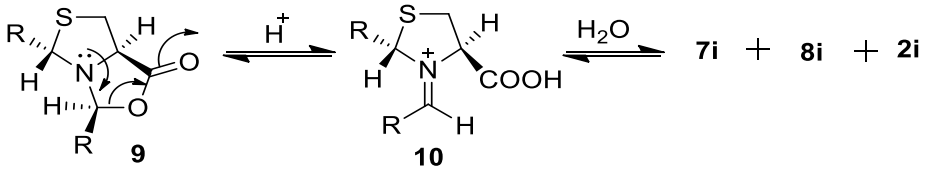
On the other hand, (*R*)-cysteine (**1**) reacted with 2-nitrobenzaldehyde (**2i**) as the carbonyl component under the same conditions to give a 46% yield of 3,5-bis(2-nitrophenyl)tetrahydro-1*H*-thiazolo[3,4-*c*]oxazol-1-one (**9**) as the sole product (Scheme 3). The obtained bicyclic compound is attributed to the high reactivity of the aldehyde and the steric congestion, which facilitate the formation of the second oxazolone ring.

The stereochemistry of **9** was established on the basis of its spectral data (see experimental and Chart 2a). The ^{1}H-NMR ($CDCl_3$/CD_3OD) sample of **9** was left at room temperature for 48h, after which time traces of the *trans*-thiazolidine-4-carboxylic acid derivative **8i** was observed together with 2-nitrobenzaldehyde in 8:1:1 ratio, respectively (Chart 2b). The ^{1}H-NMR studies of the obtained compound **9** in a different solvent ($CDCl_3$/TFA) lead to a diastereomeric mixture of 2-(2-nitrophenyl)thiazolidine-4-carboxylic acids (**7i**) and (**8i**) in a 1:1 ratio (Scheme 4). Accordingly, 2-nitrobenzaldehyde was observed and supported the suggested mechanism in scheme 4.



Scheme 3. Synthesis of 3,5-bis(2-nitrophenyl)tetrahydro-1*H*-thiazolo[3,4-*c*]oxazol-1-one **9.**

Going through the literature revealed that the diastereomeric ratio depends on (i) the conditions at which the reaction was conducted, and (ii) the ^{1}H-NMR solvent used.[39-43] It seems that using our optimal conditions in the synthesis of 2-(substituted)thiazolidine-4-carboxylic acids affects both the experimental yield and diastereomeric ratio (Table). Thus, using such conditions afforded diastereomeric mixtures of **7** and **8** in 75-98% yields, and the *cis*-diastereomer **7** was obtained as the major product in all cases. Interestingly, the *cis*-diastereomer **7h** was obtained as the sole product, and it was also lucky for us to separate thiazolo[3,4-c]oxazol-1-one **9** as the only product with no trace of the thiazolidine derivatives.

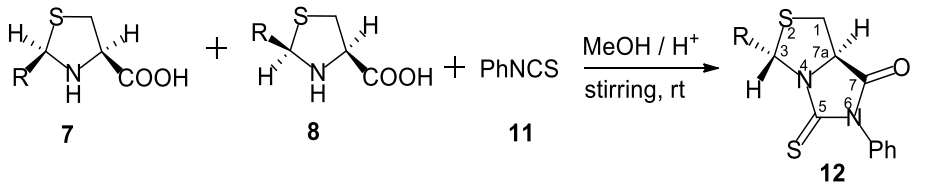


Scheme 4. Collapse of **9** into thiazolidine-4-carboxylic acids **7i** and **8i.**

Thiohydantoins are common skeletons in organic synthesis and have a broad spectrum of biological applications.[46,47] Annulation of hydantoin ring to thiazolidine derivatives showed anticancer activity (modulator of P53 activity)[11] and assumed to treat Alzheimer via interaction

with amyloid β peptide (Aβ 25-35).[48] It seemed to us that annulation of thiohydantoin moiety to thiazolidines might have biological applications.

Lalezari[49] and Balalaie[50] have reported two different methods for obtaining 6-phenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7-one (**12b**) in 86 and 97% yields, respectively. However, the same product was formed in 95% yield by using our simple and convenient procedure. Thus, stirring an equimolar mixture of thiazolidine-4-carboxylic acid (**7b**) and phenyl isothiocyanate (**11**) in acidified methanol at room temperature gave **12b** (Scheme 5). The stereochemistry of **12b** was assigned according to its spectral data and by comparison with the previously reported data.[50]



(**b**) R = H, (**c**) R = Ph, (**d**) 4-HOC_6H_4, (**e**) 4-$OMeC_6H_4$, (**f**) 4-ClC_6H_4, (**g**) R = 3-$NO_2C_6H_4$, (**h**) R = 4-$NO_2C_6H_4$

Scheme 5. Formation of thiohydantoins **12.**

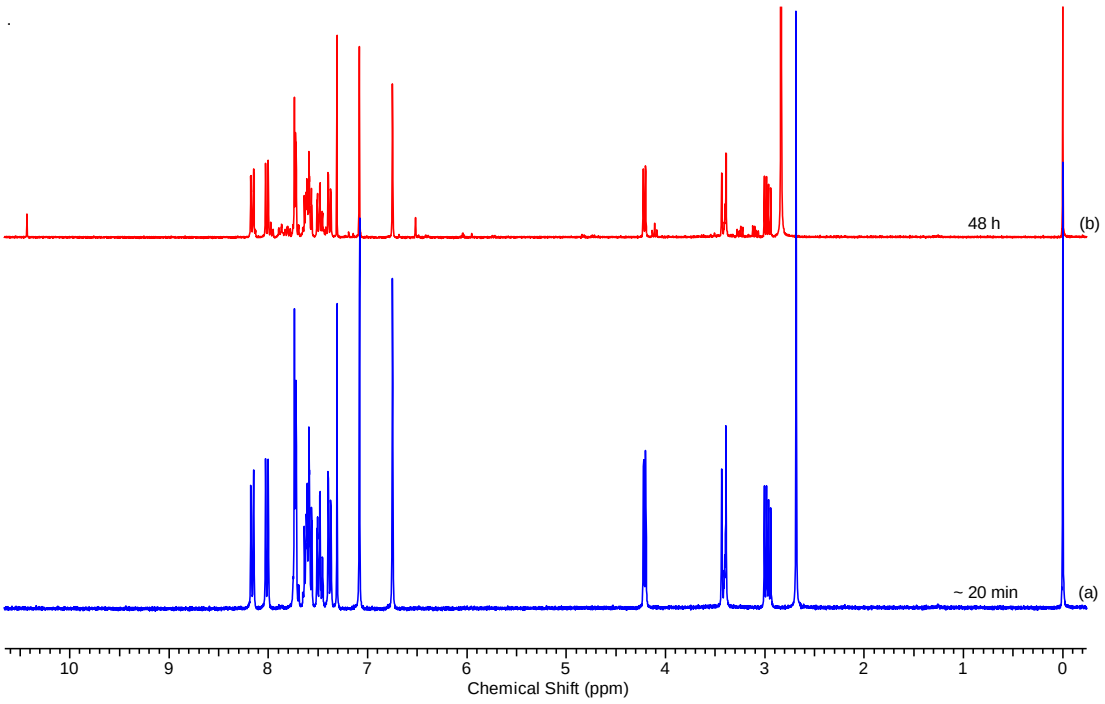


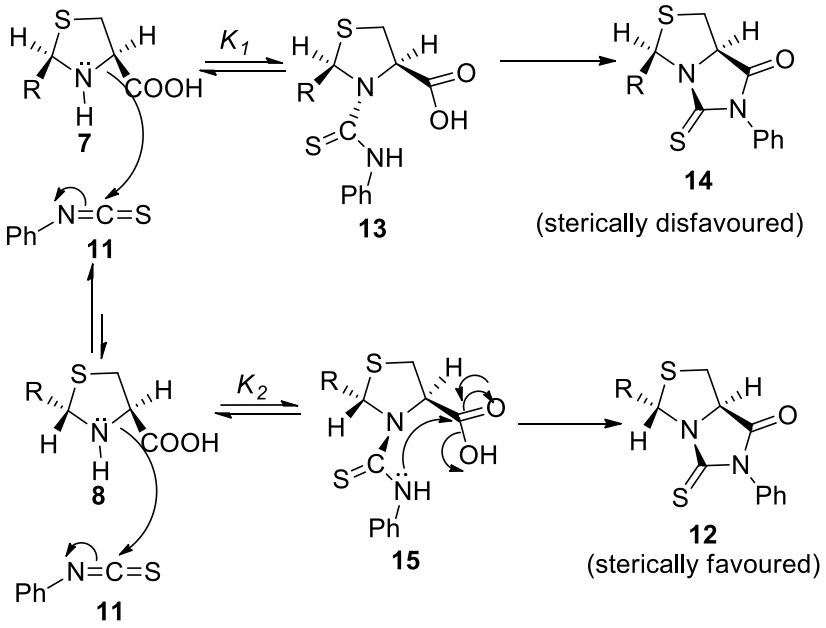
Chart 2. ^{1}H-NMR spectra ($CDCl_3$/CD_3OD) of **9.**

Similarly, the reaction of an isomeric mixture of **7c** and **8c** (R = Ph) with **11** gave 3,6-diphenyl-5-thioxo-tetrahydro-imidazo[1,5-*c*]thiazol-7-one **12c** as the only product in a 97% yield. However, the diastereomeric mixtures of **7d-h** and **8d-h** reacted in the same manner with **11** to afford

thiohydantoins **12d-h** as the only products in excellent yields (91-99%). The stereochemistry of these thiohydantoins **12** was confirmed based on the NOE data of **12c,f** (see experimental). Thiohydantoins **12** are stable and no sign of isomerization at C-3 was observed and this could be mainly attributed to the presence of thioxo-group adjacent to N-4. Our results comply with the literature work, which showed that the *N*-protection of thiazolidine-4-carboxylic acid prevented the epimerization at C-2.[36]

The possible mechanism for thiohydantoins **12** started through the preferential attack of the thiazolidine nitrogen of **7** on phenyl isothiocyanate (**11**) from the opposite face to give the favourable thiourea derivatives **13 (**K_1>>K_2) (Scheme 6).[40,51] However, such conformation of **13** prevents the formation of *cis*-thiohydantoins **14** and alternatively, the intermediate **15** would consequently lead to the *trans*-thiohydantoins **12**.

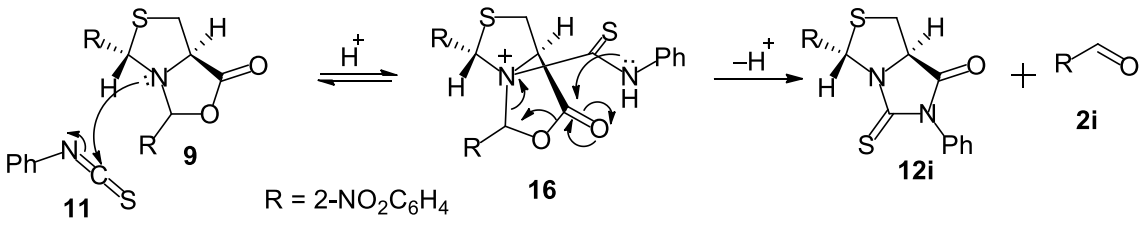
Györgydeák *et al*.,[52] reported a different mechanism for the synthesis of thiohydantoin-fused thiazolidines, assuming a break-down of C-2–N-3 bond in the thiourea intermediate to produce a ring open intermediate with a positively charged sulfur in order to change the stereochemistry at C-2. However, the same authors have refused a similar mechanism suggested by referees during their early work on *N*-acetylthiazolidines.[41] We believe that our proposed mechanism (*vide supra*) would serve well to rationalise the stereochemistry at C-3 in the obtained thiohydantoins.



Scheme 6. Plausible mechanism for thiohydantoins **12.**

Interestingly, reacting 3,5-bis-(2-nitrophenyl)dihydro-hiazolo[3,4-*c*]oxazolidine-1-one (**9**) with phenyl isothiocyanate **(11**) under the same conditions gave a 95% yield of 3-(2-nitrophenyl)-6-phenyl-5-thioxo-tetrahydro-imidazo[1,2-c]thiazol-7-one (**12i**) as the only product according to the suggested mechanism (Scheme 7). In the ^{1}H-NMR spectra of thiohydantoins **12**, H-3 appeared

deshielded and this could be attributed to the presence of thioxo-group on N-4 and the almost perpendicular dihedral angel relationship[49] between the thiazolidine ring and the C-3 aryl substituent. This arrangement positioned the H-3 proton in the deshielding area of the aryl group at C-3.



Scheme 7. Possible mechanism for thiohydantoin **12i.**

Conclusions

2-Substituted thiazolidine-4-carboxylic acids were easily obtained as nonseparable diastereomeric mixtures *via* the reaction of aldehydes with (*R*)-cysteine in acidified methanol. 4-Nitro-benzaldehyde gave only one isomer which epimerized gradually in the NMR solvent ($CDCl_3/CD_3OD$) to a mixture of diastereomers. 2-Nitrobenzaldehyde reacted with (*R*)-cysteine to afford 3,5-bis(2-nitrophenyl)tetrahydro-1*H*-thiazolo[3,4-c]oxazol-1-one (**9**) as an exclusive product which collapsed in the NMR solvents to a diastereomeric mixture of thiazolidines **7i** and **8i**. The equilibrium between the two diastereomers is time and pH dependent. The obtained thiazolidine derivatives reacted smoothly with phenyl isothiocyanate to afford the corresponding thiohydantoins.

Experimental Section

General technical data

Thin layer chromatography (TLC) was carried out on aluminium plates pre-coated with silica gel 60 F254 (Merck), and were visualised using ultraviolet light and/or aqueous $KMnO_4/I_2$. Proton nuclear magnetic resonance spectra were recorded at 300MHz on Bruker DPX300 and Oxford NMR instruments. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane (δ = 0.00) and coupling constants are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, br = broad, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, t = triplet, td = triplet of doublets. ^{13}C-NMR spectra were recorded at 75 MHz on a Bruker DPX300 instrument and chemical shifts are reported in parts per million (ppm). ^{1}H-NMR peak assignments are mainly based on DEPT135, COSY, HMQC and HMBC spectral data. Accurate masses were obtained using a Bruker Daltonics micrOTOF spectrometer. Mass spectra were recorded at 70ev

using Shimadzu GCMS-QP1000EX mass spectrometer. The IR spectra were measured on Shimadzu IR instrument. Melting points (m.p.) were determined on a Kofler hot-stage apparatus and are uncorrected. All compounds are named according to the IUPAC system using the ChemBioDraw Ultra 12.0 program.

Method (A): Synthesis of 2-substituted thiazolidine-4-carboxylic acids

Stirring with heating under reflux an equimolar mixture (0.01 mol) of the carbonyl component **2** and (R)-cysteine **1** in acidified methanol (10:0.1 v/v MeOH/AcOH, 10 mL) for an appropriate time. The corresponding thiazolidine derivatives precipitated out of hot solution during the reflux. The solvent was cooled, concentrated and filtered to afford the crude product which was crystallized from aqueous ethanol to give colourless amorphous solid.

Method (B): Synthesis of thiohydantoin 12

Stirring at room temperature an equimolar mixture (0.01 mol) of the thiazolidine derivatives **7** and **8** with phenyl isothiocyanate **11** in acidified methanol (10:0.1 MeOH/AcOH, 10 mL) for two days. The corresponding thiohydantoin derivative **12** precipitated out of solution then the solvent was evaporated under reduced pressure, and the resulting residue crystallized from a proper solvent.

(2*RS*,4*R*)-2-(2-Hydroxyphenyl)thiazolidine-4-carboxylic acid (7a and 8a). The reaction was carried out according to general procedure (method A) using salicylaldehyde **1a** as a carbonyl component and heating for 15 minutes. An isomeric mixture of **7a** and **8a** was obtained in a 1.5:1 ratio, respectively, (0.22 g, 98%)[38] (Lit., 78%)[39]; mp 160–162 ºC. IR (KBr) 3737, 3437 (broad), 3100, 2364, 1623 cm-1: MS (m/z %): 225 (M+, 40), 180 (M-45, 13), 153 (48), 137 (53), 132 (99), 120 (37), 91 (40), 77 (100), 65 (39) and 51 (88); ^{1}H-NMR ($CDCl_3$/TFA) for the major isomer **7a**, δ: 7.69-6.93 (m, 4H, Ar-H), 6.11 (s, 1H, 2-H), 5.1 (dd, 1H, *J* 4.1 and 6.8, 4-H), 3.81 (dd, 1H, *J* 8.4 and 8.1, 5-Ha) and 3.67 (dd, 1H, *J* 5.7, 5-Hb). The minor isomer **8a**, δ: 7.69-6.93 (m, 4H, Ar-H), 6.20 (s, 1H, 2-H), 5.15 (t,1H, *J* 6.6, 4-H), 3.89 (d, 1H, *J* 7.5, 5-Ha) and 3.85 (d, 1H, *J* 7.5, 5-Hb).

(*R*)-Thiazolidine-4-carboxylic acid (7b). The reaction was carried out according to general procedure (method A) using formaldehyde **2b** as a carbonyl component in acidified aqueous methanol (5:5:0.05 MeOH/H_2O/AcOH, 10 mL) and heating for 8h. Crystallization afforded **7b** (1.12 g, 84%) (Lit., 82%,[39] 98%[42]); IR (KBr) 3046, 1585 and 1487 cm^{-1}; m/z (%) 133 (M^+, 47), 55 (100), 57 (85), 60 (48), 69 (83), 73 (57), 87 (58) and 120 (55); ^{1}H-NMR ($CDCl_3$/TFA) δ: 4.99 (dd,1H, *J* 4.5 and 6.6, 4-H), 4.70 (d,1H, *J* 10.7, 2-Ha), 4.52 (d,1H, *J* 10.7, 2-Hb), 3.62 (dd, 1H, *J* 4.5 and 12.9, 5-Ha) and 3.57 (dd, 1H, *J* 6.6 and 12.9, 5-Hb).

(2*RS*,4*R*)-2-Phenylthiazolidine-4-carboxylic acid (7c and 8c). The reaction was carried out according to general procedure (method A) using benzaldehyde **2c** as a carbonyl component and heating for 1h. An isomeric mixture of **7c** and **8c** was obtained in a 2:1 ratio, respectively, (1.84 g, 88%) (Lit., 71%,[42] 89%[43]); IR (KBr) 3421, 2963, 1480, 1137 and 857 cm^{-1}; *m/z* (ESI^+) 210.0603 (100% MH^+), 232.0 (3%, MNa^+), (Found MNa^+ 232.040196 $C_{10}H_{11}NNaO_2S$ requires 232.040270); ^{1}H-NMR ($CDCl_3$/CD_3OD) for the major isomer **7c**, δ: 7.55-7.33 (m, 5H, Ar-H), 5.55 (s, 1H, 2-H), 3.99 (dd, 1H, *J* 7.3 and 8.6, 4-H), 3.52 (dd, 1H, *J* 7.3 and 10.4, 5-Ha,) and 3.20 (dd, 1H, *J* 8.6 and 10.4, 5-Hb). The minor isomer **8c**, δ: 7.55-7.33 (m, 5H, Ar-H), 5.77 (s, 1H, 2-H),

4.27 (dd, 1H, *J* 5.6 and 7.5, 4-H), 3.45 (dd, 1H, *J* 7.5 and 10.9, 5-Ha) and 3.31 (dd, 1H, *J* 5.6 and 10.9, 5-Hb).

NOE data ($CDCl_3/CD_3OD$) for **7c**:

Irradiated protons	% Enhancement				
	2-H	4-H	5-Ha	5-Hb	Ar-H
2-H		3.82	3.72	-	4.53 (δ 7.51)
4-H	3.08		1.44	-	-

NOE data ($CDCl_3/CD_3OD$) for **8c**:

Irradiated protons	% Enhancement				
	2-H	4-H	5-Ha	5-Hb	Ar-H
4-H	-		5.44	-	5.04 (δ 7.54) 2.26 (δ 7.38)

(2*RS*,4*R*)-2-(4-Hydroxyphenyl)thiazolidine-4-carboxylic acid (7d and 8d). The reaction was carried out according to general procedure (method A) using 4-hydroxybenzaldehyde **2d** as a carbonyl component and heating for 2h. An isomeric mixture of **7d** and **8d** was obtained in a 3:1 ratio, respectively, (2 g, 89%) (Lit., 91%,[39] 86%[42]); IR (KBr) 3138, 2918, 2824, 1474, 1203 and 876; cm^{-1}; *m/z* (ESI^+) 226.05 (33% MH^+), (Found MH^+ 226.053467 $C_{10}H_{12}NO_3S$ requires 226.053241); ^{1}H-NMR ($CDCl_3/CD_3OD$) for the major isomer **7d**, δ: 7.42 (d, 2H, *J* 8.6, Ar-H), 6.86 (d, 2H, *J* 8.6, Ar-H), 5.50 (s, 1H, 2-H), 4.03 (t, 1H, *J* 7.5, 4-H), 3.53 (dd, 1H, *J* 7.5 and 10.8, 5-Ha) and 3.31 (dd, 1H, *J* 7.5 and 10.8, 5-Hb). The minor isomer **8d**, δ: 7.41 (d, 2H, *J* 8.7, Ar-H), 6.85 (d, 2H, *J* 8.7, Ar-H), 5.71 (s, 1H, 2-H), 4.36 (dd, 1H, *J* 5.6 and 7.4, 4-H), 3.54 (dd, 1H, *J* 7.4 and 11.1, 5-Ha) and 3.42 (dd, 1H, *J* 5.6 and 11.1, 5-Hb).

(2*RS*,4*R*)-2-(2-Methoxyphenyl)thiazolidine-4-carboxylic acid (7e and 8e). The reaction was carried out according to general procedure (method A) using 2-methoxy-benzaldehyde **2e** as a carbonyl component and heating for 4h. An isomeric mixture of **7e** and **8e** was obtained in a 2:1 ratio, respectively, (1.8 g, 75%) (Lit., 83%,[39] 65%[43]); IR (KBr) 3420, 2960, 1459, 1269, 1190, 846 and 793 cm^{-1}; m/z (%) 240 (MH^+, 7.88), 55 (19), 57 (16), 60 (10), 69 (14), 76 (17), 87 (11), 91 (100), 103 (12), 107 (20), 119 (47), 132 (27), 135 (18), 193 (16), 207 (7); ^{1}H-NMR ($CDCl_3$/TFA) for the major isomer **7e**, δ: 7.54-7.39 (m, 4H, Ar-H), 6.02 (s, 1H, 2-H), 5.04 (dd, 1H, *J* 3.3 and 7.9, 4-H), 3.95 (s, 3H, O-Me), 3.78 (dd, 1H, *J* 7.9 and 13.0, 5-Ha) and 3.70 (dd, 1H, *J* 3.3 and 13.0, 5Hb).

(2*RS*,4*R*)-2-(4-Chlorophenyl)thiazolidine-4-carboxylic acid (7f and 8f). The reaction was carried out according to general procedure (method A) using 4-chlorobenzaldehyde **2f** as a carbonyl component and heating for 2h. An isomeric mixture of **7f** and **8f** was obtained in a 2.5:1 ratio, respectively, (2.26 g, 93%) (Lit., 73%,[39] 75%[43]); IR (KBr) 3427, 2964, 1490, 1436, 1135 and 740; cm^{-1}; *m/z* (ESI^+) 244.0 (65% MH^+), (Found MH^+ 244.019803 $C_{10}H_{11}ClNO_2S$ requires 244.019354); ^{1}H-NMR ($CDCl_3/CD_3OD$) for the major isomer **7f**, δ: 7.48 (d, 2H, *J* 8.5, Ar-H), 7.35 (d, 2H, *J* 8.5, Ar-H), 5.51 (s, 1H, 2-H), 3.98 (dd, 1H, *J* 7.3 and 8.6, 4-H), 3.51 (dd, 1H, *J* 7.3 and 10.5, 5-Ha) and 3.19 (dd, 1H, *J* 8.6 and 10.5, 5-Hb). The minor isomer **8f**, δ: 7.44 (d, 2H, *J* 8.6,

Ar-H), 7.31 (d, 2H, *J* 8.6, Ar-H), 5.76 (s, 1H, 2-H), 4.19 (dd, 1H, *J* 5.9 and 7.2, 4-H), 3.42 (dd, 1H, *J* 7.2 and 10.7, 5-Ha) and 3.26 (dd, 1H, *J* 5.9 and 10.7, 5-Hb).

NOE data ($CDCl_3/CD_3OD$) for **7f**:

Irradiated	% Enhancement				
protons	2-H	4-H	5-Ha	5-Hb	Ar-H
2-H		2.45	-	-	1.91 (δ 7.48)
4-H	3.65		1.74	-	3.19 (δ 7.48)

(2*RS*,4*R*)-2-(3-Nitrophenyl)thiazolidine-4-carboxylic acid (7g and 8g). The reaction was carried out according to general procedure (method A) using 3-nitrobenzaldehyde **2g** as a carbonyl component and heating for 8h. An isomeric mixture of **7g** and **8g** was obtained in a 2:1 ratio, respectively, (2.34 g, 92%) (Lit., 80%)[39], IR (KBr) 3447, 1548, 1429, 1197, 808 and 697 cm^{-1}; m/z (%) 255 (MH^+ , 12), 55 (17), 57 (20), 63 (67), 66 (14), 68 (17), 70 (12), 79 (100), 86 (10), 181 (9) and 194 (10); ^{1}H-NMR ($CDCl_3$/TFA) for the major isomer **7g**, δ: 8.59-7.69 (m, 4H, Ar-H), 6.09 (s, 1H, 2-H), 5.16 (brt, 1H, *J* 5.3, 4-H) and 3.88 (brd, 2-H, *J* 6.12, 5-Ha and 5-Hb). The minor isomer **8g**, δ: 8,95-7.69 (m, 4H, Ar-H), 6.16 (s, 1H, 2-H), 5.22 (t, 1H, *J* 6.4, 4-H), 3.98 (dd, 1H, *J* 6.4 and 12.6, 5-Ha) and 3.73 (dd, 1H, *J* 6.4 and 12.6, 5-Hb).

(2*R*,4*R*)-2-(4-Nitrophenyl)thiazolidine-4-carboxylic acid (7h). The reaction was carried out according to general procedure (method A) using 4-nitrobenzaldehyde **2h** as a carbonyl component and heating for 2h. Compound **7h** was obtained as the sole diastereomer, (2.26 g, 89%); IR (KBr) 3029, 1620, 1486, 1381, 1193, 1126, 874 and 778 cm^{-1}; *m/z* (ESI^+) 255.042980 (< 10% MH^+), 299.0 (< 10%, $(M+ 2Na-H)^+$), (Found $(M+ 2Na-H)^+$ 299.007241 $C_{10}H_9N_2Na_2O_4S$ requires 299.007293); ^{1}H-NMR ($CDCl_3/CD_3OD$) δ: 8.24 (d, 2H, *J* 8.8, Ar-H), 7.72 (d, 2H, *J* 8.8, Ar-H), 5.61 (s, 1H, 2-H), 4.03 (dd, 1H, *J* 7.23 and 8.7, 4-H), 3.54 (dd, 1H, *J* 7.2 and 10.4, 5-Ha) and 3.21 (dd, 1H, *J* 8.7 and 10.4, 5-Hb). The minor isomer **8h** (^{1}H-NMR sample after 24h), δ: 8.19 (d, 2H, *J* 8.6, Ar-H), 7.66 (d, 2H, *J* 8.6, Ar-H), 5.90 (s, 1H, 2-H), 4.10 (t, 1H, *J* 6.8, 4-H), 3.42 (dd, 1H, *J* 6.8 and 10.7, 5-Ha) and 3.26 (dd, 1H, *J* 6.8 and 10.7, 5-Hb).

(3*S*,5*R*,7a*R*)-3,5-Bis-(2-nitrophenyl)tetrahydro-1*H*-thiazolo[3,4-*c*]oxazol-1-one (9). The reaction was carried out according to general procedure (method A) using 2-nitrobenzaldehyde **2i** as a carbonyl component and heating for 8h. Crystallization gave **9**, (1.78 g, 46%); IR (KBr), 3034, 1375, 1203, 1018, and 684 cm^{-1}, m/z (%) 387 (M^+, 46%), 51 (100), 133 (45), 177 (43), 263 (52), 278 (48); *m/z* (ESI^+) compound **9**, 388.0600 (19% MH^+, $C_{17}H_{13}N_3O_6S$), 797.0940 (< 5%, $(2M+Na)^+$), compound **7i**/**8i**, 277.0 (< 5%, MNa^+), (Found (MNa^+ 277.025302 $C_{10}H_{10}N_2NaO_4S$ requires 277.025349); ^{1}H-NMR ($CDCl_3/CD_3OD$) δ: 8.16 (dd, 1H, *J* 1.3 and 8.1, Ar-H), 8.02 (d, 1H, *J* 7.8, Ar-H), 7.75-7.69 (m, 2H, Ar-H), 7.65-7.56 (m, 2H, Ar-H), 7.48 (dt, 1H, *J* 1.4 and 8.0, Ar-H), 7.38 (dd, 1H, *J* 1.1 and 7.7, Ar-H), 7.08 (s, 1H, 3-H), 6.75 (s, 1H, 5-H), 4.21 (dd, 1H, *J* 0.8 and 6.5, 7a-H), 3.41 (dd, 1H, *J* 0.8 and 12.5, 7-Ha) and 2.97 (dd, 1H, *J* 6.5 and 12.5, 7-Hb).

(*R*)-6-Phenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7(3*H*)-one (12b). The reaction was carried out according to general procedure (method B) using thiazolidine **7b**. Crystallization from ethanol afforded **12b** (2.38 g, 95%) (Lit., 86%,[49] 97%[50]); m.p. 158 ºC. IR (KBr) 2996, 1758, 1621, 1490, 1460, 1219, 874 and 764, cm^{-1}; m/z (%) 250 (MH^+ 251, 10), 55 (55), 59 (54), 77 (100), 86

(60), 119 (12), 135 (50), and 204 (4); ^{1}H-NMR ($CDCl_3$) δ: 7.53-7.28 (m, 5 H, Ph-H), 5.39 (d, 1H, *J* 9.7, 3-Ha), 4.86 (t, 1H, *J* 8.2, 7a-H), 4.58 (d, 1H, *J* 9.7, 3-Hb), 3.44 (dd, 1H, *J* 8.2 and 11.1, 1-Ha) and 3.23 (dd, 1H, *J* 8.2 and 11.1, 1-Hb).

(3*S*,7a*R*)-3,6-Diphenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7(3*H*)-one (12c). The reaction was carried out according to general procedure (method B) using thiazolidines **7c** and **8c**. Crystallization from ethanol afforded **12c** (3.16 g, 97%); m.p. 180 ºC. IR (KBr) 3023, 1620, 1489, 873, 778 and 674 cm^{-1}; *m/z* (ESI$^+$) 327.1 (100% MH$^+$), (Found MH$^+$ 327.062930 $C_{17}H_{15}N_2OS_2$ requires 327.062032); ^{1}H-NMR ($CDCl_3$) δ: 7.59-7.30 (m, 10 H, Ar-H), 6.81 (s, 1H, 3-H), 4.89 (dd, 1H, *J* 7.1 and 9.2, 7a-H), 3.50 (dd, 1H, *J* 7.1 and 11.1, 1-Ha) and 3.30 (dd, 1H, *J* 9.2 and 11.1, 1-Hb); ^{13}C-NMR ($CDCl_3$), δc: 184.7, 170.4, 138.6, 132.9, 129.4, 129.3, 128.9, 128.8, 128.1, 126.9, 67.0, 67.7 and 32.5.

NOE data ($CDCl_3$) for **12c**:

Irradiated protons	% Enhancement				
	3-H	7a-H	1-Ha	1-Hb	Ar-H
3-H		0.48	-	0.69	3.83 (δ 7.57)
7a-H	0.54		5.50	-	2.82 (δ 7.57)
1-Ha	-	8.38		26.67	-
1-Hb	1.51	0.83	23.92		-

(3*S*,7a*R*)-3-(4-Hydroxyphenyl)-6-phenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7(3*H*)-one (12d). The reaction was carried out according to general procedure (method B) using thiazolidines **7d** and **8d**. Crystallization from ethanol afforded **12d** (3.35 g, 98%); m.p. 178 ºC; IR (KBr) 3047, 2882, 1621, 1589, 1488, 855, 731 and 693 cm^{-1}; m/z (%) 342 (MH$^+$, 64), 55 (100), 57 (96), 77 (49), 106 (52), 135 (59), 192 (47), 205 (50), 248 (49), 299 (52), 311 (56) and 326 (60); ^{1}H-NMR ($CDCl_3$), δ: 7.54-7.30 (m, 9H, Ar-H), 6.74 (s, 1H, 3-H), 4.85 (dd, 1H, *J* 7.1 and 9.2, 7a-H), 3.48 (dd, 1H, *J* 7.1 and 11.1, 1-Ha) and 3.30 (dd, 1H, *J* 9.2 and 11.1, 1-Hb). ^{13}C-NMR ($CDCl_3$) δc: 184.7, 170.2, 137.0, 134.7, 132.7, 129.5, 129.3, 129.0, 128.4, 128.0, 66.7, 66.5 and 32.5.

(3*S*,7a*R*)-3-(2-Methoxyphenyl)-6-phenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7-one (12e). The reaction was carried out according to general procedure (method B) using thiazolidine **7e** and **8e**. Crystallization from chloroform afforded **12e** (3.24 g, 91%); m.p. 178 ºC; IR (KBr) 3001, 1487, 1294, 873and 846 cm^{-1}; m/z (%) 356 $C_{18}H_{16}N_2O_2S_2$, (MH$^+$, 32), 91 (100), 101 (37), 135 (39), 278 (63), 282 (41), 298 (41) and 327 (34); ^{1}H-NMR ($CDCl_3$), δ: 7.56-7.50 (m, 3H, Ar-H), 7.39-7.30 (m, 4H , Ar-H), 7.04 (d, 1H, *J* 7.6, Ar-H), 6.98 (d, 1H, *J* 8.3, Ar-H), 6.85 (s, 1H, 3-H), 5.20 (dd, 1H, *J* 6.9 and 10.2, 7a-H), 3.46 (dd, 1H, *J* 6.9 and 11.1, 1-Ha) and 3.30 (dd, 1, *J* 10.2 and 11.1H, 1-Hb).

(3*S*,7a*R*)-3-(4-Chlorophenyl)-6-phenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7(3*H*)-one (12f). The reaction was carried out according to the general procedure (method B) using thiazolidines **7f** and **8f** and stirring for 48h. Crystallization from chloroform afforded **12f** (3.55 g, 98.5%); m.p. 194-196 ºC; IR (KBr) 1620, 1490, 1338, 872, 778 and 515; cm^{-1}; m/z (%) 342 $C_{17}H_{13}ClN_2OS_2$, 77 (100), 86 (17), 116 (40), 135 (40), 205 (19), 116 (12), 295 (14), and 248 (10); ^{1}H-NMR ($CDCl_3$), δ: 7.54-7.30 (m, 9H, Ar-H), 6.74 (s, 1H, 3-H), 4.89 (dd, 1H, *J* 7.0 and 9.3, 7a-

H), 3.50 (dd, 1H, *J* 7.0 and 11.1, 1-Ha) and 3.31 (dd, 1H, *J* 9.3 and 11.1, 1-Hb); ^{13}C-NMR ($CDCl_3$) δ: 184.6, 170.4, 137.0, 134.7, 132.7, 129.5, 129.3, 129.0, 128.4, 128.0, 66.8, 66.4 and 32.4.

NOE data ($CDCl_3$) for **12f**:

Irradiated	% Enhancement				
protons	3-H	7a-H	1-Ha	1-Hb	Ar-H
3-H		0.50	-	0.87	4.98 (δ 7.53)
7a-H	0.42		5.99	-	2.65 (δ 7.53)
1-Ha	-	11.01		31.52	-
1-Hb	1.61	1.58	25.29		-

(3*S*,7a*R*)-3-(3-Nitrophenyl)-6-phenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7(3*H*)-one (12g). The reaction was carried out according to the general procedure (method B) using thiazolidines **7g** and **8g**. Crystallization from ethanol afforded **12g** (3.57 g, 96.5%); m.p. 200-202 °C; IR (KBr) 3056, 1620, 1489, 1342, 846 and 727 cm^{-1}; m/z (%) 371 $C_{17}H_{13}N_3O_3S_2$, 77 (100), 118 (10), 135 (35), 175 (23), 219 (12), 347 (15), 293 (12), and 324 (9); ^{1}H-NMR ($CDCl_3$/TFA), δ: 8.48 (s, 1H, Ar-H), 8.27 (td, 1H, *J* 1.2 and 8.1, Ar-H), 7.96 (dd, 1H, *J* 0.6 and 8.1, Ar-H), 7.65 (t, 1H, *J* 8.1, Ar-H), 7.56–7.52 (m, 3H, Ph-H), 7.93–7.27 (m, 2H, Ph-H), 6.80 (s, 1H, 3-H), 5.10 (dd, 1H, *J* 7.1 and 9.6, 7a-H), 3.58 (dd, 1H, *J* 7.1 and 11.0, 1-Ha) and 3.41 (dd, 1H, *J* 9.6 and 11.0, 1-Hb).

(3*S*,7a*R*)-3-(4-Nitrophenyl)-6-phenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7(3*H*)-one (12h). The reaction was carried out according to general procedure (method B) using thiazolidines **7h**. Crystallization from chloroform afforded **12h** (3.33 g, 94%); m.p. 160-162 °C; IR (KBr) 3022, 1440, 874, 753 and 629 cm^{-1}; *m/z* (ESI$^+$) 372.0 (14% MH^+), (Found MH^+ 372.046864 $C_{17}H_{14}N_3O_3S_2$ requires 372.047110); ^{1}H-NMR ($CDCl_3$), δ: 8.28 (d, 2H, *J* 8.7, Ar-H), 7.74 (d, 2H, *J* 8.7, Ar-H), 7.57-7.32 (m, 5H, Ph-H), 6.83 (s, 1H, 3-H), 4.92 (dd, 1H, *J* 7.0 and 9.4, 7a-H), 3.53 (dd, 1H, *J* 7.0 and 11.2, 1-Ha) and 3.36 (dd, 1H, *J* 9.4 and 11.2, 1-Hb).

(3*S*,7a*R*)-3-(2-Nitrophenyl)-6-phenyl-5-thioxotetrahydroimidazo[1,5-*c*]thiazol-7(3*H*)-one (12i). The reaction was carried out according to general procedure (method B) using 3,5-bis-(2-nitrophenyl)dihydrothiazolo[3,4-*c*]oxazol-1-one **9**. Crystallization from ethanol afforded **12i** (3.51 g, 95 %); m.p. 230-232 °C; IR (KBr) 2887, 1497, 1345, 853, 786 and 689 cm^{-1}; m/z (%) 371, 55 (41), 63 (100), 135 (34), 208 (22), 112 (49), 237 (24), 325 (17), and 355 (18); ^{1}H-NMR ($CDCl_3$/CD_3OD) δ: 8.17 (dd, 1H, *J* 1.2 and 8.2, Ar-H), 7.74 (dt, 1H, *J* 1.3 and 8.2, Ar-H), 7.67 (dd, 1H, *J* 1.5 and 7.9, Ar-H), 7.59-7.48 (m, 4H, Ar-H), 7.37-7.33 (m, 2H, Ar-H), 7.35 (s, 1H, 3-H), 5.08 (dd, 1H, *J* 7.4 and 9.3, 7a-H), 3.43 (dd, 1H, *J* 7.4 and 11.0, 1-Ha) and 3.36 (dd, 1H, *J* 9.3 and 11.0, 1-Hb).

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Supplementary data

The supplementary file is a pdf document showing the relevant HRMS traces that are reported in this paper.

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