Enolates of 2-Isothiocyanatocarboxylic Esters: Synthesis of Thiazolo[5,4-*d*]-thiazole Derivatives and 2-Thioxo-1,3-thiazolidine-4-carboxylates

Dariusz Cież,* Justyna Kalinowska-Tłuścik

Faculty of Chemistry, Jagiellonian University, ul. Romana Ingardena 3, 30-060 Kraków, Poland
Fax +48(12)6340515; E-mail: ciez@chemia.uj.edu.pl

Received: 19.01.2012; Accepted after revision: 09.03.2012

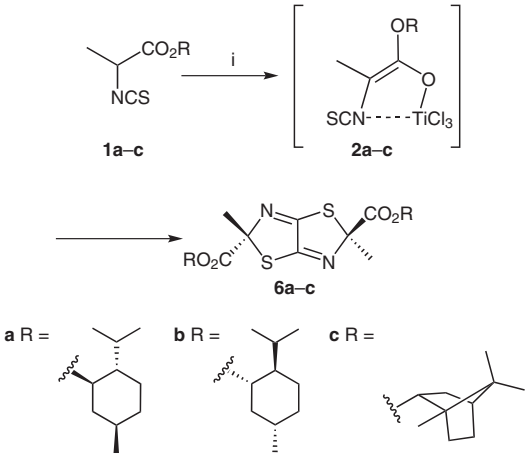
Abstract: An oxidative dimerization of titanium(IV) enolates derived from menthyl esters of 2-isothiocarboxylic acids leads to radical coupling followed by cyclization. This cascade reaction gives thiazolo[5,4-*d*]thiazole derivatives as pure enantiomers. Under similar conditions, 2-methylbutyl esters of 2-isothiocyanatocarboxylic acids undergo intermolecular oxidative dimerization to give mixtures of thiazolo[5,4-*d*]thiazoles and 2,3-diisothiocyanatosuccinates. Application of the soft enolization technique to dimethyl α,α′-diisothiocyanatodicarboxylic esters gives novel cyclic 1,2-diisothiocyanato-1,2-dicarboxylates. Sodium enolates of 2-isothiocyanatocarboxylates, on the other hand, form 5-imino-2-thioxo-1,3-thiazolidine-4-carboxylic esters by nonoxidative dimerization. The mechanisms of the two reaction pathways are discussed.

Key words: domino reactions, dimerizations, heterocycles, enols, titanium, diastereoselectivity

In synthesis, 2-isothiocyanatocarboxylic esters are mainly used in preparing five-membered heterocycles or acyclic thioureas. The earliest report on the reaction of ethyl 2-isothiocyanato-4-methylpentanoate with ammonia to give 2-thioxoimidazolidin-4-one appeared nearly 90 years ago.[1] Later reports on preparations of 2-thioxoimidazolidin-4-ones describe reactions with amines,[2] hydrazones,[3] and aminonitriles.[4] Syntheses of 1,2,3,4-thiatriazole[5] and some acyclic thioureas[6] have also been described. Thioureas derived from 2-isothiocyanatocarboxylates can serve as convenient reactants for preparation of chiral isothiazolidines that are potentially useful as antiviral agents.[7] Titanium(IV)-promoted oxidative coupling reactions of 2-isothiocyanatocarboxylic esters have been used in attempts to synthesize masked symmetric 2,3-diaminosuccinates[8] and 2-thioxoimidazolidine rings.[9] More recently, 2-isothiocyanatocarboxylic esters have been used as substrates in stereoselective Mannich additions leading to 2-thioxo-1,3-imidazolidines, which are derivatives of 2,3-diaminosuccinic acid.[10]

Titanium(IV) enolates of carboxylic esters can serve as very convenient and useful intermediates for C–C bond-formation reactions.[11] Our research in the field of titanium(IV) enolates has focused on oxidative coupling reactions to form vicinal 2,3-diisothiocyanatosuccinates[8] and pyrrole derivatives.[12] More recently, we found that titanium(IV) enolates derived from 2-nitrocarboxylic esters can be quantitatively chlorinated under oxidative conditions.[13] Our investigations on the mechanism of the oxidative coupling reaction have identified both the scope and limitations of this process. The oxidative dimerization of 2-isothiocyanatocarboxylic esters attracted our attention because the resulting 2,3-diisothiocyanato succinic acid derivatives could be regarded as masked 2,3-diamino acids.

In continuation of our previous research on the diastereoselectivity of the oxidative coupling reaction, we synthesized two novel 2-isothiocyanatocarboxylic esters, L-menthyl 2-isothiocyanatopropanoate (**1a**) and D-menthyl 2-isothiocyanatopropanoate (**1b**), that contain large chiral ester groups. Soft enolization of L-menthyl 2-isothiocyanatopropanoate (**1a**) with the titanium(IV) chloride–diisopropyl(ethyl)amine system led exclusively to a single oxidation product, but analysis of its NMR spectra and two-dimensional (2-D) NMR studies showed that this compound was not the expected 2,3-diisothiocyanatosuccinate, but was, in fact the thiazolo[5,4-*d*]thiazole **6a** (Scheme 1). The titanium(IV) enolates of D-menthyl 2-isothiocyanatopropanoate (**1b**) and *endo*-(1*S*)-bornyl 2-isothiocyanatoacetate (**1c**) also underwent oxidative coupling to give the same fused heterocyclic system in the products **6b** and **6c**, respectively.



Scheme 1 Oxidative dimerization of titanium(IV) enolates of 2-isothiocyanatopropanoates **1a**–**c** to give thiazolo[5,4-*d*]thiazole derivatives **6a**–**c**, respectively. *Reagents and conditions:* (i) $TiCl_4$, CH_2Cl_2, argon, –96 °C then DIPEA, CH_2Cl_2, –96 °C to r.t.

The ^{13}C NMR spectra of both the thiazolo[5,4-*d*]thiazole derivatives **6a** and **6b** exhibited double signals for all the nonequivalent carbon atoms. This suggested that the prod-

SYNTHESIS 2012, 44, 1736–1744
Advanced online publication: 23.04.2012
DOI: 10.1055/s-0031-1290825; Art ID: SS-2012-Z0069-OP

ucts might each consist of a mixture of two diastereoisomeric forms. However, the two products showed equal but opposite specific rotations, which is typical of enantiomers rather than diastereoisomers. Indeed, an X-ray crystal structure analysis of **6a** showed that the C-2 and C-5 atoms have absolute configurations of *R* and *S*, respectively (Figure 1), indicating that the oxidative coupling reactions of L- and D-menthyl 2-isothiocyanatopropanoates **1a** and **1b** are highly diastereoselective.

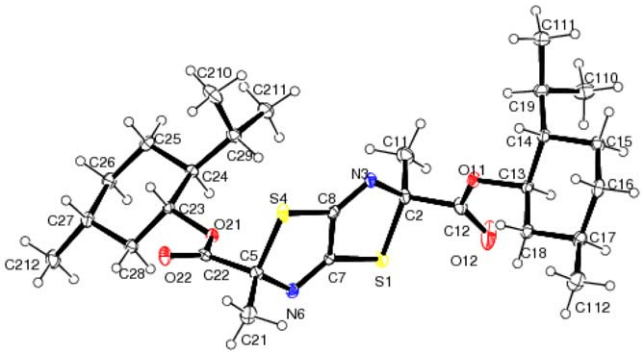
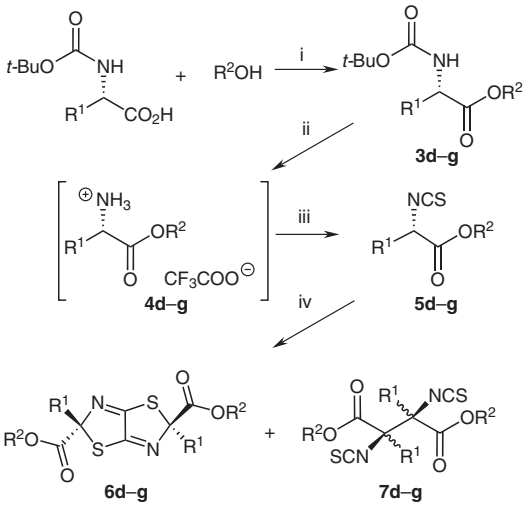


Figure 1 Molecular structure of di-L-menthyl (2*R*,5*S*)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-*d*]thiazole-2,5-dicarboxylate (**6a**) as determined by x-ray crystallographic analysis; the atom displacement ellipsoids are drawn at the 30% probability level[14]

Our results suggested that the size of the ester group has a significant effect on the oxidative coupling of titanium(IV) enolates derived from 2-isothiocyanatocarboxylates and that the reaction can give either a 2,3-diisothiocyanatosuccinic ester or a fused thiazolo[5,4-*d*]thiazole system. To verify this, we prepared chiral (2*S*)-2-methylbutyl (2*S*)-2-isothiocyanatopropanoate (**5d**) in three steps from commercial *N*-(*tert*-butoxycarbonyl)alanine and (2*S*)-(–)-2-methylbutan-1-ol. Deprotection of the ester **3d** by trifluoroacetic acid gave the nonisolable ester of L-alanine **4d**, which was transformed into (2*S*)-2-methylbutyl (2*S*)-2-isothiocyanatopropanoate (**5d**) by the thiophosgene method. The designed ester group is smaller than the menthyl substituent, but is branched. Chiral isothiocyanato ester **5d** was transformed into the corresponding titanium(IV) enolate, which underwent dimerization to give coupling products (Scheme 2). Gas chromatography–mass spectrometric analysis of the reaction mixture showed that the reaction gave two products with the same molecular mass but different fragmentation patterns. NMR studies on the isolated products showed that the oxidative coupling had produced both the thiazolo[5,4-*d*]thiazole **6d** and the 2,3-diisothiocyanatosuccinate derivative **7d**. Titanium(IV) enolates of (2*S*)-2-methylbutyl (2*S*)-2-isothiocyanato-4-methylpentanoate (**5e**) and (2*S*)-2-methylbutyl (2*S*)-2-isothiocyanato-3-phenylpropanoate (**5f**) similarly gave DL-2,3-diisothiocyanatosuccinates **7e** and **7f**, respectively, as the main products. The DL-diastereoselectivity of the coupling process was in excess of 95%. Traces of the *meso* forms **7e** and **7f** and of the fused thiazolo[5,4-d]thiazole derivatives **6e** and **6f** were detected by GC analysis of the reaction mixture. The cyclohexyl ester of 2-isothiocyanatopropanoate **5g** gave DL-2,3-diisothiocyanatosuccinate **7g** and *meso*-thiazolo[5,4-d]thiazole **6g** in a 2:3 ratio.

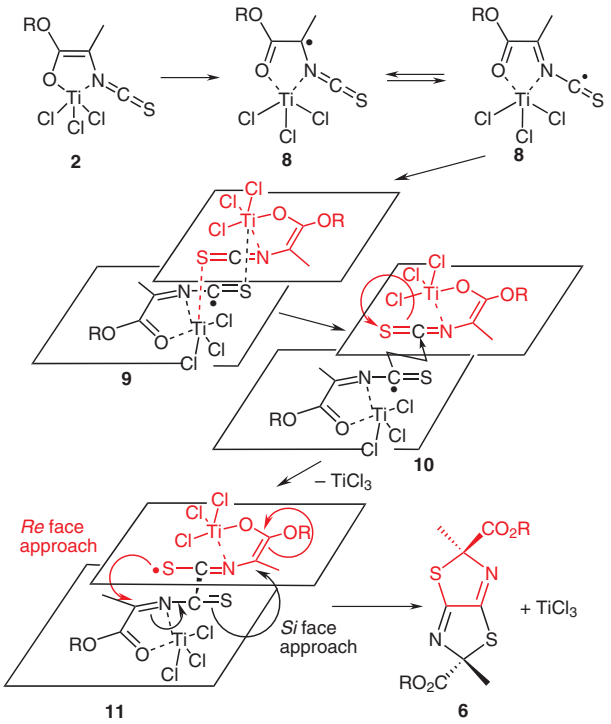


Scheme 2 Titanium(IV) enolates derived from 2-isothiocyanatocarboxylates bearing medium-sized ester groups underwent oxidative dimerization to give two oxidation products; **d**: R^2 = (2*S*)-$CH_2CH(Me)Et$; R^1 = Me, **e**: R^2 = (2*S*)-$CH_2CH(Me)Et$; R^1 = *i*-Bu, **f**: R^2 = (2*S*)-$CH_2CH(Me)Et$; R^1 = Bn; **g**: R^2 = Cy; R^1 = Me. *Reaction conditions*: (i) DCC, DMAP, CH_2Cl_2; (ii) 5% TFA in CH_2Cl_2; (iii) $CSCl_2$, $NaHCO_3$, CH_2Cl_2/H_2O; (iv) $TiCl_4$, CH_2Cl_2, argon, –96 °C, then DIPEA, CH_2Cl_2, –96 °C to r.t.

An analysis of the competition between the two different oxidation processes showed that substituents at C-2 had an opposite effect on the dimerization reaction to that of the ester group. Branched and bulky ester groups apparently hindered the formation of 2,3-diisothiocyanatosuccinic esters and promoted the oxidative coupling to form thiazolo[5,4-*d*]thiazole derivatives, whereas medium-sized substituents at C-2 promoted the formation of the corresponding 2,3-isothiocyanatosuccinates. In each case, however, the final products consisted of equilibrium mixtures of the two types of dimer.

The highly diastereoselective oxidative coupling reaction leading to the thiazolo[5,4-*d*]thiazole system appears to be a cascade radical process that commences with oxidation of the titanium(IV) enolate to a radical **8**. This step is mediated by titanium(IV) ions that undergo reduction to titanium(III) species. We assume that the dimeric transition state that Matsumura[15] postulated as being typical of oxidative coupling reactions that lead to 2,3-diisothiocyanatosuccinates is not formed in the presence of large ester groups because of steric repulsion. The radical **8** undergoes intermolecular coupling to form a new C–C single bond between the two isothiocyanate groups, resulting in intermediate **10**. This step initiates a cascade reaction involving double thiolation of the imine function to give **11**, which finally undergoes ring closure to give the thiazolo[5,4-*d*]thiazole system **6** (Scheme 3). This domino radical cyclization shows a very high diastereoselectivity in forming a thiazolo[5,4-*d*]thiazole core in which the C-2

and C-5 atoms have opposite configurations. This phenomenon can be explained in terms of a highly ordered transition state that forms three-dimensional structures in solution. The titanium(IV) enolates undergo self-assembly and self-organization processes in solution as a result of the coordination properties of the titanium ions. We propose a reaction mechanism based on a dimeric transition state, as previously suggested for oxidative coupling of phenylacetate derivatives,[15a,b] except that in our model, we assume that two enolate subunits are linked by titanium(IV) ions and form a three-dimensional transition state **9** in which the bulky ester substituents are located in the opposite peripheral parts of the structure. The assumption that the bulky ester groups will be located opposite one another turns out to be helpful in explaining the diastereoselectivity of the reaction. The addition of the sulfur radical at the *re*-face of the enolate **11** is followed by attack of the second sulfur radical at the *si*-face. In this way, the reaction leads to the fused thiazolo[5,4-*d*]thiazole system with opposite configurations at the C-2 and C-5 positions.



Scheme 3 A tentative reaction mechanism that explains the very high diastereoselectivity of the oxidation process

Investigations of the competition between two oxidative coupling processes led us to conclude that 2,3-diisothiocyanatocarboxylic esters **7** can be obtained only when the 2-isothiocyanatocarboxylates contain small or medium-sized ester groups. The presence of bulky or branched ester substituents appears to change the reaction mechanism and leads to a domino process that gives the thiazolo[5,4-*d*]thiazole derivatives **6**. This differences in reaction mechanism appear to arise from the presence of distinct transition states for each of the two processes and it precludes the use of chiral auxiliaries for stereoselective formation of 2,3-diisothiocyanatocarboxylic esters. We therefore designed some 2-isothiocyanatocarboxylic esters that contained bulky chiral ester groups but which were unable to form the thiazolo[5,4-*d*]thiazole system because of the presence of a rigid structure that prevented the formation of the transition state **9**. These reactants, which were diesters of diols with 2-isothiocyanatocarboxylic acids, were prepared in three step from several chiral diols [(*R*)- and (*S*)-1,1′-binaphthalene-2,2′-diol, and 1,2;5,6-di-*O*-cyclohexylidene-D-mannitol] and protected amino acids. After esterification and deprotection, the amino groups were transformed into isothiocyanate functions by the thiophosgene method to give the desired diesters **12**–**15** (Figure 2). We assumed that the chiral ester auxiliaries would promote enantioselective oxidative coupling of the 2-isothiocyanatocarboxylic fragments to give the corresponding chiral 2,3-diisothiocyanatosuccinic acid derivatives. However, reactions of diesters **12**–**15** with the titanium(IV) chloride/diisopropyl(ethyl)amine oxidizing system failed to give any dimerization products. Although the reactants readily formed double titanium(IV) enolates, oxidative coupling was restrained and only the starting material was recovered. As expected, the recovered reactants **13**–**15** showed nearly complete racemization at the α-positions in the 2-isothiocyanatocarboxylic fragments. The experiment proved that the formation of 2,3-diisothiocyanatosuccinates and thiazolo[5,4-*d*]thiazole derivatives is markedly dependent on the spatial structure of the transition state. The structure of the transition state is determined by interactions of the enolates derived from the 2-isothiocyanatocarboxylic esters. These results differ from those previously described by Periasamy[15b] for stereoselective oxidative coupling of chiral binaphth-2-yl arylacetates. It is likely that the titanium(IV) enolates formed from the isothiocyanatoacetates underwent isomerization before coupling and that they formed a complex that was unable to dimerize. Titanium(IV) enolates derived from binaphth-2-yl arylacetates, on the other hand, are more stable and therefore capable of giving the corresponding oxidative dimerization prod-

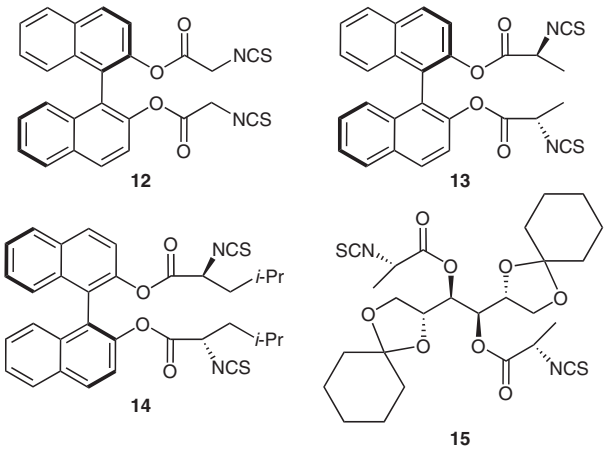
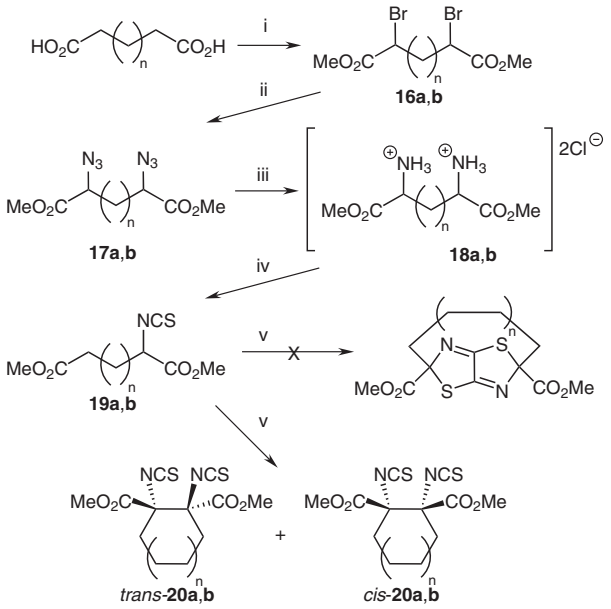


Figure 2 Chiral diesters of 2-isothiocyanatocarboxylic acids can be transformed into double enolates by the soft-enolization technique, but they do not undergo oxidative coupling

ucts. The labilities of titanium complexes and their stereochemical rearrangements are known and have been previously reported.[16a,b]

Our next experiment was designed to confirm our observations concerning the chemo- and regioselectivity of the oxidative coupling. We investigated the oxidative dimerization of acyclic, enolizable diisothiocyanato esters derived from dicarboxylic acids. The substrates, which were esters of α,α′-diisothiocyanatosuberic and α,α′-diisothiocyanatosebacic acids, (**19a** and **19b**, respectively), were prepared in several steps from the corresponding α,α′-dibromodicarboxylates **16a** and **16b**. We expected that the presence of a long hydrocarbon chain would hinder oxidative coupling to form the bicyclic thiazolo[5,4-*d*]thiazole (Scheme 4) and would, instead, give the products of intramolecular cyclization. Indeed, our experiments showed that the double titanium(IV) enolates formed from dimethyl α,α′-diisothiocyanatodicarboxylates **19a** and **19b** or their diethyl analogues undergo an oxidative dimerization to give the corresponding cyclic 1,2-diisothiocyanato-1,2-dicarboxylates **20a** and **20b**, respectively, which represent a new group of cyclic dicarboxylic acids . Unlike the oxidative dimerization of simple 2-isothiocyanatocarboxylates, the degree of diastereoselectivity in the formation of the 1,2-diisothiocyanato-1,2-dicarboxylates **20a** and **20b** was low, and nearly equimolar amounts of the *cis*- and *trans*-diastereoisomers were obtained. Yields of products **20a** and **20b** were moderate, but we did not find any traces of thiazolo[5,4-*d*]thiazole derivatives. Because of their similar properties, it was impossible to separate the *cis*- and *trans*-forms of 1,2-diisothiocyanato-1,2-dicarboxylates **20a** and **20b**, and therefore the NMR spectra of these products included data for both diastereoisomers. On the basis of the integration data, we hypothesized that one diastereoisomer exists as two conformers. Analysis of the possible conformations of *cis*- and *trans*-**20a** showed that only the *trans*-diastereoisomer could have two different conformational energies corresponding to the two ring-flipped forms. These forms differ in terms of the spatial orientation of the vicinal isothiocyanate and ester groups, which can be either diaxial or diequatorial, respectively.

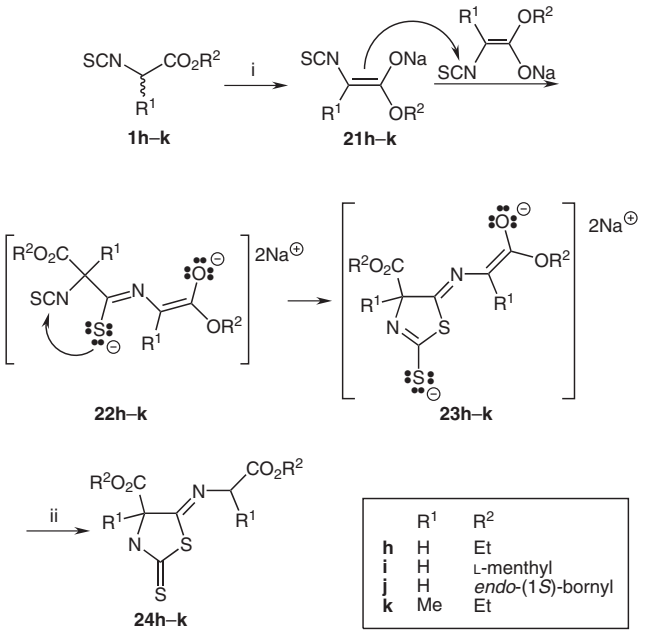


Scheme 4 Synthesis and oxidative coupling of α,α′-diisothiocyanatodicarboxylates; **a**: n = 1, **b**: n = 2. *Reagents and conditions*: (i) $SOCl_2$, Br_2, then MeOH; (ii) NaN_3, DMF; (iii) Ph_3P then aq HCl, MeOH; (iv) $CSCl_2$, $NaHCO_3$, $CHCl_3/H_2O$; (v) $TiCl_4$, CH_2Cl_2, argon, –96 °C then DIPEA, CH_2Cl_2, –96 °C to r.t.

Unlike *trans*-**20a**, the second diastereoisomer, *cis*-**20a**, shows equivalent conformational energies for the two ring-flipped conformers.[17] We therefore assigned the double signals to the *trans*-**20a** diastereoisomer. Analysis of the NMR data recorded for the eight-membered 1,2-diisothiocyanato-1,2-dicarboxylate **20b** showed an excess of one diastereoisomer, but the conformational diversity of the cyclooctane ring prevented us from identifying which diastereoisomer, *cis*- or *trans*-**20b**, is the main product of the oxidative coupling. An attempt to prepare chiral 1,2-diisothiocyanato-1,2-dicarboxylates failed: oxidative coupling of chiral L-menthyl or (2*S*)-2-methylbutyl diesters of α,α′-diisothiocyanatosebacic acid did not give any products, whereas the use of diethyl α,α′-diisothiocyanatosuberate or α,α′-diisothiocyanatosebacate led to oxidative dimerization. This experiment proved that the size of the ester group plays a major role in the intramolecular oxidative coupling reactions.

We also compared our results pertaining to the properties and reactivities of titanium(IV) enolates with those for the corresponding sodium enolates of 2-isothiocyanatocarboxylates. We chose sodium as a counterion for enolate formation because the stability of the sodium enolates should prevent any accidental oxidative coupling processes. Unlike titanium(IV) enolates, alkali metal enolates tend to undergo oxidative coupling reactions only in the presence of oxidizing agents.[18] 2-Isothocyanatocarboxylates **1** readily gave the sodium enolates **21** on treatment with sodium hydride in anhydrous *N*,*N*-dimethylformamide, but the enolates spontaneously underwent intermolecular dimerization to give the 5-imino-2-thioxo-1,3-thiazolidine-4-carboxylic esters **24** in moderate-to-good yields (Scheme 5). Products **24** were isolated by pouring the reaction mixture into ice–water and neutralizing the resultant basic solution. Both the ester groups were stable and aqueous workup did not cause hydrolysis. The transformation could be described in terms of a two-step mechanism (Scheme 5) involving addition of the sodium enolate **21** to the isothiocyanate group and subsequent cyclization of the intermediate **22** after repeated addition of the sulfur anion to the isothiocyanate function. The 5-imino-2-thioxo-1,3-thiazolidine-4-carboxylic ester product remains in an anionic form as the disodium salt **23**, which can be readily converted into the desired product **24** by treatment with an acid. Our suggested mechanism, in which enolization at the chiral center of the 2-isothiocyanatocarboxylic ester is followed by racemization, explains the low stereoselectivity of this reaction. The use of a substoichiometric amounts of sodium hydride resulted in a

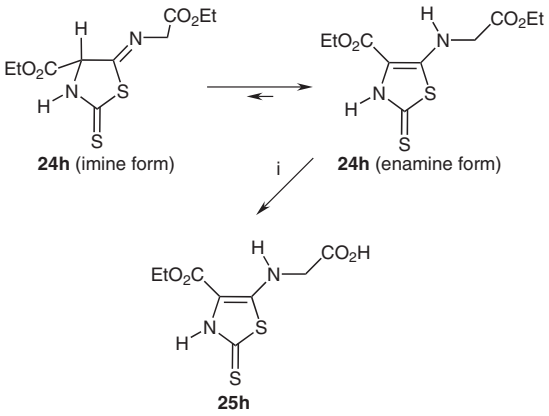
dramatic decrease in the yield. This showed that the first step of the reaction, enolate attack on the isothiocyanate group, was only possible when the second reactant was also present as an enolate. In other cases, the enolate reacted with the α-hydrogen atom and did not undergo an addition to the isothiocyanate function of the 2-isothiocyanatocarboxylate.



Scheme 5 A tentative reaction mechanism suggested for the intermolecular cyclization of sodium enolates. *Reagents and conditions*: (i) NaH, DMF, r.t.; (ii) AcOH, H_2O.

NMR spectra of the 1,3-thiazolidine-4-carboxylic esters **24h**–**j** derived from ethyl isothiocyanoacetates **1h**–**j**, respectively, showed that the 2-thioxo-1,3-thiazolidines **24h**–**j** exist mainly as the enamine tautomers formed by a 1,3-hydrogen shift from C-4 to the imine group (Scheme 6). Unlike the dimers derived from isothiocyanatoacetates, 5-imino-2-thioxo-1,3-thiazolidine-4-carboxylic ester **24k**, prepared from ethyl 2-isothiocyanatopropanoate (**1k**) existed exclusively as the imine. Moreover, the dimer **24k** consisted of an equimolar mixture of diastereoisomers because the stereoselectivity of the intermolecular dimerization was poor. The pure enantiomers of 2-thioxo-1,3-thiazolidine-4-carboxylates **24i** and **24j** were obtained by dimerization of sodium enolates of L-menthyl and *endo*-(1*S*)-bornyl isothiocyanoacetates **1i** and **1j**, respectively.

The transformation of 5-imino-2-thioxo-1,3-thiazolidine-4-carboxylic esters **24** into carboxylic acids **25** was possible under basic or acidic conditions, but only one ester group underwent hydrolysis. Analysis of the MS/MS spectra of **25h** proved that the 4-ethoxycarbonyl group was stable and remained unchanged whereas the *N*-amino acid fragment of the 1,3-thiazolidine ring was hydrolyzed (Scheme 6). An attempt to hydrolyze both ester groups



Scheme 6 Hydrolysis of 5-imino-2-thioxo-1,3-thiazolidine-4-carboxylic ester **24h** to carboxylic acid **25h**. *Reagents and conditions*: (i) NaOH, EtOH, r.t. then aq HCl (1.0 equiv).

failed because the 1,3-thiazolidine ring decomposed under the harsh conditions that were required.

In summary, we found that the reactivity of 2-isothiocyanatocarboxylates is markedly dependent on their structure, permitting their use in syntheses of novel heterocyclic systems or vicinal diisothiocyanates. Titanium(IV) enolates of 2-isothiocyanatocarboxylic esters bearing bulky esters groups gave the previously unknown fused thiazolo[5,4-*d*]thiazole system in good yields. We proposed a mechanism for this transformation that involves three consecutive steps initiated by titanium(IV) ions. From the mechanistic point of view, the cyclization can be considered as a radical domino reaction. Steric repulsions between ester substituents resulted in the formation of thiazolo[5,4-*d*]thiazole derivatives in which the two ester groups were located on opposite sides of the molecule. The structure of the product reflected the structure of the transition state. Oxidative dimerization to give 2,3-diisothiocyanates occurred when the ester groups were small or medium-sized. An interesting result was obtained during enolization of dimethyl esters of α.α′-diisothiocyanatodicarboxylic acids; intramolecular cyclization led to derivatives of 1,2-diisothiocyanato-1,2-dicarboxylic acids, in agreement with Matsumura's model of the transition state. Unfortunately, the diastereoselectivity of this process was very poor. Unlike titanium(IV) enolates, sodium enolates prepared from 2-isothiocyanatocarboxylates underwent dimerization followed by cyclization to give 5-imino-2-thioxo-1,3-thiazolidine-4-carboxylic esters in moderate-to-good yields. The resulting 2-thioxo-1,3-thiazolidines represent a new group of thiazolidine derivatives.

NMR spectra were recorded on a Bruker Avance II 300-MHz spectrometer with TMS as an internal standard. IR spectra were recorded on a Nicolet IR200 FT-IR spectrometer with a single-reflection attenuated total reflectance (ATR) head. Microanalyses were carried out by using a Vario MICRO Cube CHNS analyzer and the results were in good agreement with the calculated values. Column chromatography was performed on commercial Merck silica gel 60 (230–400 mesh ASTM). TLC analysis was carried out on Merck

TLC silica gel 60 plates. GC was performed by using a Perkin-Elmer Clarus 500 chromatograph equipped with an Elite-5ms capillary column. GC/MS analyses were performed on a Thermo Scientific ISQ Single Quadrupole GC/MS equipped with an Elite-5ms capillary column, whereas EI-MS spectra were recorded on a Finnigan MAT 95S spectrometer. Optical rotations were measured by using a Jasco P-2000 polarimeter. Melting points were measured on an Electrothermal 9100 apparatus. X-ray diffraction data were collected at 110 K on a SuperNova diffractometer (Oxford Diffraction) with MoKα radiation (λ = 0.71073 Å).

endo-(1*S*)-Bornyl (2*S*)-2-isothiocyanatopropanoate (**1c**)[10] and cyclohexyl (2S)-2-[(*tert*-butoxycarbonyl)amino]propanoate (**3g**)[19] were prepared by the procedures described in the literature.

L-Menthyl (2*R*/2*S*)-2-Isothiocyanatopropanoate (1a); Typical Procedure

A 250-mL Erlenmeyer flask was placed on a magnetic stirrer and charged with $CHCl_3$ (45 mL), H_2O (25 mL), and L-menthyl DL-alaninate hydrochloride[1] (1.86 g, 7.05 mmol). To the stirred soln were added $Cl_2C{=}S$ (0.54 mL, 0.814 g, 7.08 mmol) and $NaHCO_3$ (1.78 g, 21.19 mmol) in one portion and the mixture was stirred vigorously until the orange soln became pale (40–70 min). When the $Cl_2C{=}S$ had been consumed, the lower organic layer was separated, dried ($MgSO_4$), and concentrated. The crude oily product was purified by column chromatography [silica gel, cyclohexane–EtOAc (5:1)] to give a yellow oil; yield: 1.727 g (91%).

IR (ATR): 2955, 2928, 2870, 2059, 1741, 1454, 1374, 1289, 1205, 1151 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.77 and 0.76 (2d, *J* = 6.96 Hz, 3 H, CH-CH_3), 0.87 (m, 1 H, 4-CH_aH_e), 0.91 (d, *J* = 7.00 Hz, 3 H, CH_3-CH-CH_3), 0.92 (d, *J* = 6.52, 3 H, CH_3-CH-CH_3), 1.05 (m, 2 H, 3-CH_aH_e, 6-CH_aH_e), 1.46 (m, 2 H, 5-C*H*-CH_3 and 2-CH), 1.58 (d, *J* = 7.09 Hz, 3 H, β-CH_3), 4.75 and 4.74 (m, 1 H, ABX spin system, OCH), 1.68 (m, 1 H, 4-CH_aH_e), 1.72 (m, 1 H, 3-CH_aH_e), 1.86 (m, 1 H, CH_3-C*H*-CH_3), 2.02 (m, 1 H, 6-CH_aH_e), 4.28 and 4.27 (2q, *J* = 7.09 Hz, 1 H, α-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 16.0, 19.5, 20.8, 20.7, 21.9, 23.4, 23.3, 26.3, 26.2, 31.34, 34.1, 40.6, 46.9, 55.1, 55.0, 77.2, 76.9, 137.6, 137.4, 168.8, 168.7.

Anal. Calcd for $C_{14}H_{23}NO_2S$: C, 62.41; H, 8.61; N, 5.20. Found: C, 62.35; H, 8.60; N, 5.28.

D-Menthyl (2*R*/2*S*)-2-Isothiocyanatopropanoate (1b)

Yield: 2.29 g (85%); yellow oil.

GC-MS (EI, 70 eV): *m/z* (%) = 69 (68), 83 (100), 86 (53), 139 (88), 183 (19), 269 (3) $[M]^+$.

Anal. Calcd for $C_{14}H_{23}NO_2S$: C, 62.41; H, 8.61; N, 5.20. Found: C, 62.49; H, 8.51; N, 5.33.

L-Menthyl Isothiocyanatoacetate (1i)

Yield: 2.50 g (76%); yellowish oil; $[\alpha]_D^{24}$ –75.9 (*c* 0.011, $CHCl_3$); R_f = 0.51 (cyclohexane–EtOAc, 5:1).

IR (ATR): 2957, 2928, 2871, 2073, 1748, 1455, 1370, 1271, 1210, 981, 958 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.90 Hz, 3 H, CH-CH_3), 0.86 (m, 1 H, 4-CH_aH_e), 0.90 (d, *J* = 6.92 Hz, 3 H, CH_3-CH-CH_3), 0.91 (d, *J* = 6.30 Hz, 3 H, CH_3-CH-CH_3), 1.05 (m, 2 H, 3-CH_aH_e, 6-CH_aH_e), 1.50 (m, 2 H, 5-C*H*-CH_3 and 2-CH), 1.69 (m, 2 H, 3-CH_aH_e and 4-CH_aH_e), 1.83 (m, 1 H, CH_3-C*H*-CH_3), 2.03 (m, 1 H, 6-CH_aH_e), 4.18 (s, 2 H, CH_2NCS), 4.78 (td, *J* = 4.41 and 10.1 Hz, 1 H, OC*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 20.7, 21.9, 23.4, 26.9, 34.0, 31.4, 40.7, 46.5, 46.9, 77.2, 138.6, 165.7.

Anal. Calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.29; N, 5.48. Found: C, 61.21; H, 8.22; N, 5.55.

***endo*-(1*S*)-Bornyl Isothiocyanatoacetate (1j)**

Yield: 1.55 g (51%); colorless oil; $[\alpha]_D^{24}$ –29.4 (*c* 0.007, $CHCl_3$); R_f = 0.41 (cyclohexane–EtOAc, 5:1).

IR (ATR): 2956, 2882, 2083, 1752, 1454, 1350, 1270, 1211 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 1.01 (m, 1 H, 3-CH_{endo}), 1.32 (m, 2 H, 5-CH_{endo} and 6-CH_{exo}), 1.72 (m, 1 H, 4-CH), 1.76 (m, 1 H, 5-CH_{exo}), 1.93 (m, 1 H, 6-CH_{endo}), 2.40 (m, 1 H, 3-CH_{exo}), 4.22 (s, 2 H, α-CH_2), 5.00 (m, 1 H, ABX spin system, OCH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 18.8, 19.7, 27.1, 28.0, 36.6, 44.8, 46.6, 48.0, 48.9, 82.9, 137.5, 166.4.

Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.73; H, 7.36; N, 5.59.

(2*S*)-2-Methylbutyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]propanoate (3d); Typical Procedure

A 100-mL Erlenmeyer flask was charged with CH_2Cl_2 (50 mL), *N*-Boc-L-alanine (2 g, 10.57 mmol), and DCC (2.177 g, 10.57 mmol), and the mixture was stirred at r.t. for 30 min. (2*S*)-(–)-2-Methylbutan-1-ol (1.20 mL, 0.983 g, 11.14 mmol) and DMAP (0.123 g, 1.01 mmol) were added and the mixture was stirred overnight then concentrated under reduced pressure. The residue was dissolved in EtOAc(80 mL), and the soln was filtered and washed successively with 5% aq HCl (36 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a crude product that was purified by column chromatography [silica gel, $CHCl_3$–MeOH (30:1)] to give a colorless oil; yield: 1.96 g (72%); $[\alpha]_D^{24}$ –4.1 (*c* 0.011, $CHCl_3$).

IR (ATR): 3361, 2967, 2935, 2880, 1712, 1505, 1455, 1366, 1248, 1160, 1064 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.42 Hz, 3 H, CH_2CH_3), 0.91 (d, *J* = 6.75 Hz, 3 H, CHCH_3), 1.18 (m, 1 H, CH_aH_b), 1.37 (d, *J* = 7.20 Hz, 3 H, CHCH_3), 1.41 (m, 1 H, CH_aH_b), 1.43 (s, 9 H, CH_3), 1.70 (m, 1 H, C*H*CH_3), 3.94 (dd, *J* = 6.61 and 10.8 Hz, 1 H, OCH_aH_b), 3.98 (dd, *J* = 6.05 and 10.8 Hz, 1 H, OCH_aH_b), 4.30 (m, 1 H, C*H*NH), 5.05 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 16.3, 18.8, 25.9, 28.3, 34.1, 49.3, 69.8, 79.7, 155.1, 173.4.

Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 60.15; H, 9.75; N, 5.51.

(2*S*)-2-Methylbutyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-methylpentanoate (3e)

Yield: 2.39 g (75%); colorless oil; $[\alpha]_D^{24}$ –3.2 (*c* 0.004, $CHCl_3$).

IR (ATR): 3352, 2961, 2933, 2875, 1712, 1505, 1462, 1366, 1249, 1160, 1047, 1048 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 7.42 Hz, 3 H, CHCH_3), 0.91 (t, *J* = 5.30 Hz, 3 H, CH_2CH_3), 0.92 (2d, *J* = 5.16 Hz, 6 H, CHCH_3), 1.17 (sept, 1 H, C*H*Me_2), 1.42 (s, 9 H, CH_3), 1.46 (m, 1 H, CH_aH_b), 1.48 (m, 1 H, CH_aH_b), 1.71 (m, 3 H, C*H*CH_3 and CH_2-*i*-Pr), 3.94 (dd, *J* = 6.76 and 10.8 Hz, 1 H, OCH_aH_b), 3.99 (dd, *J* = 5.88 and 10.8 Hz, 1 H, OCH_aH_b), 4.28 (m, 1 H, C*H*NH), 4.92 (br d, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 16.3, 21.9, 22.7, 24.8, 25.9, 28.3, 34.1, 41.9, 52.1, 66.7, 79.7, 155.3, 173.5.

Anal. Calcd for $C_{16}H_{31}NO_4$: C, 63.76; H, 10.37; N, 4.65. Found: C, 63.65; H, 10.52; N, 4.69.

(2*S*)-2-Methylbutyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropanoate (3f)

Yield: 2.52 g (71%); colorless oil; $[\alpha]_D^{24}$ +32.3 (*c* 0.004, $CHCl_3$).

IR (ATR): 3367, 2965, 2932, 2878, 1712, 1496, 1455, 1364, 1249, 1162, 1053, 1018 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (m, 6 H, CHCH_3 and CH_2CH_3), 1.14 (m, 1 H, CH_aH_b), 1.38 (m, 1 H, CH_aH_b), 1.41 (s, 9

H, CH_3), 1.68 (m, 1 H, C*H*CH_3), 3.08 (m, 2 H, CH_2Ph), 3.86 (dd, *J* = 6.74 and 10.8 Hz, 1 H, OC$H_a$$H_b$), 3.99 (dd, *J* = 5.96 and 10.8 Hz, 1 H, OC*H*$_a$$H_b$), 4.58 (m, 1 H, C*H*NH), 4.98 (br d, 1 H, NH), 7.13 (m, 2 H, ArH), 7.25 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 16.3, 25.9, 28.2, 33.9, 38.4, 54.4, 69.9, 79.8, 126.9, 128.5, 129.2, 136.1, 155.0, 171.9.

Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.95; H, 8.58; N, 4.22.

(2*S*)-2-Methylbutyl (2*S*)-2-Isothiocyanatopropanoate (5d); Typical Procedure

A three-necked 100-mL flask equipped with an argon inlet and protected against moisture was placed on a magnetic stirrer and charged with a soln of amino ester **3c** (1.764 g, 6.80 mmol) in CH_2Cl_2 (55 mL). TFA (12.4 mL, 19.03 g, 167 mmol) was added and the mixture was stirred under argon at r.t. for 2.5 h. When the deprotection was completed, the CH_2Cl_2 and TFA were evaporated under reduced pressure at 45 °C and residue was transferred into a 250-mL Erlenmeyer flask and dissolved in $CHCl_3$ (40 mL). Next, Cl_2C=S (0.52 mL, 0.786 g, 6.80 mmol) was added dropwise to the flask followed by $NaHCO_3$ (1.714 g, 20.4 mmol) and H_2O (60 mL), and the mixture was intensively stirred for 1 h. The lower organic layer was separated, dried ($MgSO_4$), and concentrated to a crude oily product that was purified by distillation under reduced pressure (124–126 °C at 9 mmHg) to give a yellowish oil; yield: 0.75 g (55%); bp 124–126 °C (9 mmHg); $[\alpha]_D^{23}$ 17.8 (*c* 0.003, $CHCl_3$).

IR (ATR): 2964, 2935, 2878, 2059, 1743, 1458, 1379, 1289, 1198, 1149, 1054 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.42 Hz, 3 H, CH_2CH_3), 0.95 (d, *J* = 6.76 Hz, 3 H, CHCH_3), 1.22 (m, 1 H, CH_aH_b), 1.44 (m, 1 H, C$H_a$$H_b$), 1.59 (d, *J* = 7.10 Hz, 3 H, CHCH_3), 1.77 (m, 1 H, C*H*CH_3), 4.01 (dd, *J* = 6.62 and 10.5 Hz, 1 H, OC$H_a$$H_b$), 4.08 (dd, *J* = 5.94 and 10.5 Hz, 1 H, OC*H*$_a$$H_b$), 4.33 (q, *J* = 7.10 Hz, 1 H, C*H*NCS).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 16.3, 19.5, 25.9, 34.0, 54.9, 70.9, 137.3, 169.0.

GC-MS (EI, 70 eV): *m/z* (%) = 71 (57), 86 (100), 132 (9), 201 (8) $[M]^+$.

Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96. Found: C, 53.78; H, 7.65; N, 7.05.

(2*S*)-2-Methylbutyl (2*S*)-2-Isothiocyanato-4-methylpentanoate (5e)

Yield: 1.10 g (67%); yellow viscous oil; $[\alpha]_D^{24}$ –45.6 (*c* 0.002, $CHCl_3$).

IR (ATR): 2961, 2933, 2875, 2058, 1744, 1464, 1387, 1316, 1269, 1192, 1149 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (m, 12 H, CH_3), 1.22 (m, 1 H, CH_aH_b), 1.49 (m, 1 H, C$H_a$$H_b$), 1.80 (m, 4 H, C*H*$CH_3$, C$H_2$-*i*-Pr, C*H*$Me_2$), 4.01 (dd, *J* = 6.65 and 10.8 Hz, 1 H, OC$H_a$$H_b$), 4.08 (dd, *J* = 5.91 and 10.8 Hz, 1 H, OC*H*$_a$$H_b$), 4.27 (m, 1 H, ABX spin system, C*H*NCS).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 16.3, 21.2, 22.7, 25.1, 25.9, 34.0, 42.1, 58.1, 70.9, 136.8, 169.0.

Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.22; H, 8.70; N, 5.76. Found: C, 59.15; H, 8.64; N, 5.86.

(2*S*)-2-Methylbutyl (2*S*)-2-Isothiocyanato-3-phenylpropanoate (5f)

Yield: 0.98 g (52%); orange oil; $[\alpha]_D^{23}$ –54.8 (*c* 0.013, $CHCl_3$).

IR (ATR): 2963, 2932, 2877, 2060, 1741, 1457, 1381, 1334, 1268, 1199, 1014 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.40 Hz, 3 H, CH_2CH_3), 0.90 (d, *J* = 6.76 Hz, 3 H, CHCH_3), 1.18 (m, 1 H, CH_aH_b), 1.38 (m, 1 H, C$H_a$$H_b$), 1.78 (m, 1 H, C*H*$CH_3$), 3.13 (dd, *J* = 8.12 and 13.8 Hz, 1 H, PhC$H_a$$H_b$), 3.26 (dd, *J* = 4.95 and 13.8 Hz, 1 H, PhC*H*$_a$$H_b$), 3.97 (dd, *J* = 6.61 and 10.5 Hz, 1 H, OC$H_a$$H_b$), 4.07 (dd, *J* = 5.93 and 10.5 Hz, 1 H, OC*H*$_a$$H_b$), 4.46 (m, 1 H, ABX spin system, C*H*NCS), 7.24 (m, 2 H, ArH), 7.32 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 16.3, 25.8, 34.0, 39.7, 60.9, 71.0, 127.6, 128.7, 129.3, 135.1, 137.9, 168.0.

Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05. Found: C, 65.04; H, 6.78; N, 5.12.

Cyclohexyl (2*S*)-2-Isothiocyanatopropanoate 5g

Yield: 1.12 g (77%); yellow oil.

IR (ATR): 2936, 2859, 2058, 1739, 1450, 1287, 1201, 1150, 1010 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (m, 6 H, cyclohexyl), 1.57 (d, *J* = 7.09 Hz, 3 H, CH_3), 1.73 (m, 2 H, cyclohexyl), 1.83 (m, 2 H, cyclohexyl), 4.28 (q, *J* = 7.09 Hz, 1 H, OCH), 4.86 (m, 1 H, ABX spin system, C*H*NCS).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 23.4, 25.2, 31.3, 55.0, 75.1, 137.4, 168.4.

Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.21; H, 7.20; N, 6.44.

Di-L-menthyl (2*R*,5*S*)-2,5-Dimethyl-2,5-dihydro[1,3]thiazolo[5,4-*d*][1,3]thiazole-2,5-dicarboxylate (6a); Typical Procedure

Ester **1a** (1.954 g, 7.23 mmol) was dissolved in anhyd CH_2Cl_2 (30 mL) under argon and the soln was cooled to –96 °C. A soln of $TiCl_4$ (0.88 mL, 1.522 g, 8.02 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the mixture was stirred for 30 min at –96 °C. When a yellow titanium(IV) complex had formed, a soln of DIPEA (1.40 mL, 1.04 g, 8.09 mmol) in CH_2Cl_2 (4 mL) was added dropwise to give a deep-blue titanium(IV) enolate. The mixture was stirred for 60 min at –96 °C then the cooling bath was removed and the soln was allowed to warm to r.t. After 24 h, the brown mixture was quenched with sat. aq NH_4Cl and the organic phase was dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by column chromatography [silica gel, $CHCl_3$–MeOH (30:1)]. The product was isolated as the first fraction and crystallized (MeOH) to give colorless crystals;[19] yield: 1.43 g (76%); mp 122–123 °C; $[\alpha]_D^{23}$ –72.2 (*c* 0.01, acetone); R_f = 0.80 ($CHCl_3$–MeOH, 30:1).

IR (ATR): 3480, 2956, 2932, 2869, 1729, 1620, 1462, 1384, 1372, 1259, 1125 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 6.9 Hz, 3 H, CH_3-CH-CH_3), 0.73 (d, *J* = 6.9 Hz, 3 H, CH_3-CH-CH_3), 0.87 (m, 2 H, 4-CH_a-H_e), 0.89 (m, 12 H, CH_3-CH-CH_3 and CH-CH_3), 1.05 (m, 4 H, 3-C$H_a$$H_e$, 6-C$H_a$$H_e$), 1.46 (m, 4 H, 5-C*H*-$CH_3$ and 2-CH), 1.66 (m, 2 H, 4-$CH_a$$H_e$), 1.70 (m, 2 H, 3-$CH_a$$H_e$), 1.86 (m, 2 H, CH_3-C*H*-CH_3), 2.02 (m, 2 H, 6-$CH_a$$H_e$), 2.05 (s, 3 H, β-$CH_3$), 2.01 (s, 3 H, β-$CH_3$), 4.69 (m, 2 H, ABX spin system, CH-O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2, 16.3, 20.6, 20.7, 21.9, 23.3, 23.5, 26.2, 26.3, 26.6, 27.1, 31.3, 34.1, 40.1, 40.2, 46.9, 77.1, 77.3, 98.9, 99.1, 168.1, 168.3, 177.9, 178.1.

MS (EI, 70 eV): *m/z* (%) = 83 (97), 139 (17), 171 (100), 216 (16), 261 (17), 399 (23), 537 (22) $[M - H]^+$.

Anal. Calcd for $C_{28}H_{44}N_2O_4S_2$: C, 62.65; H, 8.26; N, 5.22. Found: C, 62.33; H, 8.52; N, 5.00.

Di-D-menthyl (2*R*,5*S*)-2,5-Dimethyl-2,5-dihydro[1,3]thiazolo[5,4-*d*][1,3]thiazole-2,5-dicarboxylate (6b)

Yield: 1.53 g (82%); colorless crystals; mp 122–123 °C; $[\alpha]_D^{23}$ +71.9 (*c* 0.01, acetone).

Anal. Calcd for $C_{28}H_{44}N_2O_4S_2$: C, 62.65; H, 8.26; N, 5.22. Found: C, 62.36; H, 8.48; N, 5.12.

Di-*endo*-(1*S*)-bornyl (2*R*,5*S*)-2,5-Dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate (6c)

Yield: 0.847 g (44%); yellow oil; R_f = 0.90 ($CHCl_3$–MeOH, 30:1).

IR (ATR): 2953, 2878, 1736, 1483, 1453, 1377, 1256, 1152, 1116 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (m, 18 H, 6 CH_3), 1.00 (m, 2 H, 3-CH_{endo}), 1.31 (m, 4 H, 5-CH_{endo} and 6-CH_{exo}), 1.61 (m, 2 H, 4-CH), 1.76 (2 s, 6 H, α-CH_3), 1.98 (m, 4 H, 5-CH_{exo} and 6-CH_{endo}), 2.36 (m, 2 H, 3-CH_{exo}), 4.95 (m, 2 H, ABX spin system, CH-O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 13.5, 18.8, 19.6, 19.7, 26.2, 27.1, 27.3, 27.8, 27.9, 36.3, 44.8, 47.9, 48.0, 49.0, 49.1, 82.4, 82.5, 98.9, 99.0, 170.4, 176.6.

Anal. Calcd for $C_{28}H_{40}N_2O_4S_2$: C, 63.14; H, 7.60; N, 5.26. Found: C, 62.98; H, 7.75; N, 5.12.

Bis[(2*S*)-2-methylbutyl] (2*R*,5*S*)-2,5-Dimethyl-2,5-dihydro[1,3]thiazolo[5,4-*d*][1,3]thiazole-2,5-dicarboxylate (6d) and Bis[(2*S*)-2-methylbutyl] 2,3-Diisothiocyanato 2,3-dimethylsuccinate (7d)

A soln of isothiocyanatopropanoate **5c** (0.652 g, 3.24 mmol) in CH_2Cl_2 (40 mL) was cooled to –96 °C under argon and $TiCl_4$ (0.39 mL, 0.675 g, 3.56 mmol) was added in one batch. The mixture was stirred for 20 min at –96 °C then a soln of DIPEA (0.62 mL, 0.463 g, 3.58 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The soln turned deep blue owing to the formation of the titanium(IV) enolate. The mixture was stirred at –96 °C then the cooling bath was removed and soln was allowed to warm to r.t. After 4 h, when the substrate was fully consumed (GC), the mixture was poured into sat. aq NH_4Cl (80 mL). The lower organic phase was separated, dried ($MgSO_4$), and concentrated to give a crude mixture of dimers **6c** and **7c**, which were purified by column chromatography [silica gel, $CHCl_3$–MeOH (50:1)].

Bis[(2*S*)-2-methylbutyl] (2*R*,5*S*)-2,5-Dimethyl-2,5-dihydro[1,3]thiazolo[5,4-*d*][1,3]thiazole-2,5-dicarboxylate (6d)

Yield: 0.235 g (36%); colorless oil. R_f = 0.80 ($CHCl_3$–MeOH, 50:1).

IR (ATR): 3480, 2960, 2933, 2867, 1730, 1620, 1460, 1383, 1375, 1257, 1120 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.70 Hz, 6 H, CH_2CH_3), 0.91 (d, *J* = 5.91 Hz, 6 H, CH_3CH), 1.17 (m, 2 H, CH_aH_b), 1.38 (m, 2 H, CH_aH_b), 1.75 (m, 2 H, CH_3CH), 2.04 (s, 6 H, β-CH_3), 4.04 (m, 4 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 16.3, 25.9, 26.7, 34.0, 71.0, 98.9, 168.6, 178.2.

Anal. Calcd for $C_{18}H_{28}N_2O_4S_2$: C, 53.97; H, 7.05; N, 6.99. Found: C, 53.88; H, 7.15; N, 7.08.

Bis[(2*S*)-2-methylbutyl] 2,3-Diisothiocyanato 2,3-dimethylsuccinate (7d)

Yield: 0.280 g (43%); colorless oil. R_f = 0.70 ($CHCl_3$–MeOH, 50:1).

IR (ATR): 2963, 2933, 2877, 2022, 1740, 1459, 1382, 1257, 1095, 961 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.45 Hz, 6 H, CH_2CH_3), 0.98 (d, *J* = 6.77 Hz, 6 H, CH_3CH), 1.25 (m, 2 H, CH_aH_b), 1.47 (m, 2 H, CH_aH_b), 1.74 (s, 6 H, β-CH_3), 1.79 (m, 2 H, CH_3CH), 4.08 (m, 4 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 16.4, 22.5, 25.9, 34.0, 70.5, 72.0, 140.6, 167.9.

GC-MS (EI; 70 eV): *m/z* (%) = 71 (100), 130 (33), 200 (24), 201 (31), 401 (2) $[M + H]^+$.

Anal. Calcd for $C_{18}H_{28}N_2O_4S_2$: C, 53.97; H, 7.05; N, 6.99. Found: C, 53.85; H, 7.14; N, 6.92.

Dimethyl 2,7-Diisothiocyanatosuberate (19a); Typical Procedure

A 250-mL Erlenmeyer flask was placed on a magnetic stirrer and charged with a suspension of dimethyl 2,7-diaminosuberate dihydrochloride **18a** (1.801 g, 5.90 mmol) in $CHCl_3$ (60 mL). $Cl_2C{=}S$ (0.99 mL, 1.493 g, 12.98 mmol) and $NaHCO_3$ (3.272 g, 38.95 mmol) were added to the stirred soln followed by H_2O (40 mL) added carefully in a dropwise manner. The mixture was then stirred for 2.5 h. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, $CHCl_3$– MeOH (30:1)] to give a yellowish waxy solid; yield: 1.55 g (83%); mp 47–48 °C; R_f (TLC plates) = 0.90 ($CHCl_3$–MeOH, 30:1).

IR (ATR): 2956, 2935, 2862, 2066, 1745, 1436, 1220, 1168, 986 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (m, 4 H, CH_2), 1.92 (m, 4 H, CH_2), 3.81 (s, 6 H, OCH_3), 4.29 (m, 2 H, ABX spin system, CHNCS).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 33.1, 53.2, 59.2, 137.7, 168.7.

Anal. Calcd for $C_{12}H_{16}N_2O_4S_2$: C, 45.55; H, 5.10; N, 8.85. Found: C, 45.67; H, 5.20; N, 8.66.

Dimethyl 2,9-Diisothiocyanatosebacate (19b)

Yield: 1.524 g (75%); yellow oil; R_f = 0.90 ($CHCl_3$–MeOH, 30:1).

IR (ATR): 2931, 2859, 2059, 1744, 1437, 1331, 1265, 1206, 1176, 986 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (m, 4 H, CH_2), 1.43 (m, 4 H, CH_2), 1.88 (m, 4 H, CH_2), 3.81 (s, 6 H, OCH_3), 4.28 (m, 2 H, ABX spin system, CHNCS).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 28.4, 33.4, 53.1, 59.4, 137.2, 168.9.

Anal. Calcd for $C_{14}H_{20}N_2O_4S_2$: C, 48.82; H, 5.85; N, 8.13. Found: C, 48.74; H, 5.90; N, 8.24.

Dimethyl *cis*- and *trans*-1,2-Diisothiocyanatocyclohexane-1,2-dicarboxylate (20a)

A soln of diester **19a** (1.451 g, 4.58 mmol) in CH_2Cl_2 (40 mL) was cooled to –96 °C under argon and $TiCl_4$ (1.11 mL, 1.920 g, 10.1 mmol) was added in one batch. The mixture was stirred for 20 min at –96 °C before a soln of DIPEA (1.74 mL, 1.300 g, 10.1 mmol) in CH_2Cl_2 (4 mL) was added in a dropwise manner. The soln turned deep blue as a result of the formation of the titanium(IV) enolate. The mixture was stirred at –96 °C for 30 min and then the cooling bath was removed and soln was allowed to warm to r.t. After 5 h, when the substrate was fully consumed (TLC), the mixture was poured into sat. aq NH_4Cl (80 mL). The lower organic phase was separated, dried ($MgSO_4$), and concentrated. The resulting crude product was purified by column chromatography [silica gel, $CHCl_3$–MeOH (30:1)] to give a yellow solid; yield: 0.88 g (61%; near equimolar mixture of *cis*- and *trans*-diastereoisomers); R_f = 0.85 ($CHCl_3$–MeOH, 30:1).

IR (ATR): 2936, 2865, 2032, 1741, 1466, 1368, 1233, 1180, 1095, 1015 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.70 (m, 4 H, CH_2), 1.96 (m, 2 H, CH_2), 2.29 (m, 2 H, CH_2), 3.91, 3.86 and 3.84 (s, 6 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 20.2 and 20.0 (CH_2), 33.5, 32.0 and 31.9 (CH_2), 54.3, 53.9 and 53.6 (OCH_3), 75.2, 73.1, and 69.3 (α-C), 142.2 and 139.4 (NCS), 167.7 (COO).

Anal. Calcd for $C_{12}H_{14}N_2O_4S_2$: C, 45.85; H, 4.49; N, 8.91. Found: C, 45.94; H, 4.67; N, 8.84.

Dimethyl *cis*- and *trans*-1,2-Diisothiocyanatocyclooctane-1,2-dicarboxylate (20b)

Yield: 0.84 g (54%); yellow solid; R_f = 0.85 ($CHCl_3$–MeOH, 30:1).

IR (ATR): 2935, 2863, 2035, 1740, 1465, 1368, 1238, 1183, 1097, 1018 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (m, 2 H, CH_2), 1.34 (m, 6 H, CH_2), 1.88 (m, 2 H, CH_2), 2.03 (m, 2 H, CH_2), 3.87, 3.85, 3.82, and 3.81 (s, 6 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 24.6, and 24.4 (CH_2), 28.8 and 28.1 (CH_2), 34.1 and 33.4 (CH_2), 54.1, 53.9, and 53.1 (OCH_3), 75.9 (α-C), 141.1, 140.8, and 140.4 (NCS), 167.8, 167.7 and 167.2 (COO).

Anal. Calcd for $C_{14}H_{18}N_2O_4S_2$: C, 49.11; H, 5.30; N, 8.18. Found: C, 48.95; H, 5.43; N, 8.28.

Ethyl 5-[(2-Ethoxy-2-oxoethyl)amino]-2-thioxo-2,3-dihydro-1,3-thiazole-4-carboxylate (24h)

A 250-mL Erlenmeyer flask, protected from moisture by a $CaCl_2$ guard tube, was placed on a stirrer and charged with anhyd DMF (90 mL) and ethyl isothiocyanatoacetate (3.77 g, 0.026 mol). The mixture was cooled to 0 °C on an ice bath. NaH (0.834 g, 0.035 mol) was carefully added in several portions to the stirred soln and then the ice bath was removed and the mixture was stirred for 2 h at r.t. The red-brown soln was poured into cold H_2O and acidified to pH 5 with 10% aq HCl aq. The resulting yellow precipitate was filtered off and crystallized (EtOH) to give the pure pale-yellow product. The filtrate was extracted with EtOAc (2 × 100 mL), and the organic layers were washed successively with H_2O (80 mL) and brine (50 mL) then dried ($MgSO_4$) and concentrated. The brown residue was crystallized (EtOH) to give a second portion of the product; total yield: 2.45 g (65%); mp 188 °C.

IR (ATR): 3362, 3077, 2974, 2913, 1742, 1652, 1592, 1511, 1428, 1211, 1183, 1020 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.15 Hz, 3 H, CH_3), 1.36 (t, *J* = 7.14 Hz, 3 H, CH_3), 3.90 (d, *J* = 5.78 Hz, 2 H, CH_2), 4.27 (q, *J* = 7.15 Hz, 2 H, OCH_2), 4.32 (q, *J* = 7.14 Hz, 2 H, OCH_2), 7.11 (br s, 1 H, NH), 9.77 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 14.4 (CH_3), 48.1 (CH_2), 61.3 (OCH_2), 62.2 (OCH_2), 106.2 (C=C), 153.9 (C=C), 158.5 (CO_2Et), 168.1 (CO_2Et), 176.8 (C=S).

Anal. Calcd for $C_{10}H_{14}N_2O_4S_2$: C, 41.37; H, 4.83; N, 9.65. Found: C, 41.45; H, 4.73; N, 9.82.

Acknowledgment

We are grateful to the Polish Ministry of Science and Higher Education (Grant No. N N204 310037) and the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (contract no. POIG.02.01.00-12-023/08) for financial support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Kodama, H. *Chem. Zentralbl.* **1923**, *94*, 206.
(2) (a) Berlin, A. Ya.; Levi, I. S. *J. Gen. Chem. USSR (Engl. Transl.)* **1963**, *33*, 846. (b) Tsogoeva, S. B.; Hateley, M. J.; Yalalov, D. A.; Meindl, K.; Weckbecker, C.; Huthmacher, K. *Bioorg. Med. Chem.* **2005**, *13*, 5680. (c) Floch, L.; Uher, M.; Lesko, J. *Collect. Czech. Chem. Commun.* **1989**, *54*, 206. (d) Dobosz, M.; Pachuta-Stec, A. *Acta Pol. Pharm.* **1994**, *51*, 457. (e) Ryczek, J. *J. Heterocycl. Chem.* **2003**, *40*, 665. (f) Chowdhury, A. Z.; Shaifullah, M.; Shibata, Y. *Chem. Pharm. Bull.* **2001**, *49*, 391.
(3) (a) Bates, S. R. E.; Guthrie, D. J. S.; Elmore, D. T. *J. Chem. Res., Miniprint* **1993**, *2*, 0201. (b) Foye, W. O.; Dabade, S. V.; Kelley, C. J.; Lebrun, E.; Rapenbusch, R. *Med. Chem. Res.* **1998**, *8*, 542.
(4) (a) Masquelin, T.; Sprenger, D.; Baer, R.; Gerber, F.; Mercadal, Y. *Helv. Chim. Acta* **1998**, *81*, 646. (b) Cabon, G.; Gaucher, B.; Gegout, A.; Heulle, S.; Masquelin, T. *Chimia* **2003**, *57*, 248.
(5) Floch, L.; Martvoň, A.; Uher, M.; Leško, J.; Weis, W. *Collect. Czech. Chem. Commun.* **1977**, *42*, 2945.
(6) (a) Dobosz, M.; Pitucha, M.; Wujec, M. *Acta Pol. Pharm.* **1996**, *53*, 31. (b) Veverka, M.; Marchalin, M. *Collect. Czech. Chem. Commun.* **1987**, *52*, 113.
(7) (a) Cież, D.; Szneler, E. *Monatsh. Chem.* **2005**, *136*, 2059. (b) Cież, D.; Szneler, E. *J. Chem. Res.* **2007**, 200.
(8) Cież, D. *Tetrahedron* **2007**, *63*, 4510.
(9) Cież, D.; Kalinowska-Tłuścik, J.; Peyrat, S.; Touko, E. P.; Trzewik, B.; Zwoliński, K. *Synthesis* **2008**, 3261.
(10) Cież, D.; Kalinowska-Tłuścik, J.; Marchewka, J. *Aust. J. Chem* **2012**, in press; DOI: 10.1071/CH11463.
(11) Periasamy, M. *ARKIVOC* **2002**, *(vii)*, 151.
(12) Cież, D. *Org. Lett.* **2009**, *11*, 4282.
(13) Cież, D.; Kalinowska-Tłuścik, J. *Synlett* **2012**, *23*, 267.
(14) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
(15) (a) Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809. (b) Rao, V. D.; Periasamy, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1151.
(16) (a) Weingarten, H.; Miles, M. G.; Edelmann, N. K. *Inorg. Chem.* **1968**, *7*, 879. (b) Ribeiro, N.; Fetzer, L.; Streiff, S.; Désaubry, L. *Synlett* **2010**, 2928.
(17) Penn, J. H.; Plants, R. C.; An, L. *Chem. Commun. (Cambridge)* **1999**, 2359.
(18) Alvarez-Ibarra, C.; Csákÿ, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478.
(19) Hayashida, O.; Sebo, L.; Rebek, J. *J. Org. Chem.* **2002**, *67*, 8291.
(20) Crystallographic data for compound **6a** have been deposited with the accession numbers CCDC 862700 and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

