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Titanium(IV)-mediated synthesis of 2,3-diisothiocyanato-succinic acid diesters and 3,6-dithioxo-piperazine derivatives

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Abstract—Oxidative homocoupling of titanium(IV) enolates of 2-isothiocyanato-carboxylic esters resulted in the synthesis of 2,3-diisothiocyanato-succinic acid diesters. The reactions were carried out using DIPEA/$TiCl_4$ oxidizing system and led to chiral dimers (instead of *meso*) as main products. Titanium(IV) enolates derived from hindered 2-isothiocyanato-carboxylates did not undergo the oxidative homocoupling but gave 3,6-dithioxo-piperazines.

1. Introduction

Carbon–carbon bond formation via oxidative homocoupling of enolate anions is a widespread method for synthesis of 2,3-disubstituted succinic acid derivatives.[1] Titanium(IV) enolates of phenylacetic acid esters prepared by the use of $TiCl_4$ and amine (R_3N) can be easily coupled owing to the oxidative properties of $TiCl_4/R_3N$ system.[2] An application of amine/$TiCl_4$ oxidizing agent led to the diastereoselective synthesis of chiral- and *meso*-2,3-diphenyl-succinic acid esters,[3] the enantioselective synthesis of (*R*,*R*) and (*S*,*S*)-2,3-disubstituted succinic acids,[4] and the enantioselective preparation of 2,3-diphenyl-1,4-butanediol.[5] A tentative reaction mechanism has been firstly proposed by Matsumura et al.[3] for oxidative homocoupling of arylacetic esters. Matsumura et al. assumed that titanium(IV) enolates formed a dimeric intermediate where two aryl groups were located opposite to each other in separate planes. Oxidation of such intermediate led to 2,3-diaryl-succinic acid derivatives of high stereoselectivity for the chiral diastereoisomer. Two years later, Kise et al. noted that steric hindrance was able to considerably inhibit an oxidative dimerization of substituted esters[4b] bearing a tertiary C-2 carbon atom. A recently described reaction of methyl mandelate with amine/$TiCl_4$ system leading to 2,3-diphenyl-tartrate ester as a by-product[6] revealed that the oxidative formation of carbon–carbon bonds is also possible for more hindered esters. This observation prompted us to apply an amine/$TiCl_4$ oxidizing agent for the synthesis of 2,3-diisothiocyanato-succinic acid derivatives from esters of 2-isothiocyanato-carboxylic acids. This article describes the results of our investigations and suggests the scope and limitations of this procedure.

2. Results and discussion

A wide application of vicinal diisothiocyanates in organic syntheses[7] was the main reason for our search for the novel and more efficient preparation of these reactants. Vicinal diisothiocyanates of a general formula SCN–C(R)(R′)–C(R′)(R)–NCS represented, however, a class of rare organic compounds. There were only a few articles concerning the synthesis of such derivatives.[8] Moreover, the known procedures leading to this class of compounds were relatively complicated and unproductive.

In our research, we focused on the synthesis of unknown vicinal diisothiocyanates—derivatives of succinic acid. We expected that an oxidative homocoupling of starting 2-isothiocyanato-carboxylic esters **1** derived from α-amino acids[9] would lead to the desired 2,3-diisothiocyanato-succinic acids. The reaction of 2-isothiocyanato-propionic acid methyl ester **1a** was carried out in CH_2Cl_2 under argon using 1.2 equiv of $TiCl_4$ and DIPEA at low temperature. After 24 h, a TLC analysis showed that the reaction was finished and there were no traces of the starting 2-isothiocyanato-carboxylic methyl ester **1a**. NMR spectra of the crude product showed that the reaction gave a mixture consisting predominantly of the DL-stereoisomer of 2,3-diisothiocyanato-2,3-dimethyl-succinic acid dimethyl ester **2a** (Scheme 1). The ratio of both stereoisomers (DL/*meso*) was estimated based on NMR spectroscopy to be 85:15. Product **2a** was isolated and purified using column chromatography. Its structure was confirmed by spectral data. The results of all oxidative couplings, which we carried out are summarized in Table 1.

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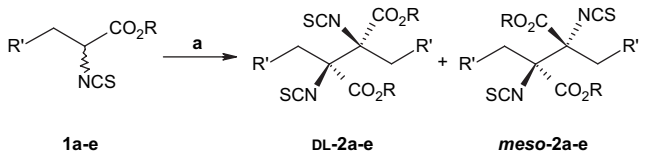


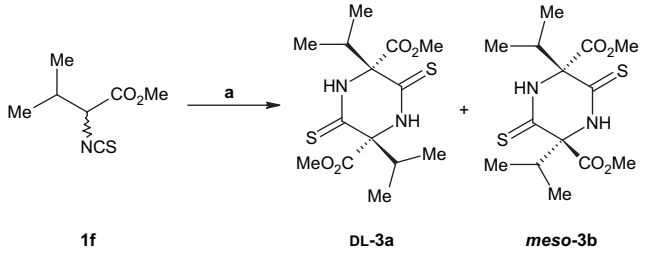
Scheme 1. The synthesis of vicinal diisothiocyanates. Reagents and conditions: (a) (i) $TiCl_4$, −96 °C, 30 min, under Ar; (ii) DIPEA, −96 °C to rt, 2–20 h, under Ar. Yields (DL+*meso*): 65–95%. **a**: R′=H; **b**: R′=*i*Pr; **c**: R′=Ph; **d**: R′=CH_2SCH_3; R=Me; **e**: R′=H, R=Et.

Table 1. Oxidative homocoupling of isothiocyanato-carboxylates SCN–CH(R)–COOR′ in $TiCl_4/R_3N$ system at −96 °C

Compound	R	R′	Time (h)	DL/*meso*	Yield of DL (%)
2a	CH_3	H	3	85:15[a]	78
2b	CH_3	$CH(CH_3)_2$	5	82:18[b]	61
2c	CH_3	C_6H_5	5	86:14	73
2d	CH_3	CH_2SCH_3	20	84:16	54
2e	C_2H_5	H	4	81:19	77

[a] Dimerization at 0 °C decreased the DL/*meso* ratio of **2a** to 69:31 (25% yield of DL+*meso*).
[b] Application of Et_3N instead of DIPEA led to the mixture of diastereoisomers with DL/*meso* ratio 85:15.

Irrespective of the nature of a substituent at C-3 in the starting 2-isothiocyanato-carboxylic esters **1a–d** were the ratios of obtained diastereomers comparable (see Table 1). Similarly, the use of the isothiocyanato-carboxylic ethyl ester **1e** did not affect the ratio of DL- and *meso*-stereoisomer.



Scheme 2. Preparation of symmetrical 3,6-dithioxo-piperazine-2,5-dicarboxylic acid dimethyl esters from 2-isothiocyanato-carboxylates trisubstituted at C-3 carbon. Reagents and conditions: (a) (i) $TiCl_4$, −96 °C, 30 min, under Ar; (ii) DIPEA, −96 °C to rt, 72 h, under Ar.

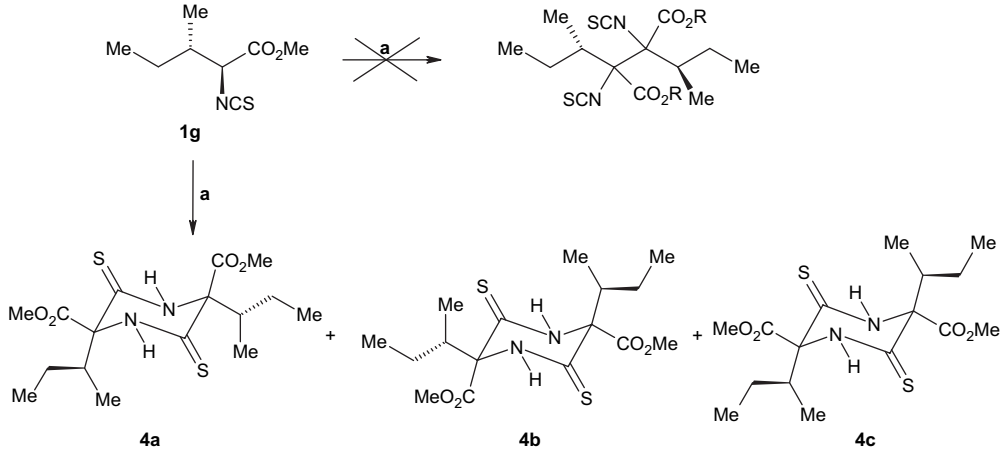
The yields of products depended on the temperature in which the titanium(IV) enolates were generated. The best outcomes were achieved when the enolates were prepared at −96 °C. Enolization and homocoupling of methyl 2-isothiocyanato-propionate **1a** at 0 °C gave only a 25% yield and the DL/*meso* ratio of **2a** decreased (Table 1).

In continuation of our research we found that 2-isothiocyanato-3-methyl-butyric acid methyl ester **1f**, having only one hydrogen atom at C-3 carbon, did not give any oxidative homocoupling product but it formed a symmetrical piperazine derivative **3** as an equimolar mixture of two diastereomers: DL-**3a** and *meso*-**3b** (Scheme 2).

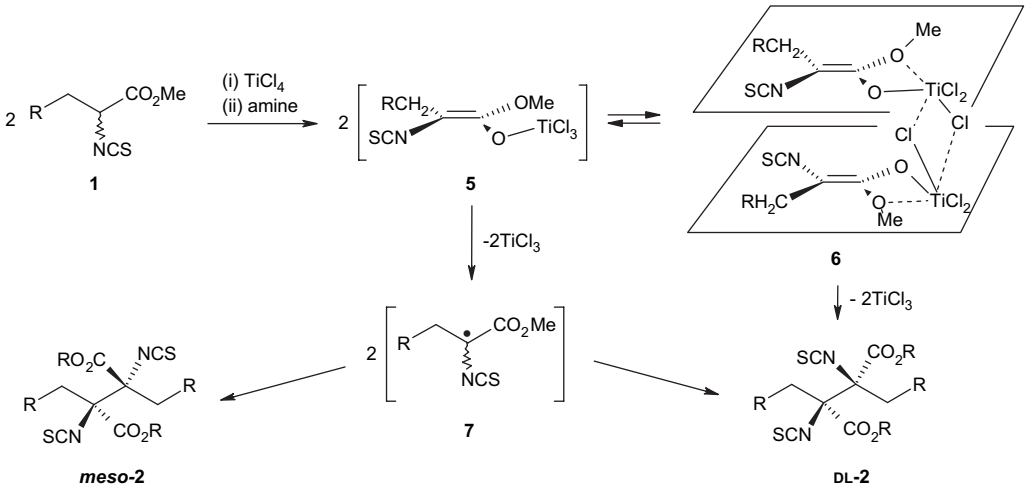
Analogously, the dimerization of (2*S*,3*S*)-2-isothiocyanato-3-methyl-pentanoic acid methyl ester **1g**, derived from L-isoleucine, did not lead to the desired vicinal diisothiocyanate but gave three diastereomers of a 3,6-dithioxo-piperazine derivative **4** (Scheme 3). These results showed clearly that the oxidative coupling of 2-isothiocyanato-carboxylic esters proceeded only for isothiocyanato-carboxylates that were mono- and disubstituted at C-3 carbon atom.

Taking into consideration the tentative mechanism of the oxidative coupling suggested by Matsumura et al.,[3] we explained this phenomenon as a result of a competition between two independent processes. The first process (Scheme 4), the oxidative homocoupling of titanium(IV) enolates, proceeded under kinetic control at low temperature for all 2-isothiocyanato-carboxylic esters bearing a primary or secondary carbon atom C-3. Deep blue titanium(IV) enolate **5** can form vicinal diisothiocyanates **2** in two different ways. After conversion to dimer **6**, in which two RCH_2 groups are located opposite to each other, the reaction leads to chiral diastereomer DL-**2**. Elimination of titanium(III) chloride from the enolate **5** generates an α-carbomethoxy radical **7**, which can couple to give *meso*-**2** rather then DL-**2** diastereomer.

For more hindered isothiocyanato-carboxylates having a tertiary carbon C-3, the oxidative homocoupling was considerably inhibited. We assume that the presence of two alkyl substituents at the C-3 carbon atom gave rise to strong steric repulsions. As a result, the formation of dimeric intermediate



Scheme 3. Three diastereomers of 3,6-dithioxo-piperazine-2,5-dicarboxylic acid dimethyl esters **4a–4c** were obtained from 2-isothiocyanato-carboxylate **1g**. A ratio of **4a/4b/4c** (based on the NMR data): 1:1:1.9. Reagents and conditions: (a) (i) $TiCl_4$, −96 °C, 30 min, under Ar; (ii) DIPEA, −96 °C to rt, 72 h, under Ar.



Scheme 4. The tentative mechanism of the oxidative coupling of 2-isothiocyanato-carboxylates (according to Matsumura et al.).[3]

as well as its oxidation was considerably hindered. Thus the second, thermodynamic controlled process—an intermolecular addition of enolate anion to isothiocyanate group—predominated. Consequently, the 2-isothiocyanato-carboxylic esters derived from DL-valine and L-isoleucine gave symmetrical 3,6-dithioxo-piperazine-2,5-dicarboxylic acid diesters **3** and **4** instead of the desired 2,3-diisothiocyanato-succinates.

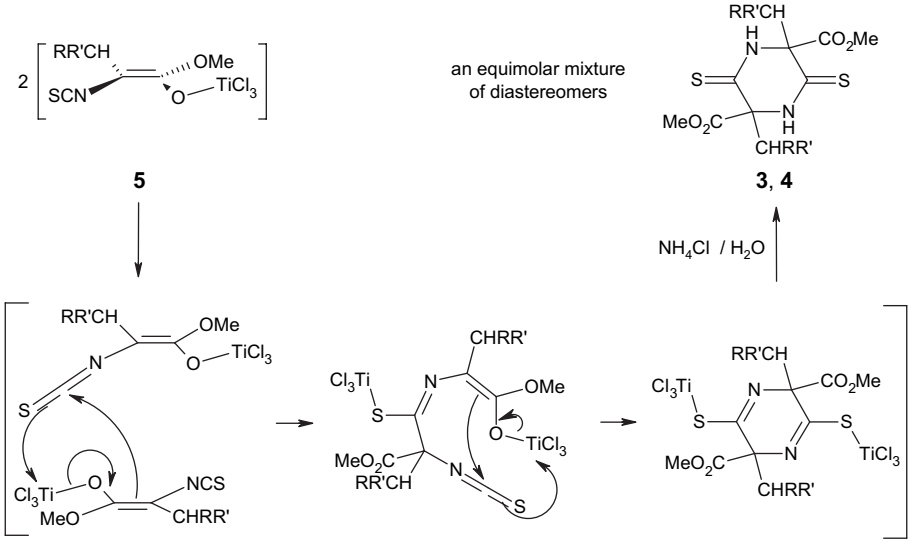
Based on the NMR data we noted that the process leading to piperazine derivatives was not diastereoselective and an equimolar mixture of diastereomers was obtained. This fact prompted us to propose a tentative mechanism for this reaction where two consecutive additions of enolate anions **5** to isothiocyanate groups formed all possible diastereomers of piperazine ring **3** and **4** (Scheme 5).

Purification of the piperazine derivative **3** was carried out using column chromatography followed by a fractional crystallization from ethanol. As a result we isolated two diastereomers of 2,5-diisopropyl-3,6-dithioxo-piperazine-2,5-dicarboxylic acid dimethyl esters **3a** and **3b**. Their reaction with D-10-camphorsulfonyl chloride showed that the crystalline product **3a** was the DL form, whereas the oily **3b** was the *meso* diastereomer.

Column chromatography of **4** resulted in a partial separation of three diastereomers. Based on the NMR spectra we found that the crystalline product consisted of two diastereomers: (*S*,*S*)-2,5-di-*sec*-butyl-3,6-dithioxo-piperazine-(2*R*,5*R*)-dicarboxylic acid dimethyl ester **4a** and (*S*,*S*)-2,5-di-*sec*-butyl-3,6-dithioxo-piperazine-(2*S*,5*S*)-dicarboxylic acid dimethyl ester **4b**, whereas the oily product **4c** was the pure (*S*,*S*)-2,5-di-*sec*-butyl-3,6-dithioxo-piperazine-(2*R*,5*S*)-dicarboxylic acid dimethyl ester.

3. Conclusion

This article presents simple and convenient method for the synthesis of novel, unknown vicinal diisothiocyanates, derivatives of 2,3-diisothiocyanato-succinic acid. These



Scheme 5. Formation of symmetrical piperazine derivatives—a tentative mechanism.

compounds are the part of a rare but very useful group of reactants used for the syntheses of complex heterocyclic systems. An application of the obtained vicinal diisothiocyanates in the organic synthesis is currently intensively investigated. The described protocol applies an oxidative homocoupling of titanium(IV) enolates of 2-isothiocyanato-carboxylic esters and it is the first example of the oxidative dimerization of enolate anions bearing isothiocyanate functional groups. In comparison with earlier reported oxidative couplings of arylacetic acid derivatives, we broadened the application of the amine/$TiCl_4$ oxidizing system on the coupling of 2,2-disubstituted esters. We found that the described procedure may be suitable for the oxidative coupling of 2-isothiocyanato-carboxylates bearing a primary or secondary carbon C-3. 2-Isothiocyanato-carboxylates derived from valine and isoleucine, having a tertiary carbon atom C-3, undergo a different intermolecular cyclization owing to steric hindrances and give novel, unknown 3,6-dithioxo-piperazine-2,5-dicarboxylic acid diesters.

4. Experimental

4.1. General methods

NMR spectra were determined on a Bruker Avance II 300 MHz spectrometer (using TMS as an internal standard), IR spectra were measured with a Bruker IFS 48 FT spectrometer in KBr pellets, and MS spectra were recorded on a Finnigan MAT 95S apparatus. Microanalyses were carried out using Euro-EA 3018 analyzer and their results were in good agreement with the calculated values. Optical rotations were measured on a Polamat A (Zeiss, Jena) polarimeter with 0.5 dm tube. Column chromatography was performed using commercial Merck silica gel 60 (70–230 mesh). Melting points were measured on an Electrothermal 9100 apparatus.

4.2. General procedure for the synthesis of 2,3-diisothiocyanato-succinic acid esters

A solution of 2-isothiocyanato-carboxylic esters **1a–e**[9] (10 mmol) in anhydrous methylene chloride (45 mL) was cooled to −96 °C under argon and titanium(IV) chloride (1.22 mL, 11 mmol) in methylene chloride (5 mL) was added gradually. The reaction mixture was stirred for 30 min at −96 °C and diisopropyl-ethylamine (DIPEA) (1.91 mL, 11 mmol) in methylene chloride (5 mL) was added dropwise. A solution of deep blue titanium(IV) enolate was stirred for 1 h at −96 °C, allowed to warm, and stirred under argon at rt for 2–20 h. After the dimerization was completed the reaction mixture was quenched with ammonium chloride solution (60 mL, satd aq) and the organic layer was separated and dried ($MgSO_4$). Then the solvent was removed under reduced pressure and the crude products (mixtures of *chiral*- and *meso*-diastereomer) were purified and separated using column chromatography (ethyl acetate/cyclohexane 1:5).

4.2.1. DL-2,3-Diisothiocyanato-2,3-dimethyl-succinic acid dimethyl ester (2a). Oxidative coupling of (*R*/*S*)-2-isothiocyanato-propionic acid methyl aster (**1a**) (1.45 g, 10 mmol) afforded **2a** (2.25 g, 78%) after column chromatography as a viscous yellowish oil. [Found: C, 41.71; H, 4.14; N, 9.65. $C_{10}H_{12}N_2O_4S_2$ requires: C, 41.65; H, 4.19; N, 9.71%.] R_f (ethyl acetate/cyclohexane 1:5) 0.38; ν_{max} (liquid film) 3004, 2954, 2040, 1749, 1265 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.86 (6H, s, OCH_3), 1.75 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.1, 140.7, 70.6, 53.9, 22.2; *m*/*z* (EI, 70 eV) 288 (4, M^+), 229 (6), 145 (47), 144 (100%).

Partial data for *meso*-2,3-diisothiocyanato-2,3-dimethyl-succinic acid dimethyl ester were determined from the mixture: δ_H (300 MHz, $CDCl_3$) 3.86 (6H, s, OCH_3), 1.75 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.3, 140.9, 71.4, 53.9, 22.4.

4.2.2. DL-2,3-Diisobutyl-2,3-diisothiocyanato-succinic acid dimethyl ester (2b). Oxidative coupling of (*S*)-2-isothiocyanato-4-methyl-pentanoic acid methyl ester (**1b**) (1.87 g, 10 mmol) afforded **2b** (2.29 g, 61%) after column chromatography as a viscous colorless oil. [Found: C, 51.63; H, 6.33; N, 7.35. $C_{16}H_{24}N_2O_4S_2$ requires: C, 51.59; H, 6.49; N, 7.52%.] R_f (ethyl acetate/cyclohexane 1:5) 0.35; ν_{max} (liquid film) 2958, 2874, 2037, 1746, 1231 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.86 (6H, s, OCH_3), 2.03 (2H, dd, *J* 13.9, 5.4 Hz, CH_aH_b), 1.95 (2H, dd, *J* 13.9, 7.5 Hz, CH_aH_b), 1.73 (2H, m, CH), 1.00 (6H, d, *J* 6.6 Hz, CH_3), 0.83 (6H, d, *J* 6.6 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 168.2, 139.9, 75.5, 54.0, 41.0, 25.3, 23.8, 21.8.

4.2.3. DL-2,3-Dibenzyl-2,3-diisothiocyanato-succinic acid dimethyl ester (2c). Oxidative coupling of (*S*)-2-isothiocyanato-3-phenyl-propionic acid methyl ester (**1c**) (2.21 g, 10 mmol) afforded **2c** (3.22 g, 73%) after column chromatography as a colorless solid, mp 132–133 °C. [Found: C, 60.09; H, 4.79; N, 6.18. $C_{22}H_{20}N_2O_4S_2$ requires: C, 59.98; H, 4.57; N, 6.36%.] R_f (ethyl acetate/cyclohexane 1:5) 0.42; ν_{max} (KBr) 3084, 2955, 2034, 1747, 1212 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33 (6H, m, Ph), 7.17 (4H, m, Ph), 3.79 (6H, s, OCH_3), 3.53 (2H, d, *J* 13.5 Hz, CH_aH_b), 3.46 (2H, d, *J* 13.5 Hz, CH_aH_b); δ_C (75 MHz, $CDCl_3$) 167.4, 141.5, 133.2, 130.5, 128.6, 127.9, 77.2, 53.9, 40.1; *m*/*z* (EI, 70 eV) 440 (1 M^+), 381 (1), 221 (48), 220 (31), 91 (100%).

Partial data for *meso*-2,3-dibenzyl-2,3-diisothiocyanato-succinic acid dimethyl ester were determined from the mixture: δ_H (300 MHz, $CDCl_3$) 7.33 (6H, m, Ph), 7.17 (4H, m, Ph), 3.73 (2H, d, *J* 13.2 Hz, CH_aH_b), 3.70 (6H, s, OCH_3), 3.22 (2H, d, *J* 13.2 Hz, CH_aH_b); δ_C (75 MHz, $CDCl_3$) 167.6, 141.2, 133.0, 129.9, 129.3, 128.0, 77.2, 53.6, 40.7.

4.2.4. DL-2,3-Diisothiocyanato-2,3-bis-(2-methylsulfanyl-ethyl)-succinic acid dimethyl ester (2d). Oxidative coupling of (*R*/*S*)-2-isothiocyanato-4-methylsulfanyl-butyric acid methyl ester (**1d**) (2.05 g, 10 mmol) afforded **2d** (2.23 g, 54%) as a viscous yellow oil after column chromatography. [Found: C, 41.22; H, 5.01; N, 6.82. $C_{14}H_{20}N_2O_4S_4$ requires: C, 41.15; H, 4.93; N, 6.86.] R_f (ethyl acetate/cyclohexane 1:5) 0.35; ν_{max} (liquid film) 2953, 2917, 2037, 1746, 1262 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.88 (6H, s, OCH_3), 2.36 (6H, m, CH_aH_b and SCH_2), 2.17 (2H, m, CH_aH_b), 2.11 (6H, s, SCH_3); δ_C (75 MHz, $CDCl_3$) 167.2, 142.3, 75.2, 54.3, 33.5, 29.2, 15.7.

4.2.5. DL-2,3-Diisothiocyanato-2,3-dimethyl-succinic acid diethyl ester (2e). Oxidative coupling of (*R*/*S*)-2-

isothiocyanato-propionic acid ethyl ester (**1e**) (1.59 g, 10 mmol) afforded **2e** (2.43 g, 77%) after column chromatography as a viscous yellowish oil. [Found: C, 45.44; H, 5.15; N, 8.86. $C_{12}H_{16}N_2O_4S_2$ requires: C, 45.54; H, 5.10; N, 8.85.] R_f (ethyl acetate/cyclohexane 1:5) 0.44; ν_{max} (liquid film) 2985, 2906, 2039, 1745, 1260 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.29 (4H, m, OCH_2), 1.73 (6H, s, CH_3), 1.36 (6H, t, J 7.2 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 167.8, 140.6, 70.4, 63.5, 22.2, 14.0.

Partial data for *meso*-2,3-diisothiocyanato-2,3-dimethyl-succinic acid diethyl ester were determined from the mixture: δ_H (300 MHz, $CDCl_3$) 4.29 (4H, m, OCH_2), 1.73 (6H, s, CH_3), 1.36 (6H, t, J 7.2 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 167.8, 140.6, 71.3, 63.5, 22.3, 14.0.

4.3. General procedure for the synthesis of 3,6-dithioxo-piperazine-2,5-dicarboxylic acid dimethyl esters (3 and 4)

A solution of 2-isothiocyanato-carboxylic esters **1f–g**[9] (20 mmol) in anhydrous methylene chloride (65 mL) was cooled to −96 °C under argon and titanium(IV) chloride (2.44 mL, 22 mmol) in methylene chloride (7 mL) was added gradually. The reaction mixture was stirred for 30 min at −96 °C and diisopropyl-ethylamine (DIPEA) (3.82 mL, 22 mmol) in methylene chloride (7 mL) was added dropwise. A solution of deep blue titanium(IV) enolate was stirred for 30 min at −96 °C, allowed to warm, and stirred under argon at rt for 72 h. After the dimerization was completed the reaction mixture was quenched with ammonium chloride solution (100 mL, satd aq), the organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The crude products **3** and **4** were purified using column chromatography (ethyl acetate/cyclohexane 1:6) and fractional crystallization from 95% ethanol.

4.3.1. DL-2,5-Diisopropyl-3,6-dithioxo-piperazine-2,5-dicarboxylic acid dimethyl ester (3a). An intermolecular dimerization of (*R*/*S*)-2-isothiocyanato-3-methyl-butyric acid methyl ester (**1f**) (3.47 g, 20 mmol) led to a mixture of DL- and *meso*-diastereomers **3a** and **3b**. The crude product **3** was purified using column chromatography (ethyl acetate/cyclohexane 1:6) giving a first fraction enriched in the diastereomer **3a** (R_f: 0.48). Crystallization from 95% ethanol afforded pure **3a** (1.10 g, 31%) as colorless needles, mp 106–107 °C. [Found: C, 48.32; H, 6.41; N, 8.13. $C_{14}H_{22}N_2O_4S_2$ requires: C, 48.53; H, 6.40; N, 8.08.] ν_{max} (KBr) 3212, 2967, 1731, 1631, 1256 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.82 (6H, s, OCH_3), 2.66 (2H, septet, J 6.6 Hz, C*H*$(CH_3)_2$), 1.10 (6H, d, J 6.6 Hz, CH–C*H*$_3$), 0.97 (6H, d, J 6.6 Hz, CH–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 177.0. 169.2, 108.4, 53.3, 37.2, 18.2, 16.6; *m*/*z* (EI, 70 eV) 346 ($15M^+$), 287 (10), 285 (100), 259 (26), 243 (97), 211 (52).

4.3.2. *meso*-2,5-Diisopropyl-3,6-dithioxo-piperazine-2,5-dicarboxylic acid dimethyl ester (3b). Evaporation of the mother liquor after crystallization of **3a** gave an oily product enriched in the diastereomer **3b**. Column chromatography of this mixture (ethyl acetate/cyclohexane 1:6) afforded pure **3b** (0.99 g, 28%) as a viscous oil. [Found: C, 48.40; H, 6.32; N, 8.05. $C_{14}H_{22}N_2O_4S_2$ requires: C, 48.53; H, 6.40; N, 8.08.] ν_{max} (liquid film) 3208, 2970, 2935, 1733, 1630, 1255 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.83 (6H, s, OCH_3), 2.67 (2H, septet, J 6.9 Hz, C*H*$(CH_3)_2$), 1.09 (6H, d, J 6.9 Hz, CH–C*H*$_3$), 0.94 (6H, d, J 6.9 Hz, CH–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 176.9, 169.3, 108.4, 53.3, 37.6, 18.1, 16.3.

4.3.3. (*S*,*S*)-2,5-Di-*sec*-butyl-3,6-dithioxo-piperazine-(2*S*,5*S*)-dicarboxylic acid dimethyl ester and (*S*,*S*)-2,5-di-*sec*-butyl-3,6-dithioxo-piperazine-(2*R*,5*R*)-dicarboxylic acid dimethyl ester (4a + 4b). Intermolecular dimerization of (2*S*,3*S*)-2-isothiocyanato-3-methyl-pentanoic acid methyl ester (**1f**) (3.74 g, 20 mmol) led to a mixture of three diastereomers **4a**–**4c**. The crude product **4** was purified using column chromatography (ethyl acetate/cyclohexane 1:6) giving, as a first fraction, an equimolar mixture of the diastereomers **4a/4b** (R_f: 0.61) as a pale yellow solid (127 g, 33%), mp 69–70 °C. [Found: C, 50.89; H, 7.05; N, 7.56. $C_{16}H_{26}N_2O_4S_2$ requires: C, 51.31; H, 7.00; N, 7.48.] ν_{max} (KBr) 3211, 2967, 1732, 1629, 1248 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 2.35 (2H, m, CH), 1.56 (2H, m, CH–CH_aH_b–CH_3), 1.37 (2H, m, CH–CH_aH_b–CH_3), 0.94 (6H, d, J 7.8 Hz, CH–C*H*$_3$), 0.91 (6H, t, J 7.2 Hz, CH_2–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 177.1, 176.8, 169.4, 169.3, 108.6, 108.6, 53.3, 43.8, 43.7, 25.7, 23.4, 14.8, 12.9, 12.3, 11.9.

4.3.4. (*S*,*S*)-2,5-Di-*sec*-butyl-3,6-dithioxo-piperazine-(2*S*,5*R*)-dicarboxylic acid dimethyl ester (4c). Column chromatography of the crude product **4** gave **4c** in a second fraction (1.015 g, 27%) as a viscous oil. [Found: C, 51.22; H, 6.98; N, 7.39. $C_{16}H_{26}N_2O_4S_2$ requires: C, 51.31; H, 7.00; N, 7.48.] R_f (ethyl acetate/cyclohexane 1:6) 0.45; $[\alpha]_D^{22}$ +114.7 (*c* 1.9, $CHCl_3$); ν_{max} (liquid film) 3214, 2967, 1734, 1627, 1242 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.82 (6H, s, OCH_3), 2.40 (2H, m, CH), 1.54 (2H, m, CH–CH_aH_b–CH_3), 1.41 (2H, m, CH–C*H*$_a$H$_b$–CH_3), 0.95 (6H, d, J 13.5 Hz, CH–C*H*$_3$), 0.93 (6H, t, J 6.3 Hz, CH_2–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 177.0, 169.6, 108.5, 53.4, 44.2, 25.7, 12.6, 12.4.

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