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Intermolecular cycloaddition of nonstabilized azomethine ylides generated from 1,3-thiazolidine-4-carboxylic acids: synthesis of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles

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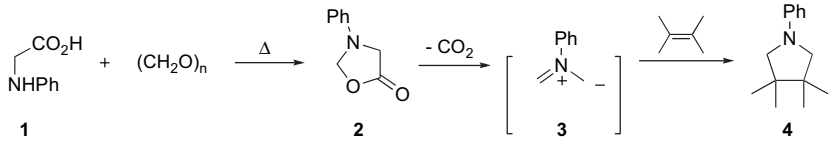
Abstract—The 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate with nonstabilized azomethine ylides, generated via the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acids with aldehydes, afforded 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives. 2-Substituted-1,3-thiazolidine-4-carboxylic acids led to the stereoselective formation of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles. Quantum-chemistry calculations were carried out allowing the rationalization of the observed stereoselective formation of the *anti*-dipole.

1. Introduction

The observation made by Rizzi that the rate of thermal decarboxylation of α-amino acids is accelerated in the presence of carbonyl compounds led to the proposal that azomethine ylide intermediates were involved.[1] This type of 1,3-dipole generation has been further explored and became an interesting route to nonstabilized azomethine ylides.

The work reported by Tsuge and co-workers has shown that the decarboxylative approach to azomethine ylides occurs via the formation of an oxazolidinone intermediate, rather than the direct decarboxylation, followed by carbon dioxide elimination. In fact, *N*-phenylaminoacetic acid **1** undergoes condensation with paraformaldehyde, under reflux, to give 3-phenyloxazolidin-5-one **2**, isolated in quantitative yield. This compound readily eliminates carbon dioxide to give the corresponding azomethine ylide **3**, which can be trapped by reacting with dipolarophiles (Scheme 1).[2a] Isolation of other *N*-substituted-oxazolidin-5-ones from the condensation of formaldehyde with α-amino acids has also been reported.[2b] Based on the cycloadducts' stereochemistry, it is possible to conclude that the formation of the 1,3-dipole is stereospecific in many instances, which is in agreement with a process via 1,3-dipolar cycloreversion of the oxazolidin-5-one intermediate.

Cyclic α-amino acids such as 1,3-thiazolidine-4-carboxylic acids can be used for the generation of nonstabilized azomethine ylides by decarboxylative condensation with carbonyl compounds. The reaction with aldehydes is reported to involve the highly stereoselective formation of the *anti*-dipole, although the subsequent cycloaddition shows little *exo*/*endo* selectivity. The nonstabilized ylides can participate in both inter- and intramolecular cycloaddition processes, originating a range of nitrogen heterocycles, including bridgehead



Scheme 1.

Keywords: Azomethine ylides; 1,3-Dipolar cycloaddition; 1,3-Thiazolidine-4-carboxylic acids; 5,7a-Dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles.
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heterocycles.[2–9] In fact, Grigg and co-workers reported the reaction of thiazolidine-4-carboxylic acids **5** with benzaldehyde, 2-pyridaldehyde, and *N*-substituted maleimides, which afforded a mixture of the *endo*- and *exo*-cycloadducts **7a–7c**, derived from the *anti*-dipoles **6**.[3] Kanemasa and co-workers have also reported that cycloadducts **7d** and **8** can be obtained as mixtures of stereoisomers from the reaction of 4-thiazolidinecarboxylic acid **5a** with paraformaldehyde and *N*-(*p*-tolyl)maleimide or dimethyl maleate, respectively.[2] The involvement of the oxazolidin-5-one intermediates is strongly supported by the observation that thiazolidine-4-carboxylic acid reacts with pivalaldehyde giving (2*R*,7a*R*)-3-*tert*-butyl-dihydro-thiazolo[3,4-*c*]oxazol-1-one selectively.[10] On the other hand, the corresponding derivative obtained from L-proline undergoes cycloaddition to tetramethyl ethylene-1,1,2,2-tetracarboxylate with loss of carbon dioxide.[11] In contrast with the preceding results, the reaction of thiazolidine-4-carboxylic acid **5a** with paraformaldehyde and an excess of methyl propiolate, under reflux in toluene, gives the interesting ring expanded product **9**[9] (Scheme 2).

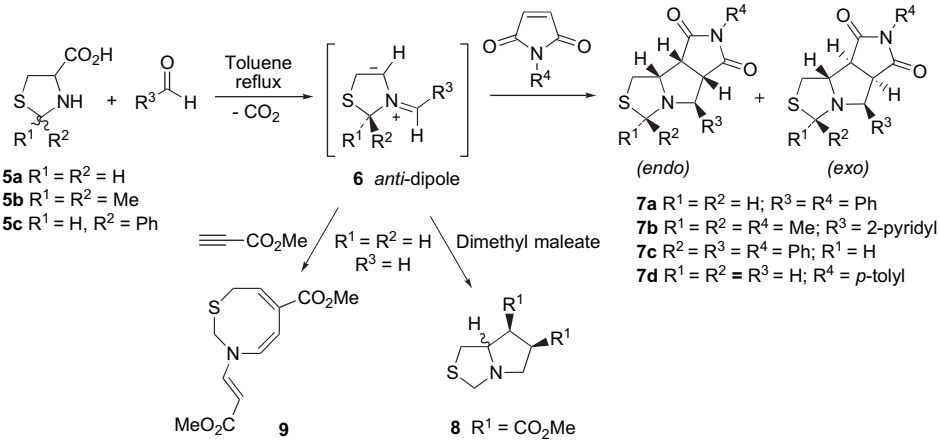
In this paper, we describe the reactivity of nonstabilized azomethine ylides generated from 1,3-thiazolidine-4-carboxylic acids toward alkynes, which led to the development of a route to 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles. The aim of the work was also to get further knowledge on the mechanism of the dipole generation. Selecting an alkyne as dipolarophile, the dimethyl acetylenedicarboxylate (DMAD), the problem of the *endo*/*exo* selectivity of the cycloaddition does not need to be considered, making easier the gathering of information concerning the stereoselectivity of the dipole generation.

2. Results and discussion

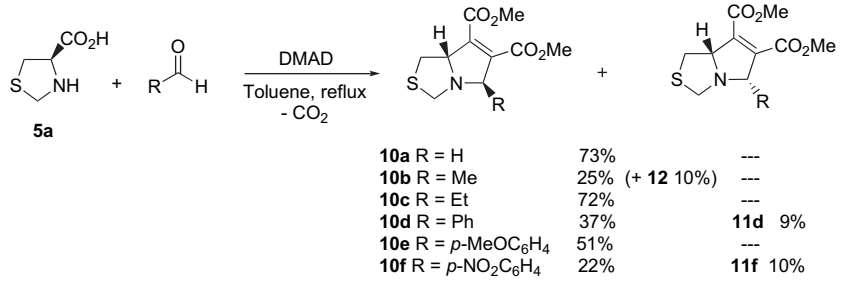
We chose the decarboxylative condensation of 2-unsubstituted-1,3-thiazolidine-4-carboxylic acid **5a** with aldehydes and the corresponding 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate to start our study (Scheme 3). The reaction with paraformaldehyde led to the synthesis of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **10a** in 73% yield, resulting from the cycloaddition of the *anti*-dipole with DMAD. From the reaction of thiazolidine **5a** with acetaldehyde, in the presence of the same dipolarophile, two products were obtained, the expected cycloadduct **10b** in 25% together with the formation of compound **12** (10%).

The synthesis of compound **12** can be rationalized as shown in Scheme 4. The iminium salt generated from the reaction of the thiazolidine **5a** with acetaldehyde, the simplest enolizable aldehyde, is converted into an enamine, which undergoes further condensation with acetaldehyde to generate the corresponding azomethine ylide. This ylide reacts with DMAD to give the 1,3-dipolar cycloadduct **12**. It is a reactivity that is similar to the one reported for the reaction of *N*-benzylglycine with acetaldehyde in the presence of *N*-(*p*-tolyl)maleimide.[5]

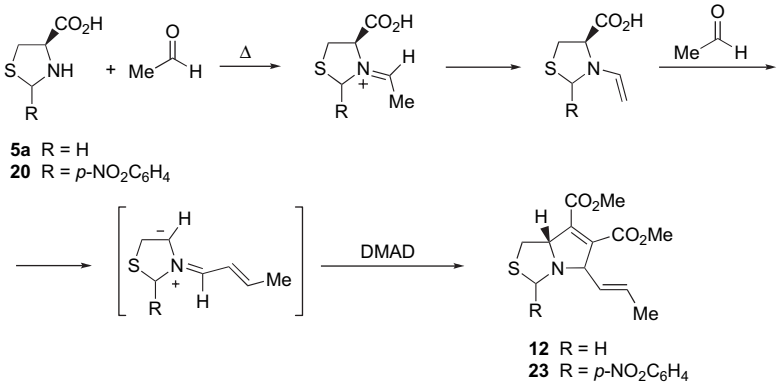
The (5*R*,7a*S*)-5-ethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole **10c** was obtained in 72% yield when the reaction



Scheme 2.



Scheme 3.



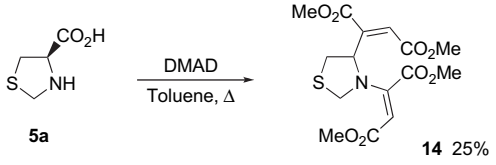
Scheme 4.

was carried out with propionaldehyde (Scheme 3). However, from the condensation of thiazolidine **5a** with benzaldehyde in the presence of DMAD the cycloadduct **10d**, derived from the *anti*-dipole, was not the only product. Compound **11d** was also obtained proving that the *syn*-dipole has also been generated. A similar result was observed when the reaction was carried out with *p*-nitrobenzaldehyde, which led to 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **10f** (22%) and **11f** (10%).

This decarboxylative condensation of thiazolidine **5a** with *p*-nitrobenzaldehyde also resulted in the formation of 2,3-di(*p*-nitrophenyl)-2,3,7,7a-tetrahydrothiazolo[3,4-*b*]oxazole **13** in 1% yield. Thus, the in situ generated nonstabilized azomethine ylide also participates in a 1,3-dipolar cycloaddition in which the carbonyl group of the aldehyde acts as dipolarophile (Scheme 5). Intramolecular 1,3-dipolar cycloaddition of this type of dipoles with carbonyl groups has been previously reported.[6]

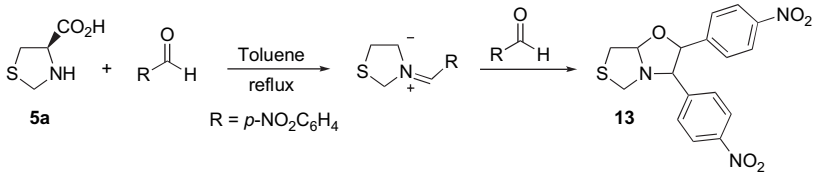
In the case of the use of *p*-methoxybenzaldehyde only cycloadduct **10e** was obtained in 51% yield (Scheme 3). The assignment of the resonances in the ^{1}H and ^{13}C NMR spectra of compound **10e** was supported by a two-dimensional HMBC ($^{1}H/^{13}C$-long range) spectrum. The stereochemistry of **10e** was established based on a NOESY spectrum where no connectivity was observed between H-7a and H-5 (Fig. 1).

The reactions described above, starting from thiazolidine **5a**, also afforded dimethyl 3,4-bis[(1,2-bis-methoxycarbonylvinyl)]thiazolidine **14** in less than 5% yield. The synthesis of **14** can be explained by considering an initial conjugated addition of thiazolidine **5a** to DMAD, followed by decarboxylation and a subsequent conjugated addition to a second molecule of DMAD. This result was confirmed by carrying out the reaction of thiazolidine **5a** with DMAD in the absence of the aldehydes, which also led to compound **14** (Scheme 6).



Scheme 6.

We turned our attention to the study of 2-substituted-1,3-thiazolidine-4-carboxylic acids. These heterocycles are obtained from the reaction of aldehydes and L-cysteine esters in a process where a new chiral center at the C-2 position of the



Scheme 5.

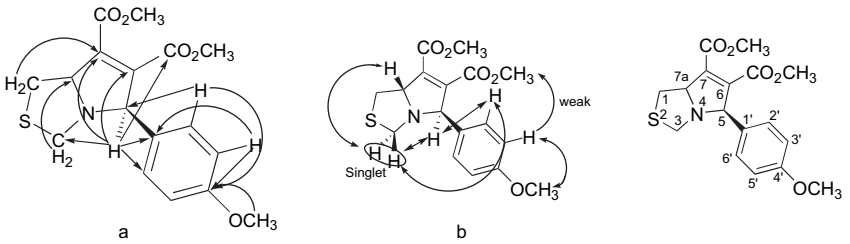
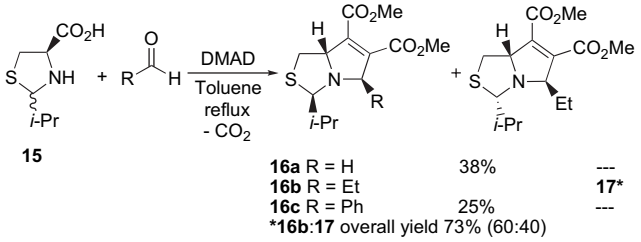


Figure 1. Main connectivities found in the HMBC spectrum (a) and NOESY spectrum (b) of compound **10e**.

thiazolidine is created leading to a mixture of the (2*S*,4*R*)- and (2*R*,4*R*)-diastereoisomers. It is known that the acylation of the diastereoisomeric mixture can lead to the selective synthesis of *N*-acyl-2-substituted-1,3-thiazolidine-4-carboxylates as pure stereoisomers with (2*R*,4*R*) or (2*S*,4*R*) stereochemistry depending on the reaction conditions.[12] In fact, 2-substituted-1,3-thiazolidine-4-carboxylates can undergo selective inversion at C-2 through a mechanism involving the opening of the ring, but the protection with the acyl group prevents this epimerization and allows the isolation of pure diastereoisomers. We set out to evaluate if a similar chemical behavior of the 2-substituted-1,3-thiazolidine-4-carboxylic acids could be observed in the synthesis of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles, namely to determine if a selective inversion at C-2 could also occur in the present case.

2-Isopropyl-1,3-thiazolidine-4-carboxylic acid **15** was prepared and condensed with aldehydes in the presence of DMAD (Scheme 7). High stereoselectivity was observed by carrying out the reaction with paraformaldehyde and benzaldehyde with exclusive isolation of the stereoisomers **16a** and **16c**, respectively. The reaction of **15** with propionaldehyde led to the synthesis of compound **16b** as the major product but stereoisomer **17** was also isolated. It is worthwhile to emphasize that all the cycloadducts obtained from the reaction of thiazolidine **15** resulted from the cycloaddition of the corresponding *anti*-dipole.

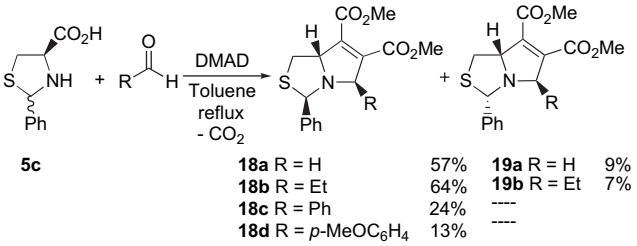


Scheme 7.

The reaction of thiazolidine **15** with acetaldehyde in the presence of DMAD led to a different outcome. Although, the expected cycloadduct **16d** could be obtained in 20% yield, the 3,5-dimethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-6,7-dicarboxylates **16e** and **16f** were also obtained in 18 and 7% yield, respectively (Scheme 8). The synthesis of **16e** and **16f** can only be explained by considering the opening of the thiazolidine ring of **15** followed by the condensation with acetaldehyde to give 2-methylthiazolidine-4-carboxylic acid, which can than react with acetaldehyde and DMAD to give the final products.

The chemistry of (2*S*,4*R*)- and (2*R*,4*R*)-2-phenyl-1,3-thiazolidine-4-carboxylic acid mixture (**5c**) as precursor of non-stabilized azomethine ylides was also studied (Scheme 9).

No evidence for the generation of the *syn*-dipole from this thiazolidine could be observed. Reactions with paraformaldehyde, propionaldehyde, benzaldehyde, and *p*-methoxybenzaldehyde in the presence of DMAD were carried out. Stereoselectivity for the formation of the (3*R*,5*R*,7a*S*)-stereoisomers was observed. In fact, with paraformaldehyde and propionaldehyde the cycloadducts **18a** and **18b** were obtained in good yields (57 and 64%) as the major products and the stereoisomers **19a** and **19b** were obtained in low yield (9 and 7%).

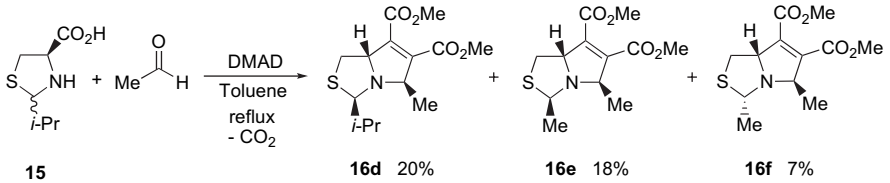


Scheme 9.

The assignment of the resonances in the ^{1}H and ^{13}C NMR spectra of compounds **18b** and **19b** was supported by a two-dimensional HMBC spectrum. In the NOESY spectrum of compound **18b**, H-7a shows connectivity with the aromatic proton H-6′ but no connectivity with H-3 nor with H-5. Correlation of H-3 with H-5 is also observed. In the NOESY spectrum of **19b**, H-7a shows connectivity with H-3 and no connectivity with H-6′ nor with H-5. No correlation was observed between H-3 and H-5. These observation allowed the establishment of the stereochemistry of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **18b** and **19b** (Fig. 2).

The reaction of thiazolidine **5c** with aromatic aldehydes in the presence of DMAD afforded the corresponding (3*R*,5*R*,7a*S*)-stereoisomers (**18c** and **18d**) exclusively, although in moderate yield (Scheme 9). The assignment of the resonances in the ^{1}H and ^{13}C NMR spectra of compound **18d** was supported by a two-dimensional HMBC spectrum. In the NOESY spectrum, H-7a shows connectivity with aromatic proton H-6′ but no connectivity with H-3 nor with H-5 was observed. On the other hand, H-3 correlates with H-5. These observations are in agreement with the (3*R*,5*R*,7a*S*) stereochemistry of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **18d** (Fig. 3).

The results of the decarboxylative condensation of *p*-nitrophenyl-1,3-thiazolidine-4-carboxylic acid **20** with aldehydes in the presence of dimethyl acetylenedicarboxylate are presented in Scheme 10. Once more, only products of the 1,3-dipolar cycloaddition of the *anti*-dipole were formed. On the other hand, selectivity for the synthesis of the (3*R*,5*R*,7a*S*)-stereoisomers was again observed.



Scheme 8.

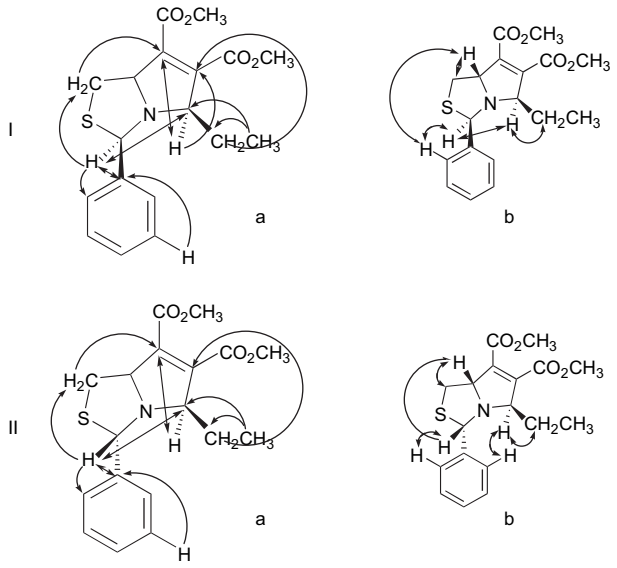
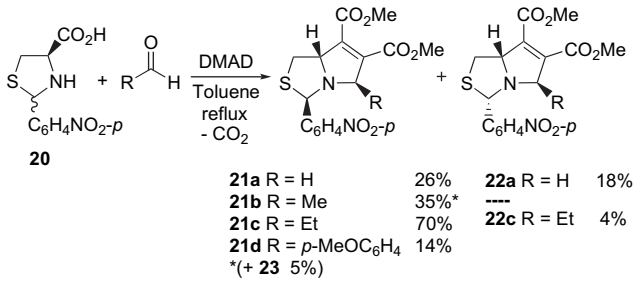


Figure 2. (I) Main connectivities found in the HMBC spectrum (a) and NOESY spectrum (b) of compound **18b**; (II) main connectivities found in the HMBC spectrum (a) and NOESY spectrum (b) of compound **19b**.

2.1. Computational study

The quantum-chemistry calculations were applied in order to explain the *anti*/*syn* selectivity of the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acid (**5a**) with aldehydes. We concentrated on the reaction steps transforming the reactants into the azomethine ylide intermediates, through thiazolidin-3-ium-4-carboxylate betaine and thiazolo[3,4-*c*][1,3]oxazol-1-one intermediates (Fig. 4). Two cases were considered: reaction with propionaldehyde (RCHO, R=Et), in which the selective formation of *anti* conformer of the 1,3-dipole intermediate was observed, and benzaldehyde (R=Ph), which led to both *anti* and *syn* forms in a 4.1:1 proportion (Scheme 3). Lack of strong interactions, particularly H-bonds, between the solvent (toluene) and the postulated reaction intermediates implies that gas-phase calculations should be, at least qualitatively, applicable in modeling of the system under study.

The general scheme for the reaction with relevant calculated data is presented in Figure 4. More detailed data on the optimized structures of the different species that are postulated to be formed along the reaction are given in Figures S1 and S2 and Tables S1–S6 (see Supplementary data).



Scheme 10.

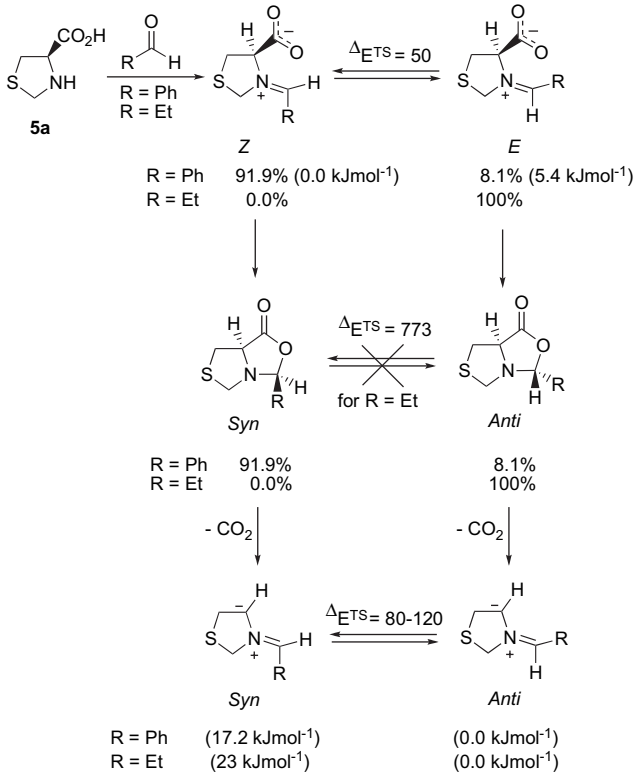


Figure 4. General schematic sequence of processes involved in the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acid (**5a**) with propionaldehyde (R=Et) or benzaldehyde (R=Ph). The *Z* and *E* letters for the thiazolidin-3-ium-4-carboxylate betaine intermediates denote the conformation with respect to C=N bond. *Anti* and *syn* indicate the arrangement around the C–N or C=N bond in the remaining intermediates depicted in the figure. The values of the zero-point corrected relative energies (in kJ mol^{-1}) are given in parentheses. The relevant barriers for the conformational conversion (in kJ mol^{-1}) and estimated conformer abundances (%) at 383 K are also given. When R=Et, the energies and abundances presented are average values and the sum of values for individual conformers differing by the conformation within the substituent.

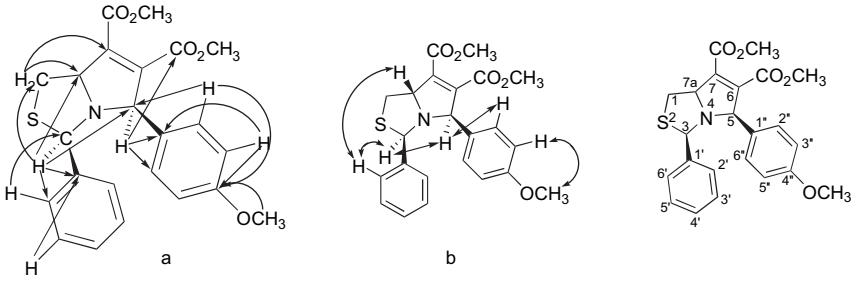


Figure 3. Main connectivities found in the HMBC spectrum (a) and NOESY spectrum (b) of compound **18d**.

The optimization of the input structures of the 1,3-thiazolidin-3-ium-4-carboxylate betaine intermediate brought both *Z* and *E* conformers for R=Ph, whereas in the case of R=Et only *E* conformers were found to be stable.

The energy barriers between *E* and *Z* isomers of the 1,3-thiazolidin-3-ium-4-carboxylate betaine intermediate in the case of R=Ph were calculated to be low enough (50 kJ mol^{-1}) to be overcome under the experimental conditions used. Therefore, it can be stated that both conformers of this species exist in equilibrium in the reaction media. Their estimated abundances at 383 K are ca. 92% (*Z*) and 8% (*E*) (see Fig. 4 and also Tables S1 and S2, where relative energies and Gibbs free energies are also presented).

The formation of the oxazolidinone ring proceeds via nucleophilic attack of the carboxylate group on the sp^2 carbon atom. The stereoselective cyclization of the *Z* and *E* conformers leads to the production of the *syn* and *anti* thiazolo[3,4-*c*][1,3]oxazol-1-one intermediates, respectively. Therefore, if only *E* form of 1,3-thiazolidin-3-ium is predicted for R=Et and both *Z* and *E* forms exist in equilibrium for R=Ph, then only *anti* conformers of thiazolo[3,4-*c*]-[1,3]oxazol-1-one are expected to be produced for R=Et, while both *syn* and *anti* forms could be expected to be obtained for R=Ph.

The calculated energy barrier for the *syn–anti* interconversion of the thiazolo[3,4-*c*][1,3]oxazol-1-one intermediates is high (>770 kJ mol^{-1}; see Fig. 4). Therefore, no isomerization can occur in this step and the percentage of *syn* and *anti* conformers of the 1,3-dipole intermediates obtained after decarboxylation can be considered to be strictly proportional to the amount of *syn* and *anti* conformers of the thiazolo[3,4-*c*][1,3]oxazol-1-one intermediates, due to the fact that decarboxylation proceeds in a concerted way.

The gas-phase calculations predict that the energy of the *syn* conformers of 1,3-dipole intermediates relative to the *anti* forms is ca. 23 and 17 kJ mol^{-1} for R=Et and Ph, respectively. Moreover, according to the calculations, the barrier heights for *syn–anti* interconversion of the 1,3-dipole intermediates are low (80–120 kJ mol^{-1}; see Fig. 4). This suggests that, once produced, the possible conformers of the 1,3-dipole intermediates exist in equilibrium. For R=Et, the abundances of the *syn* and *anti* forms calculated at the temperature of reaction are 0.3 and 99.7%, respectively. Also taking into account that only *anti* intermediate is formed after decarboxylation, the experimental observation of the sole *anti* form for R=Et is easily rationalized. Different behavior is observed when R=Ph. In this case, the ring-closing and decarboxylation reactions must give rise to both *anti* and *syn* conformers of the 1,3-dipole intermediate, since the final product was obtained in a 4.1:1 *anti*/*syn* stereoisomeric ratio. The theoretical calculations predicted that the produced amount of *syn* 1,3-dipole intermediate should be significantly higher (ca. 92%) than that of the *anti* conformer (ca. 8%), because of the lower energy of the *Z* conformer of 1,3-thiazolidin-3-ium-4-carboxylate betaine compared to *E* (see Fig. 4). On the other hand, the *anti* 1,3-dipole intermediate was predicted to be more stable than the *syn* form by ca. 17 kJ mol^{-1}. Then, after being formed in a comparatively larger amount, the *syn* conformer can be expected to partially convert to the *anti* form, while reaction with DMAD (to produce the final product, 5,7a-dihydro-1*H*,3*H*-pyrrolo-[1,2-*c*]thiazole) takes place, leading to the observed stereoisomeric ratio.

In summary, it can be stated that the practical relevance of both *anti* and *syn* conformers of the final product for R=Ph and of only the most stable *anti* form for R=Et results mainly from the conjugation of three factors: (a) the instability and, therefore, lack of the *Z* form of 3-propylidene-1,3-thiazolidin-3-ium-4-carboxylate, (b) the considerably lower energy of the *Z* form of 3-benzylidene-1,3-thiazolidin-3-ium-4-carboxylate betaine relatively to the *E* form, and (c) the concerted mechanism for the ring-closing reaction that is responsible for the formation of *anti* and *syn* conformers of 1*H*-[1,3]thiazolo[3,4-*c*][1,3]oxazol-1-one from *E* and *Z* forms of 1,3-thiazolidin-3-ium-4-carboxylate betaine, respectively.

3. Conclusion

The decarboxylative condensation of thiazolidine-4-carboxylic acids with aldehydes in the presence of DMAD leads to 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles via 1,3-dipolar cycloaddition of nonstabilized azomethine ylide intermediates. The reaction of 2-substituted-1,3-thiazolidine-4-carboxylic acids allows the exclusive or stereoselective formation of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles. Selectivity for the formation of the *anti*-dipole is observed. Only in the reaction of thiazolidine-4-carboxylic acid (**5a**) with benzaldehyde and *p*-nitrobenzaldehyde in the presence of DMAD the generation of the *syn*-dipole was detected.

Quantum-chemistry calculations were carried out allowing the rationalization of the observed stereoselective formation of the *anti*-dipole for the decarboxylative condensation of thiazolidine-4-carboxylic acid with propionaldehyde and with benzaldehyde.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker Avance 300 instrument operating at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker Avance 300 instrument operating at 75.5 MHz. The solvent is deuteriochloroform except where otherwise indicated. IR spectra were recorded on a Perkin–Elmer 1720X FTIR spectrometer. Mass spectra were recorded on an HP GC 6890/MSD5973 instrument under electron impact (EI) except where otherwise indicated. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Microanalyses were performed using an EA 1108-HNS-O Fisons instrument. Melting points were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. 1,3-Thiazolidine-4-carboxylic acids **5a**,[17,18] **5c**,[19] **15**,[20] and **20** were prepared by a procedure described earlier, starting from L-cysteine, and were isolated as a mixture of the (2*R*,4*R*) and (2*S*,4*R*) diastereoisomers.[19,21]

4.2. General procedure for the decarboxylative cycloaddition reactions

A mixture of thiazolidine-4-carboxylic acid (3.75 mmol), aldehyde (9.4 mmol), and dimethyl acetylenedicarboxylate (5.6 mmol) in toluene (40 mL), in the presence of molecular sieves, was stirred and heated under reflux for 3–4 h. The reaction mixture was then filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography [ethyl acetate–hexane].

4.2.1. Dimethyl (7a*S*)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10a. Yield 73%; yellow oil; IR (KBr) 1437, 1655, 1717 cm^{-1}; ^1H NMR δ 3.12–3.14 (2H, m), 3.79 (3H, s), 3.82 (3H, s), 3.82–3.88 (2H, m), 4.05 (2H, s), 4.60–4.65 (1H, m); ^{13}C NMR δ 39.1, 52.3, 61.8, 62.1, 75.3, 137.1, 137.8, 163.2, 163.6; MS (EI) 243 (M^+, 41%), 212 (12), 197 (100), 138 (77); HRMS (EI) *m/z* 243.0565 ($C_{10}H_{13}NOS$ [M^+], 243.0568).

4.2.2. Dimethyl (5*R*,7a*S*)-5-methyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10b. Yield 25%; white solid; mp 68.9–70.2 °C (from ethyl acetate–hexane); IR (KBr) 1662, 1722, 1735 cm^{-1}; ^1H NMR δ 1.29 (3H, d, *J*=6.8 Hz), 2.98 (1H, dd, *J*=3.4 and 11.6 Hz), 3.12 (1H, dd, *J*=7.9 and 11.6 Hz), 3.76 (3H, s), 3.79 (3H, s), 4.04 (2H, s), 4.56–4.62 (1H, m); ^{13}C NMR δ 20.5, 38.5, 52.3, 52.3, 60.0, 68.2, 73.6, 133.9, 144.0, 163.0, 164.4; MS (EI) *m/z* 257 (M^+, 2%), 211 (100), 179 (61), 152 (93). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.48; H, 6.09; N, 5.31.

4.2.3. Dimethyl 5-propenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 12. Yield 10%; yellow oil; IR (KBr) 1439, 1639, 1647, 1720 cm^{-1}; ^1H NMR δ 1.69–1.73 (3H, m), 3.00 (1H, dd, *J*=3.7 and 11.6 Hz), 3.18 (1H, dd, *J*=8.0 and 11.6 Hz), 3.78 (3H, s), 3.79 (3H, s), 4.05 (2H, s), 4.43–4.47 (1H, m), 4.59–4.65 (1H, m), 5.42–5.50 (1H, m), 5.69–5.76 (1H, m); ^{13}C NMR δ 17.7, 38.6, 52.3, 52.3, 59.2, 73.2, 75.0, 128.8, 130.3, 133.3, 143.6, 162.7, 164.3; MS (EI) *m/z* 283 (M^+, 2%), 252 (14), 237 (73), 178 (100); HRMS (EI) *m/z* 283.0878 ($C_{13}H_{17}NO_4S$ [M^+], 283.0883).

4.2.4. Dimethyl (5*R*,7a*S*)-5-ethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10c. Yield 72%; yellow oil; IR (KBr) 1437, 1639, 1721 cm^{-1}; ^1H NMR δ 0.99 (3H, t, *J*=7.3 Hz), 3.04 (1H, dd, *J*=2.9 and 11.8 Hz), 3.15 (1H, dd, *J*=7.7 and 11.8 Hz), 3.79 (3H, s), 3.81 (3H, s), 3.98–4.03 (1H, m), 4.03–4.10 (2H, m), 4.62–4.67 (1H, m); ^{13}C NMR δ 9.5, 27.5, 38.8, 52.3, 52.3, 61.6, 73.9, 74.6, 133.9, 144.1, 163.0, 164.7; MS (EI) *m/z* 271 (M^+, 3%), 242 (45), 225 (83), 210 (100); HRMS (EI) *m/z* 271.0878 ($C_{12}H_{17}NO_4S$ [M^+], 271.0877).

4.2.5. Dimethyl (5*R*,7a*S*)-5-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10d. Yield 37%; white solid; mp 53.1–54.1 °C (from ethyl acetate–hexane); IR (KBr) 1650, 1717, 2959 cm^{-1}; ^1H NMR δ 3.09 (1H, dd, *J*=3.7 and 11.5 Hz), 3.24 (1H, dd, *J*=7.9 and 11.5 Hz), 3.58 (3H, s), 3.81 (3H, s), 4.07 (2H, s), 4.78–4.84 (1H, m), 5.09 (1H, d, *J*=4.8 Hz), 7.34–7.36 (5H, m, Ar-H); ^{13}C NMR δ 38.7, 52.2, 52.4, 59.8, 73.8, 76.5, 128.0, 128.3, 128.6, 134.4, 139.2, 143.2, 162.9, 163.8; MS (EI) *m/z* 319 (M^+, 3%), 242 (45), 225 (83), 210 (100). Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 60.50; H, 5.15; N, 4.20.

4.2.6. Dimethyl (5*S*,7a*S*)-5-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 11d. Yield 9%; white solid; mp 88.7–90.5 °C (from ethyl acetate–hexane); IR (KBr) 1436, 1653, 1720, 2953 cm^{-1}; ^1H NMR δ 3.08 (1H, dd, *J*=5.8 and 11.0 Hz), 3.23 (1H, dd, *J*=7.5 and 11.0 Hz), 3.62 (3H, s), 3.67 (1H, d, *J*=10.3 Hz), 3.86 (3H, s), 3.95 (1H, d, *J*=10.3 Hz), 4.22–4.77 (1H, m), 5.39 (1H, d, *J*=2.6 Hz), 7.29–7.37 (5H, m, Ar-H); ^{13}C NMR δ 37.9, 52.3, 52.5, 54.4, 74.2, 75.3, 128.3, 129.0, 130.1, 134.0, 136.7, 141.2, 163.4, 163.8; MS (EI) *m/z* 319 (M^+, 69), 288 (12), 273 (73), 240 (45), 214 (100). Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36; N, 4.39. Found: C, 60.04; H, 5.44; N, 4.34.

4.2.7. Dimethyl (5*R*,7a*S*)-5-(*p*-methoxyphenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10e. Yield 51%; white solid; mp 60.5–61.9 °C (from ethyl acetate–hexane); IR (KBr) 1609, 1672, 1733, 2957 cm^{-1}; ^1H NMR δ 3.08 (1H, dd, *J*=3.7 and 11.5 Hz, H-1_{trans}), 3.24 (1H, dd, *J*=8.0 and 11.5 Hz, H-1_{cis}), 3.59 (3H, s, 7-CO_2CH_3), 3.80 (3H, s, 4′-OCH_3), 3.81 (3H, s, 6-CO_2CH_3), 4.06 (2H, s, H-3), 4.75–4.81 (1H, m, H-7a), 5.05 (1H, d, *J*=4.7 Hz, H-5), 6.87 (2H, d, *J*=8.6 Hz, H-2′,5′), 7.28 (2H, d, *J*=8.6 Hz, H-2′,6′). ^{13}C NMR δ 38.7 (C-1), 52.2 (6-CO_2CH_3), 52.4 (7-CO_2CH_3), 55.2 (4′-OCH_3), 59.6 (C-3), 73.6 (C-7a), 75.9 (C-5), 113.9 (C-3′,5′), 129.2 (C-2′,6′), 131.2 (C-1′), 134.0 (C-7), 143.5 (C-6), 159.6 (C-4′), 162.9 (6-CO_2CH_3), 163.9 (7-CO_2CH_3); MS (EI) *m/z* 349 (M^+, 2), 318 (5), 303 (100), 271 (19). Anal. Calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.45; H, 5.58; N, 3.97.

4.2.8. Dimethyl (5*R*,7a*S*)-5-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10f. Yield 22%; white solid; mp 102.2–103.6 °C (from ethyl acetate–hexane); IR (KBr) 1439, 1663, 1725, 2955 cm^{-1}; ^1H NMR δ 3.14 (1H, dd, *J*=3.6 and 11.7 Hz), 3.25 (1H, dd, *J*=8.0 and 11.7 Hz), 3.60 (3H, s), 3.84 (3H, s), 4.00 (1H, d, *J*=11.3 Hz), 4.06 (1H, d, *J*=11.3 Hz), 4.81–4.86 (1H, m), 5.19 (1H, d, *J*=4.9 Hz), 7.57–7.60 (2H, m, Ar-H), 8.20–8.23 (2H, m, Ar-H); ^{13}C NMR δ 38.6, 52.4, 52.6, 59.9, 74.1, 75.7, 123.8, 129.1, 136.6, 140.7, 146.9, 147.9, 162.9, 163.0; MS (EI) *m/z* 364 (M^+, 5), 318 (100), 287 (23), 213 (35); HRMS (EI) *m/z* 364.0729 ($C_{16}H_{16}N_2O_6S$ [M^+], 364.0728).

4.2.9. Dimethyl (5*S*,7a*S*)-5-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 11f. Yield 10%; yellow solid; mp 140.3–141.9 °C (from ethyl acetate–hexane); IR (KBr) 1448, 1597, 1700, 1739, 2949 cm^{-1}; ^1H NMR δ 2.81–2.86 (1H, m), 3.16–3.23 (1H, m), 3.53 (3H, s), 3.84 (3H, s), 4.04 (1H, d, *J*=9.8 Hz), 4.14 (1H, d, *J*=9.8 Hz), 4.26–4.32 (2H, m), 7.59–7.63 (2H, m, Ar-H), 8.27–8.31 (2H, m, Ar-H); MS (EI) *m/z* 364 (M^+, 24), 305 (100), 259 (28), 213 (26).

4.2.10. 2,3-Di(*p*-nitrophenyl)-2,3,7,7a-tetrahydrothiazolo[3,4-*b*]oxazole 13. Yield 1%; yellow solid; mp 137.4–138.9 °C (from ethyl acetate–hexane); IR (KBr) 1355,

1525, 1603, 2897 cm^{-1}; ^1H NMR δ 3.24 (1H, dd, J=4.6 and 12.9 Hz), 3.36 (1H, d, J=12.9 Hz), 3.86 (1H, d, J=11.6 Hz), 3.99 (1H, d, J=9.0 Hz), 4.11 (1H, d, J=11.6 Hz), 4.72 (1H, d, J=9.0 Hz), 5.56 (1H, d, J=4.4 Hz), 7.34–7.37 (2H, m), 7.41–7.44 (2H, m), 8.15–8.20 (4H, m); ^{13}C NMR δ 40.8, 59.5, 75.2, 85.7, 99.0, 123.8, 123.9, 127.4, 128.8, 143.4, 144.8, 148.0, 148.1.

4.2.11. Dimethyl (3*R*,5*R*,7a*S*)-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16a. Yield 38%; yellow oil; ^1H NMR δ 0.94 (3H, d, J=10.8 Hz), 0.97 (3H, d, J=10.8 Hz), 1.56–1.65 (1H, m), 2.91 (1H, dd, J=5.5 and 11.2 Hz), 3.15 (1H, dd, J=7.4 and 11.2 Hz), 3.75 (3H, s), 3.78 (3H, s), 3.79–3.90 (1H, m), 3.79–3.90 (1H, m), 4.15 (1H, dd, J=1.3 and 16.0 Hz), 4.57–4.64 (1H, m); ^{13}C NMR δ 19.9, 20.2, 35.3, 37.7, 52.2, 52.3, 62.5, 75.1, 83.3, 136.4, 137.6, 163.4, 163.6; MS (EI) m/z 285 (M^+, 9), 251 (22), 208 (100), 164 (8).

4.2.12. Dimethyl (3*R*,5*R*,7a*S*)-5-ethyl-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16b and dimethyl (3*S*,5*R*,7a*S*)-5-ethyl-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 17. Overall yield 73% (60:40). The products can be separated by thin layer chromatography [two elutions with ethyl acetate–hexane (1:6)].

Dimethyl (3*R*,5*R*,7a*S*)-5-ethyl-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate **16b** isolated as a white solid; mp 36.5–38.4 °C (from ethyl acetate–hexane); IR (KBr) 1664, 1730 cm^{-1}; ^1H NMR δ 0.92–1.01 (9H, m), 1.57–1.71 (3H, m), 2.89 (1H, dd, J=4.3 and 11.3 Hz), 3.21 (1H, dd, J=7.8 and 11.3 Hz), 3.78 (3H, s), 3.81 (3H, s), 3.89 (1H, d, J=8.9 Hz), 4.05–4.10 (1H, m), 4.63–4.69 (1H, m); ^{13}C NMR δ 8.3, 20.2, 20.5, 26.4, 35.1, 37.8, 52.3, 52.3, 73.4, 74.2, 83.4, 134.8, 142.5, 163.0, 164.9; MS (EI) m/z 313 (M^+, 2), 270 (100), 234 (13). Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.80; H, 7.32; N, 4.45.

Dimethyl (3*S*,5*R*,7a*S*)-5-ethyl-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate **17**; yellow oil; IR (KBr) 1436, 1657, 1723 cm^{-1}; ^1H NMR δ 0.93–1.00 (9H, m), 1.58–1.66 (3H, m), 2.93 (1H, dd, J=4.0 and 11.5 Hz), 3.25 (1H, dd, J=7.9 and 11.5 Hz), 3.78 (3H, s), 3.81 (3H, s), 4.02–4.04 (1H, m), 4.14 (1H, approx. t, J=7.4 Hz), 4.69–4.72 (1H, m); ^{13}C NMR δ 8.9, 11.9, 27.0, 35.1, 37.4, 52.3, 52.3, 73.1, 74.1, 74.2, 78.0, 134.5, 142.9, 163.0, 164.9; MS (EI) m/z 313 (M^+, 5), 299 (12), 270 (100), 252 (79).

4.2.13. Dimethyl (3*R*,5*R*,7a*S*)-3-isopropyl-5-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16c. Yield 25%; yellow oil; IR (KBr) 1437, 1658, 1747, 2957 cm^{-1}; ^1H NMR δ 0.75 (3H, d, J=6.6 Hz), 0.86 (3H, d, J=6.6 Hz), 1.60–1.61 (1H, m), 2.98 (1H, dd, J=5.3 and 11.0 Hz), 3.29 (1H, dd, J=7.8 and 11.0 Hz), 3.56 (3H, s), 3.80 (3H, s), 3.92 (1H, d, J=8.8 Hz), 4.80–4.86 (1H, m), 5.03 (1H, d, J=4.8 Hz), 7.27–7.35 (5H, m, Ar-H); ^{13}C NMR δ 19.9, 20.2, 35.1, 37.6, 52.1, 52.3, 73.1, 77.1, 82.1, 128.2, 128.3, 128.3, 134.4, 139.0, 142.4, 162.9, 163.9; MS (EI) m/z 361 (M^+, 3), 318 (100), 282 (17), 268 (5); HRMS (EI) m/z 361.1347 ($C_{19}H_{23}NO_4S$ [M^+], 361.1356).

4.2.14. Dimethyl (3*R*,5*R*,7a*S*)-3-isopropyl-5-methyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16d. Yield 20%; white oil; IR (KBr) 1436, 1656, 1723 cm^{-1}; ^1H NMR δ 0.93–1.01 (6H, m), 1.28 (3H, d, J=6.7 Hz), 1.51–1.71 (1H, m), 2.87 (1H, dd, J=5.1 and 11.0 Hz), 3.19 (1H, dd, J=7.8 and 11.0 Hz), 3.78 (3H, s), 3.81 (3H, s), 3.91 (1H, d, J=8.9 Hz), 4.01–4.05 (1H, m), 4.61–4.64 (1H, m); ^{13}C NMR δ 20.1, 20.3, 20.4, 35.3, 37.5, 52.2, 52.3, 68.3, 73.1, 82.3, 134.4, 142.9, 163.1, 164.6; MS (EI) m/z 299 (M^+, 1), 256 (100), 220 (13); HRMS (EI) m/z 299.1191 ($C_{14}H_{21}NO_4S$ [M^+], 299.1196).

4.2.15. Dimethyl (3*R*,5*R*,7a*S*)-3,5-dimethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16e. Yield 18%; oil; IR (KBr) 1437, 1662, 1726, 1738 cm^{-1}; ^1H NMR δ 1.30 (3H, d, J=6.7 Hz), 1.44 (3H, d, J=6.7 Hz), 2.96 (1H, dd, J=4.4 and 11.4 Hz), 3.33 (1H, dd, J=7.9 and 11.4 Hz), 3.79 (3H, s), 3.81 (3H, s), 4.03–4.07 (1H, m), 4.47 (1H, q, J=6.7 Hz), 4.74–4.80 (1H, m); ^{13}C NMR δ 20.6, 25.6, 37.5, 40.6, 52.3, 68.2, 70.0, 72.7, 82.0, 134.1, 143.2, 163.1, 164.6; MS (EI) m/z 271 (M^+, 6), 256 (10), 225 (100); HRMS (EI) m/z 271.0878 ($C_{12}H_{17}NO_4S$ [M^+], 271.0874).

4.2.16. Dimethyl (3*S*,5*R*,7a*S*)-3,5-dimethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16f. Yield 7%; yellow oil; IR (KBr) 1437, 1580, 1723, 1756 cm^{-1}; ^1H NMR δ 1.31 (3H, d, J=6.6 Hz), 1.61 (3H, d, J=6.7 Hz), 3.00 (1H, dd, J=3.0 and 11.7 Hz), 3.24 (1H, dd, J=8.1 and 11.7 Hz), 3.79 (3H, s), 3.83 (3H, s), 4.35–4.44 (1H, m), 4.57 (1H, q, J=6.7 Hz), 4.65–4.71 (1H, m); ^{13}C NMR δ 16.2, 22.2, 41.5, 52.7, 52.8, 62.0, 70.9, 74.7, 134.1, 144.7, 163.4, 165.0; MS (EI) 271 (M^+, 6), 256 (10), 225 (94), 166 (100); HRMS (EI) m/z 271.0878 ($C_{12}H_{17}NO_4S$ [M^+], 271.0889).

4.2.17. Dimethyl (3*R*,5*R*,7a*S*)-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 18a. Yield 57%; white solid; mp 54.5–55.4 °C (from ethyl acetate–hexane); IR (KBr) 1665, 1715, 2953 cm^{-1}; ^1H NMR δ 2.98 (1H, dd, J=7.6 and 11.7 Hz), 3.10 (1H, dd, J=3.9 and 11.7 Hz), 3.80 (3H, s), 3.81 (3H, s), 4.00 (1H, dd, J=5.3 and 16.2 Hz), 4.34 (1H, dd, J=2.0 and 16.2 Hz), 4.81–4.85 (1H, m), 5.47 (1H, s), 7.21–7.34 (3H, m, Ar-H), 7.47–7.50 (2H, m, Ar-H); ^{13}C NMR δ 37.8, 52.3, 52.4, 62.6, 75.7, 78.3, 126.6, 127.4, 128.1, 137.2, 137.4, 141.4, 163.4, 163.7; MS (EI) m/z 319 (M^+, 8), 288 (10), 273 (100), 242 (18); HRMS (EI) m/z 319.0878 ($C_{16}H_{17}NO_4S$ [M^+], 319.0888).

4.2.18. Dimethyl (3*S*,5*R*,7a*S*)-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 19a. Yield 9%; yellow oil; IR (KBr) 1436, 1646, 1723 cm^{-1}; ^1H NMR δ 3.21 (1H, dd, J=3.7 and 11.7 Hz), 3.33 (1H, dd, J=8.0 and 11.7 Hz), 3.53 (1H, d, J=16.5 Hz), 3.73 (3H, s), 3.77 (1H, d, J=16.5 Hz), 3.83 (3H, s), 4.75–4.80 (1H, m), 5.73 (1H, s), 7.35–7.38 (3H, m, Ar-H), 7.46–7.49 (2H, m, Ar-H); ^{13}C NMR δ 39.2, 52.2, 52.4, 56.2, 74.9, 77.9, 128.4, 128.5, 128.7, 135.5, 136.7, 138.0, 163.5, 166.5; MS (EI) m/z 319 (M^+, 9), 288 (11), 273 (100), 242 (19); HRMS (EI) m/z 319.0878 ($C_{16}H_{17}NO_4S$ [M^+], 319.0873).

4.2.19. Dimethyl (3*R*,5*R*,7a*S*)-5-ethyl-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 18b. Yield 64%; white solid; mp 56.8–57.9 °C (from ethyl acetate–hexane); IR (KBr) 1653, 1723, 1737, 2957 cm^{-1}; ^1H NMR δ 0.99 (3H, t, J=7.4 Hz, CH_2CH_3), 1.64–1.73 (2H, m, CH_2CH_3), 2.94 (1H, dd, J=7.4 and 11.8 Hz, H-1_{cis}), 3.02 (1H, dd, J=3.5 and 11.98 Hz, H-1_{trans}), 3.78 (3H, s, 7-CO_2CH_3), 3.83 (3H, s, 6-CO_2CH_3), 4.19–4.24 (1H, m, H-5), 4.80–4.84 (1H, m, H-7a), 5.46 (1H, s, H-3), 7.24–7.32 (3H, m, H-3′,4′,5′), 7.51–7.53 (2H, m, H-2′,6′). ^{13}C NMR δ 9.2 (CH_2CH_3), 27.5 (CH_2CH_3), 37.4 (C-1), 52.2 and 52.3 (6- and 7-CO_2CH_3), 74.2 (C-5), 75.0 (C-7a), 78.0 (C-3), 126.7 (C-2′,6′), 127.3 (C-4′), 128.0 (C-3′,5′), 134.2 (C-7), 141.9 (C-1′), 143.3 (C-6), 163.0 (6-CO_2CH_3), 164.7 (7-CO_2CH_3); MS (EI) m/z 347 (M^+, 9), 318 (21), 301 (81), 269 (100). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03; S, 9.23. Found: C, 62.16; H, 6.37; N, 4.47; S, 9.22.

4.2.20. Dimethyl (3*S*,5*R*,7a*S*)-5-ethyl-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 19b. Yield 7%; yellow oil; IR (KBr) 1436, 1658, 1724 cm^{-1}; ^1H NMR δ 0.60–0.85 (4H, m, CH_2CH_3), 0.99–1.06 (1H, m, CH_2CH_3), 3.14 (1H, dd, J=2.9 and 11.9 Hz, H-1_{trans}), 3.14 (1H, dd, J=8.1 and 11.9 Hz, H-1_{cis}), 3.76 (3H, s, 7-CO_2CH_3), 3.80 (3H, s, 6-CO_2CH_3), 4.34–4.38 (1H, m, H-5), 4.77–4.82 (1H, m, H-7a), 5.61 (1H, s, H-3), 7.35–7.37 (3H, m, H-3′,4′,5′), 7.51-7.54 (2H, m, H-2′,6′); ^{13}C NMR δ 7.7 (CH_2CH_3), 26.0 (CH_2CH_3), 39.9 (C-1), 52.2 and 52.3 (6- and 7-CO_2CH_3), 67.6 (C-5), 74.3 (C-7a), 77.7 (C-3), 128.3 (C-3′,5′), 128.9 (C-4′), 129.4 (C-2′,6′), 133.0 (C-7), 134.0 (C-1′), 145.0 (C-6), 162.7 (6-CO_2CH_3), 164.9 (7-CO_2CH_3); MS (EI) m/z 347 (M^+, 12), 318 (84), 301 (100), 269 (98).

4.2.21. Dimethyl (3*R*,5*R*,7a*S*)-3,5-diphenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 18c. Yield 24%; yellow oil; IR (KBr) 1435, 1629, 1654, 1723, 2941 cm^{-1}; ^1H NMR δ 3.07–3.10 (2H, m), 3.60 (3H, s), 3.79 (3H, s), 4.92–4.97 (1H, m), 5.28 (1H, d, J=5.0 Hz), 5.54 (1H, s), 7.24–7.34 (5H, m, Ar-H), 7.40–7.48 (5H, m, Ar-H); ^{13}C NMR δ 37.9, 52.2, 52.4, 73.5, 76.9, 77.2, 126.8, 127.3, 128.0, 128.1, 128.5, 128.7, 134.1, 139.2, 141.4, 143.1, 162.9, 163.8; MS (EI) m/z 395 (M^+, 6), 349 (100), 316 (34), 290 (31).

4.2.22. Dimethyl (3*R*,5*R*,7a*S*)-5-(*p*-methoxyphenyl)-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 18d. Yield 13%; white solid; mp 75.4–76.3 °C (from ethyl acetate–hexane); IR (KBr) 1662, 1728 cm^{-1}; ^1H NMR δ 3.08 (2H, d, J=5.9 Hz, H-1), 3.61 (3H, s, 7-CO_2CH_3), 3.78 (3H, s, 4″-OCH_3), 3.79 (3H, s, 6-CO_2CH_3), 4.88–4.93 (1H, m, H-7a), 5.23 (1H, d, J=4.9 Hz, H-5), 5.52 (1H, s, H-3), 6.86 (2H, d, J=8.7 Hz, H-3″,5″), 7.19–7.29 (3H, m, H-3′,4′,5′), 7.37 (2H, d, J=8.7 Hz, H-2″,6″), 7.44–7.47 (2H, m, H-2′,6′); ^{13}C NMR δ 38.0 (C-1), 52.2 (6-CO_2CH_3), 52.4 (7-CO_2CH_3), 55.2 (4′-OCH_3), 73.2 (C-7a), 76.7 and 76.8 (C-3 and C-5), 113.9 (C-3″,5″), 126.8 (C-2′,6′), 127.3 (C-4′), 128.1 (C-3′,5′), 129.2 (C-2″,6″), 131.2 (C-1″), 133.7 (C-7), 141.5 (C-1′), 143.4 (C-6), 159.5 (C-4″), 162.9 (6-CO_2CH_3), 164.0 (7-CO_2CH_3); MS (EI) m/z 425 (M^+, 9), 392 (6), 379 (100), 346 (30). Anal. Calcd for $C_{23}H_{23}NO_5S$: C, 64.92; H, 5.45; N, 3.29; S, 7.53. Found: C, 64.85; H, 5.71; N, 3.28; S, 7.33.

4.2.23. Dimethyl (3*R*,5*R*,7a*S*)-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 21a. Yield 35%; yellow solid; mp 100.1–100.8 °C (from ethyl acetate–hexane); IR (KBr) 1675, 1720, 2954 cm^{-1}; ^1H NMR δ 2.93 (1H, dd, J=7.6 and 11.9 Hz), 3.15 (1H, dd, J=3.6 and 11.9 Hz), 3.83 (6H, s), 4.03 (1H, dd, J=5.2 and 16.2 Hz), 4.38 (1H, dd, J=1.9 and 16.2 Hz), 4.78–4.84 (1H, m), 5.50 (1H, s), 7.68 (2H, d, J=8.8 Hz), 8.17 (2H, d, J=8.8 Hz); ^{13}C NMR δ 37.8, 52.5, 52.5, 62.8, 75.7, 77.3, 123.4, 127.7, 136.7, 137.5, 147.2, 149.0, 163.2, 163.4. Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.71; H, 4.38; N, 7.55.

4.2.24. Dimethyl (3*S*,5*R*,7a*S*)-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 22a. Yield 18%; yellow oil; IR (KBr) 1522, 1660, 1725 cm^{-1}; ^1H NMR δ 3.27 (1H, dd, J=3.7 and 11.7 Hz), 3.37 (1H, dd, J=8.0 and 11.7 Hz), 3.52–3.64 (2H, m), 3.73 (3H, s), 3.84 (3H, s), 4.79–4.81 (1H, m), 5.75 (1H, s), 7.67 (2H, d, J=8.9 Hz), 8.24 (2H, dd, J=8.9 Hz); ^{13}C NMR δ 39.6, 52.3, 52.5, 56.4, 75.0, 76.9, 123.7, 129.7, 136.9, 137.4, 142.8, 147.8, 163.1, 163.3; MS (EI) (CI) m/z 363 (MH^+, 46), 318 (11), 272 (29), 244 (100); HRMS (EI) m/z 365.0807 ($C_{16}H_{17}N_2O_6S$ [M^+], 365.0809).

4.2.25. Dimethyl (3*R*,5*R*,7a*S*)-5-methyl-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 21b. Yield 35%; yellow solid; mp 113.8–115.2 °C (from ethyl acetate–hexane); IR (KBr) 1663, 1722, 1738, 2955 cm^{-1}; ^1H NMR δ 1.39 (1H, d, J=6.7 Hz), 2.97 (1H, dd, J=7.6 and 11.7 Hz), 3.06 (1H, dd, J=4.2 and 11.7 Hz), 3.80 (3H, s), 3.85 (3H, s), 4.27–4.31 (1H, m), 4.74–4.79 (1H, m), 5.51 (1H, s), 7.70 (2H, d, J=8.7 Hz), 8.18 (2H, d, J=8.7 Hz); ^{13}C NMR δ 20.9, 37.7, 52.4, 69.2, 73.8, 75.9, 123.4, 127.8, 133.7, 143.5, 147.2, 149.4, 162.9, 164.3; MS (EI) m/z 378 (M^+, 3), 332 (84), 300 (100).

4.2.26. Dimethyl 3-(*p*-nitrophenyl)-5-propenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 23. Yield 5%; oil; ^1H NMR δ 1.69–1.73 (3H, m), 3.01–3.04 (2H, m), 3.79 (3H, s), 3.82 (3H, s), 4.63–4.65 (1H, m), 4.73–4.75 (1H, m), 5.48–5.50 (2H, m), 5.73–5.75 (1H, m), 7.67–7.70 (2H, m, Ar-H), 8.15–8.18 (2H, m, Ar-H); ^{13}C NMR δ 18.1, 38.4, 52.8, 73.7, 75.6, 76.4, 123.8, 128.3, 129.3, 131.0, 133.5, 143.6, 147.6, 149.9, 163.1, 164.6; MS (EI) m/z 404 (M^+, 2%), 357 (100), 326 (41), 299 (71).

4.2.27. Dimethyl (3*R*,5*R*,7a*S*)-5-ethyl-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 21c. Yield 70%; yellow solid; mp 98.9–102.8 °C (from ethyl acetate–hexane); IR (KBr) 1676, 1719, 1739, 2960 cm^{-1}; ^1H NMR δ 0.98 (3H, t, J=7.3 Hz), 1.68–1.74 (2H, m), 2.92 (1H, dd, J=7.6 and 12.0 Hz), 3.07 (1H, dd, J=3.3 and 12.0 Hz), 3.80 (3H, s), 3.84 (3H, s), 4.20–4.25 (1H, m), 4.80–4.84 (1H, m), 5.47 (1H, s), 7.69 (2H, d, J=8.9 Hz), 8.18 (2H, dd, J=8.9 Hz); ^{13}C NMR δ 9.3, 27.6, 37.4, 52.4, 52.5, 74.4, 75.3, 76.3, 123.4, 127.7, 133.8, 143.3, 147.2, 149.5, 152.2, 162.6, 164.5; MS (EI) m/z 392 (M^+, 5), 346 (85), 331 (57), 314 (100). Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.25; H, 4.89; N, 7.21.

4.2.28. Dimethyl (3*S*,5*R*,7a*S*)-5-ethyl-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 22c. Yield 4%; yellow oil; IR (KBr) 1676, 1719, 1739, 2960 cm^{-1}; ^1H NMR δ 0.61–0.70 (3H, m), 1.09–1.26 (2H, m), 3.21 (1H, dd, J=2.9 and 11.9 Hz), 3.37 (1H, dd, J=8.0 and 11.9 Hz), 3.78 (3H, s), 3.81 (3H, s), 4.26–4.30 (1H, m), 4.80–4.85 (1H, m), 5.63 (1H, s), 7.72 (2H, d, J=8.7 Hz), 8.25 (2H, dd, J=8.7 Hz); ^{13}C NMR δ 7.6, 26.1, 40.2, 52.4, 67.7, 74.6, 76.6, 123.5, 130.5, 133.2, 141.5, 144.4, 148.1, 162.6, 164.6; MS (EI) m/z 392 (M^+, 5), 346 (85), 331 (57), 314 (100). Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.25; H, 4.89; N, 7.21.

4.2.29. Dimethyl (3*R*,5*R*,7a*S*)-5-(*p*-methoxyphenyl)-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 21d. Yield 14%; yellow oil; IR (KBr) 1513, 1610, 1664, 1729, 2943 cm^{-1}; ^1H NMR δ 3.07 (1H, dd, J=7.5 and 11.6 Hz), 3.13 (1H, dd, J=4.5 and 11.6 Hz), 3.62 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 4.86–4.92 (1H, m), 5.23 (1H, d, J=4.9 Hz), 6.88 (2H, d, J=8.7 Hz), 7.35 (2H, d, J=8.7 Hz), 7.62 (2H, d, J=8.8 Hz), 8.12 (2H, d, J=8.8 Hz); ^{13}C NMR δ 38.0, 52.4, 52.5, 55.2, 73.4, 75.5, 76.9, 114.0, 123.4, 127.8, 129.2, 130.7, 133.3, 143.3, 147.2, 149.0, 159.7, 163.8; MS (CI) m/z 471 (MH^+, 96), 441 (61), 393 (21), 363 (100); HRMS (EI) m/z 471.1225 ($C_{23}H_{23}N_2O_7S$ [M^+], 471.1228).

4.3. Dimethyl 3,4-bis[(1,2-bis-methoxycarbonylvinyl)]-thiazolidine 14

A mixture of thiazolidine-4-carboxylic acid **5a** (0.49 g, 3.75 mmol) and dimethyl acetylenedicarboxylate (0.79 g, 5.6 mmol) in toluene (40 mL), in the presence of molecular sieves, was stirred and heated under reflux for 3–4 h. The reaction mixture was then filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography [ethyl acetate–hexane (1:2) then ethyl acetate–hexane (1:1)]. Yield 25%; yellow solid; mp 115.9–116.7 °C (from ethyl acetate–hexane); IR (KBr) 1587, 1703, 1722 cm^{-1}; ^1H NMR δ 2.84 (1H, dd, J=7.8 and 16.9 Hz), 3.04 (1H, dd, J=6.8 and 16.9 Hz), 3.72 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 4.25 (2H, br s), 4.56 (1H, approx. t, J=6.8 and 7.8 Hz), 7.31 (1H, s), 7.63 (1H, s); ^{13}C NMR δ 34.6, 52.0, 52.3, 52.4, 53.0, 59.3, 65.4, 103.6, 134.7, 135.1, 146.1, 168.1, 168.6, 169.0, 169.8; MS (EI) m/z 373 (M^+, 39%), 200 (31), 169 (100), 114 (88). Anal. Calcd for $C_{15}H_{19}NO_8S$: C, 48.25; H, 5.13; N, 3.75. Found: C, 48.34; H, 4.96; N, 3.63.

4.3.1. Computational methods. The input structures of conformers of thiazolidin-3-ium-4-carboxylate betaine intermediates (namely 3-propylidene- and 3-benzylidene-1,3-thiazolidin-3-ium-4-carboxylate) have been prepared by setting the C=N–C–C angle for ca. 0 and 180° (*Z* and *E* configurations, respectively). The *anti* (*E*) and *syn* (*Z*) configurations of the C–N–C–C or C=N–C–C angle were considered for 3-ethyl- and 3-phenyldihydro-1*H*-[1,3]thiazolo[3,4-*c*]-[1,3]oxazol-1-one and the 1,3-dipole intermediates (3-propylidene-1,3-thiazolidin-3-ium-4-ide and 3-benzylidene-1,3-thiazolidin-3-ium-4-ide). In all cases, conformational isomers were taken into account for the structures with R=Et due to the rotational freedom within the substituent. All input structures were subjected to geometry optimization and frequency calculations at the DFT level of approximation (B3LYP method[13,14]) with the standard 6-31+G(d) basis set. The nature of the stationary points resulting from geometry optimization was checked by analysis of the corresponding Hessian matrices. Thermochemical properties (at 298.15 and 383.15 K, the latter being the temperature at which the reactions were conducted) were computed for all calculated conformers and their relative abundances were estimated using the $\Delta G^o = RT \ln K_c$ equation, where ΔG^o is the standard Gibbs free energy relative to the most stable conformer and K_c is the concentration ratio of a given conformer to the most stable conformer. The transition states for conformational interconversions were also calculated at the same level of theory, with the STQN[15] (QST3) method, for chosen pairs of conformers differing by internal rotation around the C=N or C–N bond. All the above-mentioned calculations were performed using Gaussian 03.[16]

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Supplementary data

The optimized structures of the intermediates of decarboxylative condensation of 2-unsubstituted-1,3-thiazolidine-4-carboxylic acid with propionaldehyde and with benzaldehyde. Relative zero-point energies, Gibbs free energies, and abundances of conformers of 3-propylidene-1,3-thiazolidin-3-ium-4-carboxylic acid, 3-benzylidene-1,3-thiazolidin-3-ium-4-carboxylic acid, 3-ethyldihydro-1*H*-[1,3]thiazolo-[3,4-*c*][1,3]oxazol-1-one, and 3-phenyldihydro-1*H*-[1,3]-thiazolo[3,4-*c*][1,3]oxazol-1-one, calculated based on ΔG values. Main connectivities found in the HMBC and NOE spectra of compounds **10e**, **18b**, and **19b**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.029.

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