Tetrahedron: *Asymmetry* 19 (2008) 2184–2191

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Axially chiral *N*-(*o*-aryl)-2-thioxo-oxazolidine-4-one and rhodanine derivatives: enantiomeric separation and determination of racemization barriers

Esra Müjde Yılmaz, İlknur Doğan *

Boğaziçi University, Chemistry Department, Bebek, 34342 İstanbul, Turkey

ARTICLE INFO

Article history:
Received 30 July 2008
Accepted 3 September 2008
Available online 9 October 2008

ABSTRACT

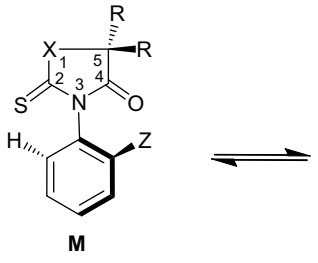
Axially chiral 5,5-dimethyl-3-(*o*-aryl)rhodanine, 3-(*o*-aryl)rhodanine and 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-oxazolidinone derivatives have been synthesized as racemates and the energy barriers to enantiomerization have been determined by dynamic ^{1}H NMR or by following the thermal equilibration of the separated enantiomers using chiral HPLC. The barriers to rotation about the N_{sp2}–C_{aryl} single bond were found to be 82–129 kJ/mol. The racemization barriers in these compounds are affected by the size of the *ortho*-substituent on the aryl ring. The magnitude of the barriers was found to change linearly with the van der Waals radii of the *ortho*-halogen substituents.

1. Introduction

Non-biaryl, axially chiral compounds have been receiving considerable attention[1–9] due to their interesting stereochemistries and also due to their potential uses as catalysts and ligands for asymmetric syntheses.[10] Thus, the synthesis of such atropisomeric compounds with high enantiomeric stability, their chiral separations and the determination of their barriers to enantiomerization are of importance in chiral chemistry.

Based on our experiences with thermally interconvertible, axially chiral compounds,[11–19] the synthesis of *N*-*ortho*-aryl-substituted heterocyclic compounds, as shown in Scheme 1, has been planned.

These compounds possess axial chirality because of the non-planar ground states of the molecules caused by the restricted rotation about the N_{sp2}–C_{aryl} single bond, around which 180° rotation forms *M* and *P* enantiomers. The racemic compounds shown in Scheme 1 are expected to have thermally stable enantiomers at room temperature which will, depending on the nature of the *ortho*-substituent, become thermally interconvertible at higher temperatures. We have recently reported[20] the enantiodifferentiation of some of these compounds (±)-**1**–**4** and (±)-**9**–**12**, using ^{1}H and ^{13}C NMR by applying the dirhodium method.[21] Herein, we report the synthesis of compounds (±)-**1**–**12** as racemates, their resolutions via chiral HPLC and the determination of their activation barriers to enantiomerization. Compounds (±)-**1**–**4** and (±)-**9**–**12** have been synthesized as racemates either by the reaction of *o*-arylisothiocyanates with α-hydroxyisobutyrate[11] or by treatment of



(±)-**1** R= CH_3; X= O Z= F
(±)-**2** R= CH_3; X= O Z= Cl
(±)-**3** R= CH_3; X= O Z= Br
(±)-**4** R= CH_3; X= O Z= I
(±)-**5** R= CH_3; X= S Z= F
(±)-**6** R= CH_3; X= S Z= Cl
(±)-**7** R= CH_3; X= S Z= Br
(±)-**8** R= CH_3; X= S Z= I

(±)-**9** R= H; X= S Z= F
(±)-**10** R= H; X= S Z= Cl
(±)-**11** R= H; X= S Z= Br
(±)-**12** R= H; X= S Z= I

Scheme 1. The synthesized compounds.

o-arylisothiocyanates with the corresponding thioglycolic acid ethyl ester.[11] Compounds (±)-**5**–**8** have been synthesized from the corresponding dithiocarbamate salts, which have been prepared according to a modified Kaluza synthesis.[22]

2. Results and discussion

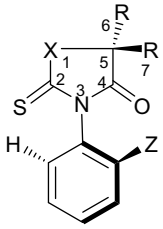
2.1. NMR results

The ^{1}H and ^{13}C NMR (Tables 1 and 2, respectively) clearly demonstrated the chirality of the compounds by the non-equivalence

* Corresponding author. Tel.: +90 212 359 6620; fax: +90 212287 2467.
E-mail address: dogan@boun.edu.tr (İ. Doğan).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.09.001

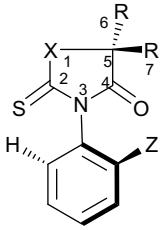
Table 1
400 MHz ^{1}H NMR spectroscopic data for the compounds (±)-**1**–**12** in $CDCl_3$ at 30 °C



Compound no.	X	R	Z	δ of 5-CH_3 (ppm)	δ of 5-CH_2 (ppm)	δ of aromatic (ppm)
(±)-**1**	O	CH_3	F	1.75[a]	—	7.25–7.53
				1.14 and 1.16[b,c]		6.60–7.20
(±)-**2**	O	CH_3	Cl	1.75 and 1.77[b]	—	7.26–7.62
(±)-**3**	O	CH_3	Br	1.76 and 1.79[b]	—	7.30–7.76
(±)-**4**	O	CH_3	I	1.75 and 1.82[b]	—	7.20–8.20
(±)-**5**	S	CH_3	F	1.72 and 1.76[b,d]	—	7.34–7.59
(±)-**6**	S	CH_3	Cl	1.74 and 1.76[b,d]	—	7.49–7.68
				1.80 and 1.84[b]		7.25–7.57
(±)-**7**	S	CH_3	Br	1.75 and 1.76[b,d]	—	7.43–7.81
(±)-**8**	S	CH_3	I	1.80 and 1.85[b]	—	7.25–7.74
				1.76 and 1.79[b,d]	—	7.23–7.98
(±)-**9**	S	H	F	—	$\delta_A = 4.16$, $\delta_B = 4.27$[e]	7.25–7.50
					$\delta_A = 2.79$, $\delta_B = 2.82$[c,e]	7.09–7.20
(±)-**10**	S	H	Cl	—	$\delta_A = 4.19$, $\delta_B = 4.25$[e]	7.15–7.40
				—	$\delta_A = 2.75$, $\delta_B = 2.88$[f]	6.50–6.90
(±)-**11**	S	H	Br	—	$\delta_A = 4.21$, $\delta_B = 4.27$[e]	7.22–7.76
				—	$\delta_A = 2.69$, $\delta_B = 2.87$[f]	6.37–7.01
(±)-**12**	S	H	I	—	$\delta_A = 4.19$, $\delta_B = 4.26$[e]	7.20–8.10
				—	$\delta_A = 2.70$, $\delta_B = 2.90$[f]	6.13–7.23

[a] Only one singlet was observed.
[b] Diastereotopic methyl protons.
[c] Solvent is toluene-d_8.
[d] Solvent is DMSO-d_6.
[e] AB type splitting.
[f] Solvent is benzene-d_6.

Table 2
100 MHz ^{13}C NMR spectroscopic data for the compounds (±)-**1**–**12** in $CDCl_3$ at 30 °C



Compound no.	X	R	Z	C-2	C-4	C-5	C-6,7	C-aromatic
(±)-**1**	O	CH_3	F	188.0	173.6	87.5	22.3, 25.3	128.3–158.
(±)-**2**	O	CH_3	Cl	187.8	174.9	87.4	23.4, 24.1	128.3, 132.2
(±)-**3**	O	CH_3	Br	188.0	175.8	88.0	23.2, 25.1	123.3–136.2
(±)-**4**	O	CH_3	I	187.4	174.6	87.6	23.7, 24.1	98.1–140.4
(±)-**5**	S	CH_3	F	197.0[a]	177.3[a]	54.1[a]	24.8[a], 25.9[a]	123.5–158.1[a]
(±)-**6**	S	CH_3	Cl	198.4	178.8	56.1	26.9, 28.3	128.1–133.3
(±)-**7**	S	CH_3	Br	198.4	178.7	56.2	27.0, 28.3	123.0–134.8
(±)-**8**	S	CH_3	I	200.2[b]	179.0[b]	57.0[b]	26.5[b], 28.0[b]	100.0–140.0[b]
(±)-**9**	S	H	F	200.0	173.6	37.0	—	117.3–160.2
(±)-**10**	S	H	Cl	198.0	172.6	36.6	—	128.2–133.0
(±)-**11**	S	H	Br	199.5	171.9	35.6	—	128.5–135.8
(±)-**12**	S	H	I	197.6	172.6	36.9	—	98.4–140.3

[a] Solvent is benzene-d_6.
[b] Solvent is DMSO-d_6.

of the protons or methyl groups present on C-5 of the heterocyclic ring, which are diastereotopic owing to the stereostructures of the compounds. The ground states of the compounds are non-planar due to the restricted rotation about the N_{sp2}–C_{aryl} bond, making this bond a chiral axis. Figure 1 demonstrates a typical ^{1}H NMR spectrum showing the AB splittings of the diastereotopic methylene protons. The chemical shift differences between the diastereotopic groups can be expected to be influenced by the anisotropic influence of the substituent at the *ortho*-position, as well as by the dihedral angles between the two rings, which in turn can be determined largely by the size of the *ortho*-aryl substituents. The magnitude of the chemical shift difference in every series was

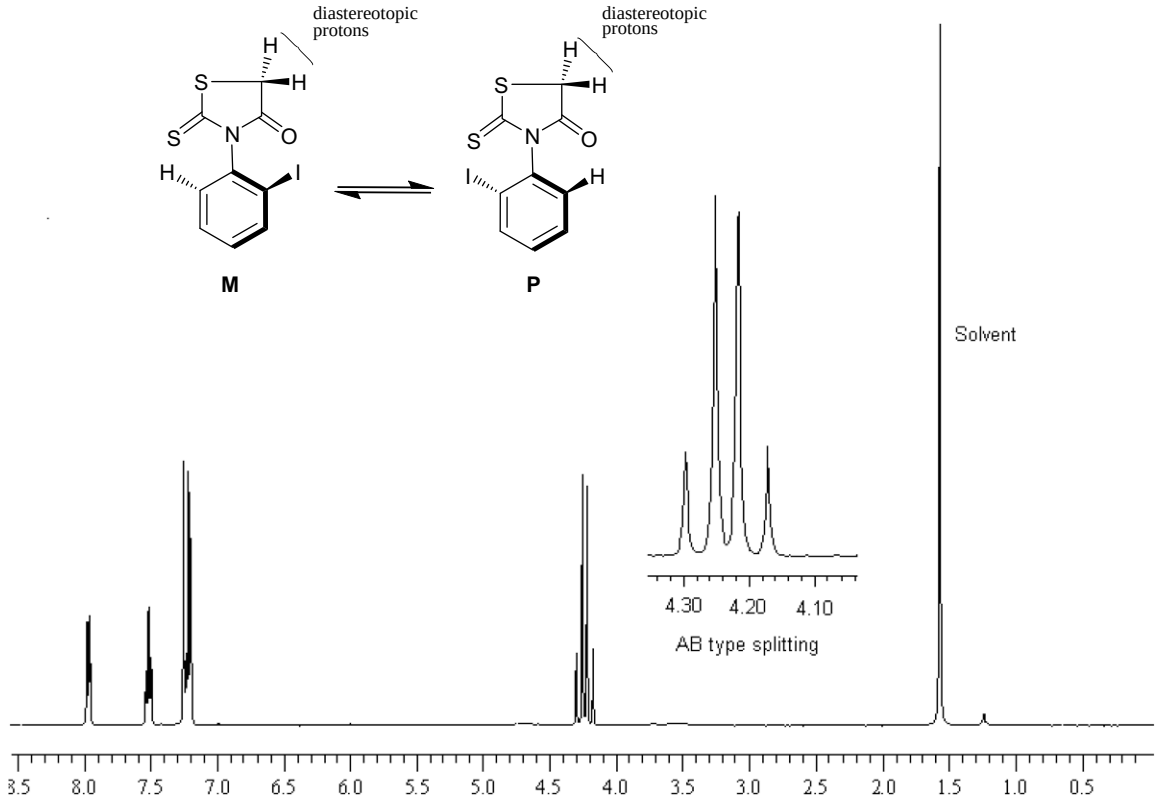


Figure 1. The 400 MHz ^{1}H NMR spectrum of compound (±)-**12** in $CDCl_3$.

found to increase from 0.02 ppm for *o*-fluoro derivatives to 0.07 ppm for the *o*-iodo compounds. The chemical shift difference of the diastereotopic carbon atoms (Table 2), however, did not seem to depend on the nature and size of the *ortho*-substituent. Also, a strong solvent dependence of the C-5 hydrogens was observed, which amounted to 1.5 ppm on going from aromatic solvents (toluene-d_8, benzene-d_6) to polar solvents ($CDCl_3$).

2.2. Chiral chromatography

The enantiomers of compounds (±)-**2**–**12** were resolved or enriched micropreparatively on analytical or semipreparative Chiralpak AD-H columns using hexane–ethanol mixtures as an eluent (Table 3).

Table 3
Chromatographic data for the separation of enantiomers of (±)-**2**–**12** on Chiralpak AD-H columns

Compound no.	Eluent (v/v) hexane/ethanol	Flow rate (ml/min)	k'_1	k'_2	α
(±)-**2**[a]	95:5	0.8	2.09	2.56	1.22
(±)-**3**[a]	95:5	0.8	2.12	2.47	1.16
(±)-**4**[a]	95:5	0.8	2.54	2.99	1.18
(±)-**5**[b]	95:5	2.5	2.11	2.43	1.15
(±)-**6**[a]	95:5	0.6	1.65	2.77	1.67
(±)-**7**[b]	90:10	3.0	0.88	1.27	1.44
(±)-**8**[b]	90:10	3.0	1.14	1.31	1.15
(±)-**9**[b]	90:10	3.5	8.16	13.5	1.65
(±)-**10**[b]	95:5	4.5	6.49	10.12	1.56
(±)-**11**[a]	50:50	0.6	3.64	4.34	1.19
(±)-**12**[a]	50:50	0.6	3.19	4.51	1.41

[a] Analytical Chiralpak AD-H column was used.
[b] Semi-preparative Chiralpak AD-H column was used.

The cellulose- or amylose-based carbamate columns showed good enantioselectivities for these *N*-*ortho*-phenyl-substituted cyclic thiocarbamate structures. The enantiomers of compound (±)-**1** could not be resolved due to its fast racemization. The ^{1}H NMR of this compound showed the diastereomeric methyl protons at C-5; the energy barrier for this compound was therefore determined by temperature dependent NMR, as explained later in the text.

It was observed that the rhodanine derivatives (±)-**9**–**12**, which are unsubstituted at C-5, were better retained (Table 3) on a chiralpak AD-H column than the corresponding 5,5-dimethyl compounds (±)-**2**–**8**.

2.3. Barriers to racemization

After the enantiomers of (±)-**2**–**12** were resolved by chiral chromatography, thermal racemizations were performed on the single enantiomers, as has been described before,[19] (Fig. 2) in order to determine the activation energy barriers to racemization (Table 4).

The *ortho*-iodo compounds (±)-**8** and (±)-**12** could not be racemized at 78 °C using ethanol as solvent. The Chiralpak IB column enabled the use of toluene as solvent for the racemization of these compounds at 105 °C and 110 °C, respectively, for the determination of activation energies for enantiomeric interconversion. The racemization barriers for these compounds were determined as 128.2 kJ/mol and 129.0 kJ/mol, respectively (Table 4).

The energy barrier for the racemization of compound (±)-**10** was previously determined in diglyme at 387 K as 121.2 kJ/mol.[12] The barrier for this compound in this work was found to be 119.5 kJ/mol when the racemization was carried out in ethanol at 348 K. The difference appears more likely to be a temperature effect, rather than a solvent effect, when the activation barrier of the structurally similar *N*-(*o*-tolyl)rhodanine determined at different temperatures and solvents is compared. For this compound, an activation barrier of 109.3 kJ/mol was found[19] in ethanol at 333 K, whereas a value of 114.4 kJ/mol had been reported[12] in

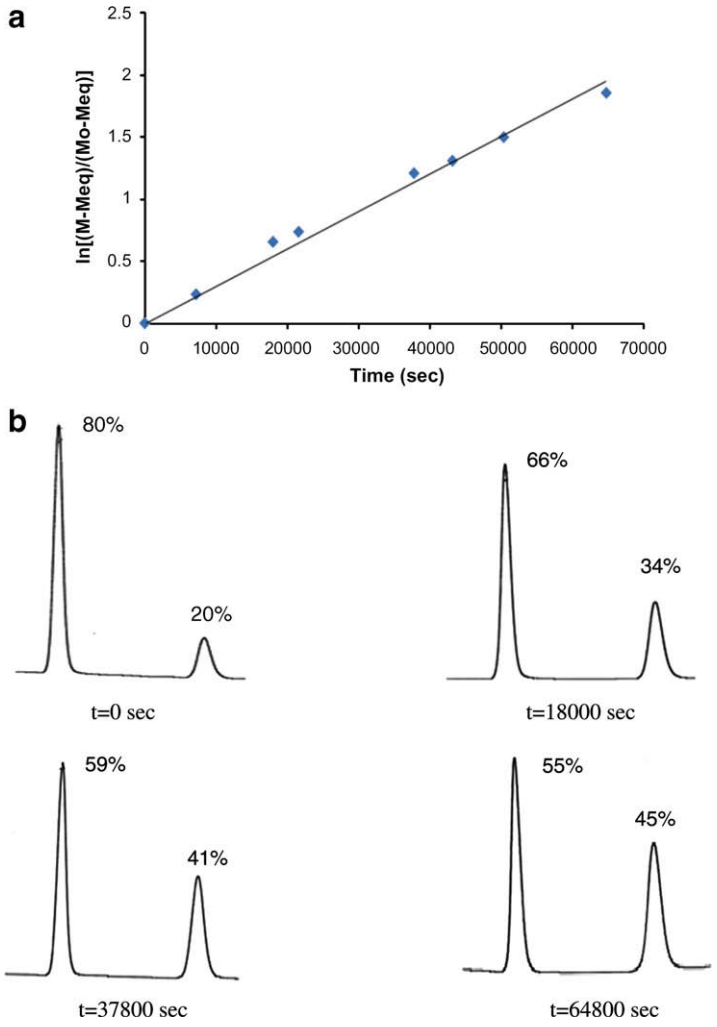


Figure 2. The plot of $\ln(([M]-[M]_{eq})/([M]_o-[M]_{eq}))$ versus time at 353 K for the slope of which gives the rate of enantiomerization. (b) The liquid chromatograms taken to follow the thermal racemization of the second eluted enantiomer of compound (±)-**10** at 353 K. Column: Chiralpak AD-H. Eluent Hexane:Ethanol 90:10. Flow rate: 0.6 ml/min. UV detection at λ = 240 nm.

diglyme at 348 K. When we repeated the same racemization in this work at 348 K in ethanol, we found a barrier of 115.8 kJ/mol. Furthermore, for compound 5,5-dimethyl-*N*-(*o*-tolyl)-2-thioxo-oxazolidine-4-one, the barrier that was determined[12] in diglyme (104.3 kJ/mol) at 330 K was found to be quite close to the one found in ethanol in this work as 103.8 kJ/mol at 328 K. Thus, the temperature at which the racemization has been carried out should be taken into consideration when comparing the energy barriers of interconvertible enantiomers.

Table 4
The activation barriers to racemization for the compounds (±)-**1**–**12**

Compound	Solvent	T (K)	k (s^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})
(±)-**1**	DMSO-d_6	386[a]	61.9[b]	82.0 ± 0.5[c]
	Toluene-d_8	356[a]	19.5[b]	79.0 ± 0.5[c]
(±)-**2**	Ethanol	343[d]	5.0×10^{-5}[e]	112.6 ± 0.7[f]
(±)-**3**	Ethanol	343[d]	1.0×10^{-5}[e]	117.2 ± 0.7[f]
(±)-**4**	Ethanol	348[d]	2.0×10^{-6}[e]	124.0 ± 0.7[f]
(±)-**5**	Ethanol	280[d]	1.0×10^{-4}[e]	89.8 ± 0.7[f]
(±)-**6**	Ethanol	348[d]	2.5×10^{-5}[e]	116.3 ± 0.7[f]
(±)-**7**	Ethanol	348[d]	4.0×10^{-6}[e]	121.6 ± 0.7[f]
(±)-**8**	Toluene	378[d]	3.0×10^{-5}[e]	128.2 ± 0.7[f]
(±)-**9**	Ethanol	280[d]	5.0×10^{-5}[e]	91.0 ± 0.7[f]
(±)-10	Diglyme	387[d]	7.4×10^{-4}[e]	121.2 ± 0.2[g]
	Ethanol	348[d]	1.5×10^{-5}[e]	119.5 ± 0.7[f]
(±)-**11**	2-Propanol	351[d]	3.0×10^{-6}[e]	123.6 ± 0.7[f]
(±)-**12**	Toluene	383[d]	2.0×10^{-5}[e]	129.0 ± 0.7[f]

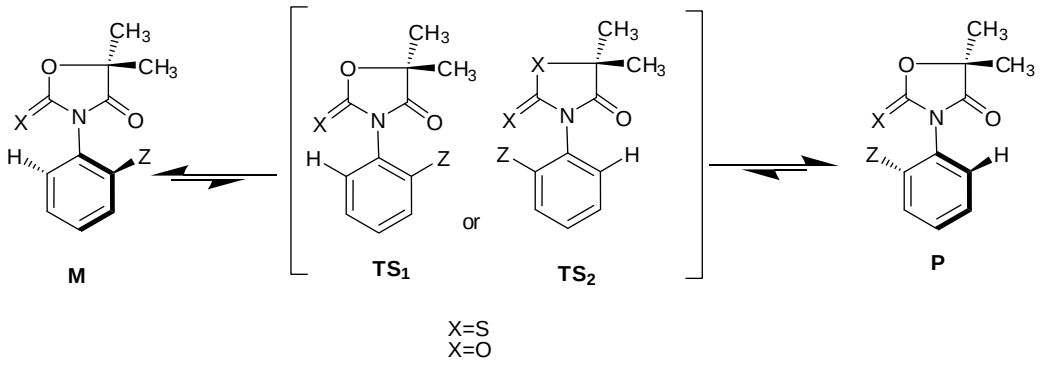
[a] The solvent in which the racemization took place.
[b] Rate constant at the coalescence temperature.
[c] Free energy of activation determined by 400 MHz temperature dependent NMR.
[d] The temperature at which the thermal racemization has been performed.
[e] The rate constant of interconversion between the enantiomers.
[f] Free energy of activation determined by resolution-racemization via HPLC.
[g] Value from Ref. 12.

Compounds (±)-**1**–**12** studied in this work are racemizing through rotation around the C_{aryl}–N_{sp2} single bond. Therefore, the molecules may in principle pass through two different planar transition states [Scheme 2, TS_1 (X = S) and TS_2 (X = S)].

While TS_2 (X = S), which has the sulfur passing the Z group, might experience a higher steric hinderance than the one that has the smaller-sized oxygen (TS_1), both may in principle contribute to the racemization.

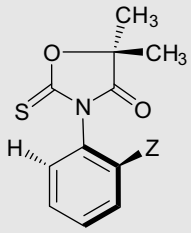
Comparing the energy barriers of 5,5-dimethyl-2-thioxo-4-oxazolidinones (±)-**1**–**4** determined in this work (despite different temperatures of measurements), with the barrier of 5,5-dimethyl-2,4-oxazolidinediones that have been reported earlier[16] (Table 5) reveals that the former has barriers larger than 25 kJ/mol for the *o*-fluoro derivative and 29, 29, 30, 30.5 kJ/mol for the Cl, Br, I and CH_3 derivatives, respectively. Thus, the 2-thioxo group increased the barrier to rotation by about 30 kJ/mol when substituted for the carbonyl at the 2-position of the heterocyclic ring.

In the case of 5,5-dimethyl-oxazolidinediones, although the bond lengths of the O–C and C–C bonds of the heterocyclic ring



Scheme 2. Rotational isomers of 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-oxazolidinone (X = S) and 5,5-dimethyl-3-(*o*-aryl)-2,4-oxazolidinedione (X = O) derivatives.

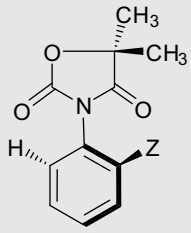
Table 5
Comparison of the racemization barriers of 5,5-dimethyl-*N*-(*o*-aryl)-2-thioxo-4-oxazolidinone and the corresponding 2,4-oxazolidinedione derivatives



M and **P**

5,5-Dimethyl-*N*-(*o*-aryl)-2-thioxo-4-oxazolidinone derivatives

Z	$\Delta G^{\neq}$	T (K)
F	82.0	386
Cl	112.6	343
Br	117.2	348
I	124.0	348
CH_3	103.8	328



M and **P**

5,5-Dimethyl-*N*-(*o*-aryl)-2,4-oxazolidinedione derivatives

Z	$\Delta G^{\neq *}$	T (K)
F	57.3	247
Cl	83.2	377
Br	86.6	395
I	94.2	293
CH_3	73.5	321

*Values taken from reference 16

should be different, if the two transition states (Scheme 2, TS_1 and TS_2, X = O) are assumed to be equally populated because the Z group will pass through the oxygen atoms in both, the actual rate constants for these compounds will be twice as low as the observed ones.[23] Taking this fact into account, the recalculated activation barriers for 5,5-dimethyl-*N*-(*o*-aryl)-2,4-oxazolidinediones would have been 58.8, 85.4, 88.9, 95.8 and 75.3 kJ/mol for Z = F, Cl, Br, I and CH_3, respectively, which are still far smaller than the observed barriers for 5,5-dimethyl-*N*-(*o*-aryl)-2-thioxo-4-oxazolidinones (Table 5). Thus, it seems likely that both transition states, TS_1 and TS_2 (Scheme 2, X = S), are contributing to the barrier rather than TS_1 (Scheme 2, X = S) predominantly.

It was found that for the halogen series, the barriers showed a remarkable linearity with the van der Waals radii of the halogens[24] (Fig. 3). Hence, it can be concluded that if the type of interactions between the *ortho*-substituent and the exocyclic groups (C=O and C=S in this case) are similar (mainly dipolar repulsions in the planar transition state), the barrier observed is directly proportional to the size of the substituent.

The oxazolidine–thiones (±)-**1**–**4** have barriers to rotation that are about 4 kJ/mol lower than that of the corresponding thiazolidine–thiones (±)-**5**–**8**. The decrease in the bond length in going from S–C to O–C should cause this difference. Comparing the barriers of (±)-**5**–**8** with (±)-**9**–**12** shows that the 5,5-dimethyl substitution decreases the barriers slightly (by about 2 kJ/mol).

2.4. Temperature dependent NMR

The activation energy for the racemization of compound (±)-**1**, 5,5-dimethyl-3-(*o*-fluorophenyl)-2-thioxo-4-oxazolidinone, has been determined by a temperature dependent NMR experiment (Fig. 4).

At the probe temperature of 30 °C, diastereotopic 5,5-dimethyl signals were observed at 1.72 and 1.65 ppm, respectively. At higher temperatures, where the rotation became faster, the two singlets slowly came to coalescence (Fig. 4) from which the first-order rate constant for the interconversion of the *M* and *P* enantiomers was determined[25] and substitution of the rate constant in the Eyring equation gave the ΔG value.[25] The activation energy values determined by temperature dependent ^{1}H NMR in DMSO-d_6 were 3 kJ/mol higher (82 kJ/mol) than the one determined in toluene-d_8 (79 kJ/mol). The slightly higher value obtained in DMSO-d_6 for this *o*-fluoro-substituted compound may be due to the higher polarity of this solvent compared to toluene-d_8.

3. Conclusions

Axially chiral 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-oxazolidinones, (±)-**1**–**4**, 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-thiazolidinones, (±)-**5**–**8**, and 3-(*o*-aryl)-2-thioxo-4-thiazolidinones, (±)-**9**–**12**, have been synthesized as racemates.

The chirality of the compounds has been proven by the presence of diastereotopic protons or carbon atoms detected by ^{1}H NMR or ^{13}C NMR spectroscopy. The chemical shift differences between the diastereotopic groups are affected by the anisotropic influence of the substituent at the *ortho*-position as well as by the dihedral angles between the two rings, which in turn will be determined largely by the size of the *ortho*-aryl substituents.

The interconvertible enantiomers of compounds (±)-**2**–**12** were found to be thermally stable at 7 °C and their micropreparative

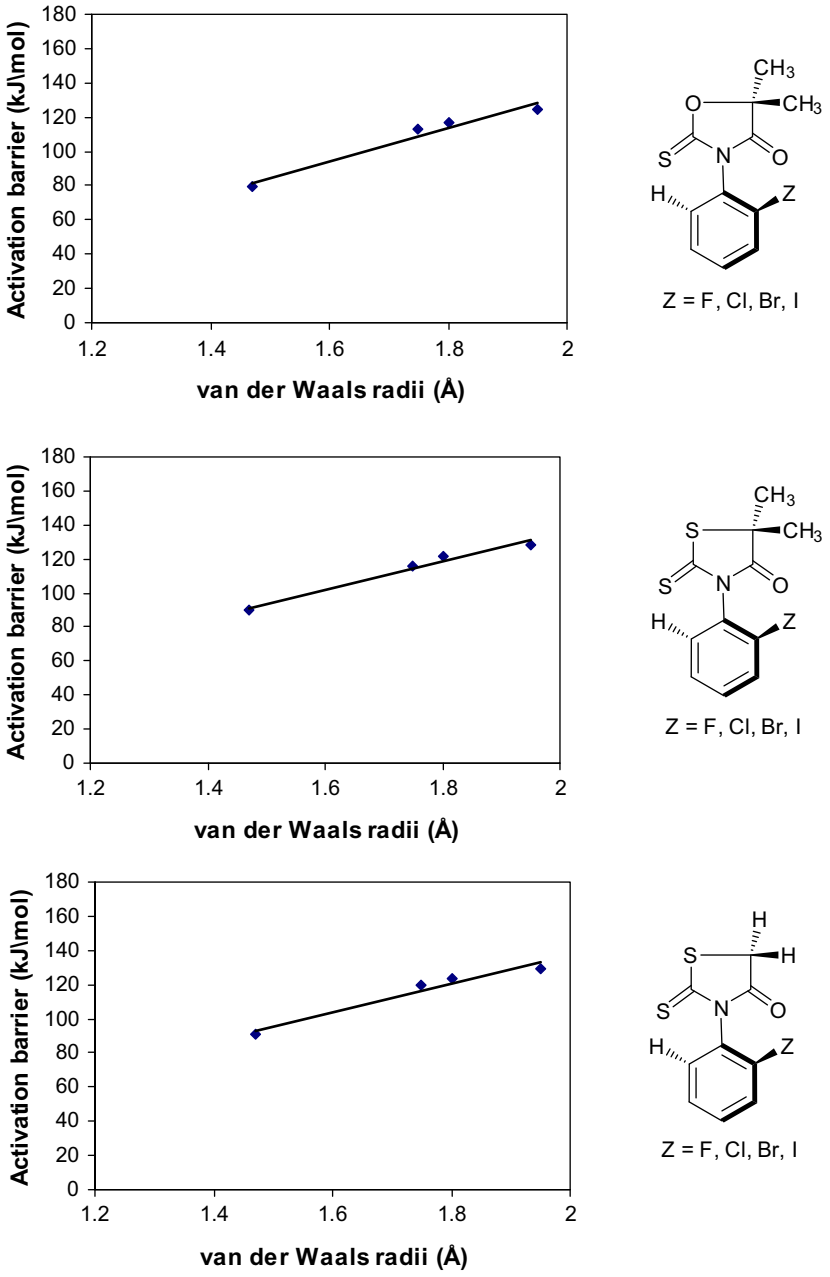


Figure 3. The plot of activation barriers versus van der Waals radii of the *o*-substituted halogens for the series of 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-oxazolidinones (±)-**1**–**4**, 5,5-dimethyl-3-(*o*-aryl)rhodanines (±)-**5**–**8** and 3-(*o*-aryl)rhodanines (±)-**9**–**12**.

resolutions were achieved by HPLC on the chiralpak AD-H and IB columns. The barriers to rotation around the C_{Aryl}–N_{sp2} bond in these compounds were determined by a subsequent thermal racemization as 90–129 kJ/mol. The energy barrier for the faster rotating *o*-fluoro derivative (±)-**1** was determined by temperature dependent ^{1}H NMR and found to be 79 kJ/mol in toluene-d_8 and 82 kJ/mol in DMSO-d_6.

4. Experimental

The ^{1}H NMR and ^{13}C NMR spectra of all compounds were recorded on a Varian-Mercury VX-400 MHz and 100 MHz NMR spectrometer (T = 303 K). IR analyses were performed on a Mattson Genesis II FTIR using KBr discs. Liquid chromatography analyses with UV detector (λ = 254 nm) were performed using Chiralpak AD-H column (Daicel Ltd, particle size: 5 μm, column size: 250 × 4.6 mm), Semi-preparative Chiralpak AD-H column (Daicel Ltd, particle size: 5 μm, column size: 250 × 10 mm) and Chiralpak IB column (Daicel Ltd, particle size: 5 μm, column size: 250 × 4.6 mm). Thermohypersil-Keystone column pocket was used for the temperature control of the chiral columns. Separations were carried out at T = 280 K. Elemental analyses were performed on a Thermo Scientific FlashEA 1112 elemental analyzer. Melting points were recorded using an Electrothermal 9100 melting point apparatus.

4.1. Syntheses

4.1.1. General procedure for the preparation of 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-oxazolidinones[11]

The 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-oxazolidinones, compounds (±)-**1**–**4**, were synthesized by the reaction of the

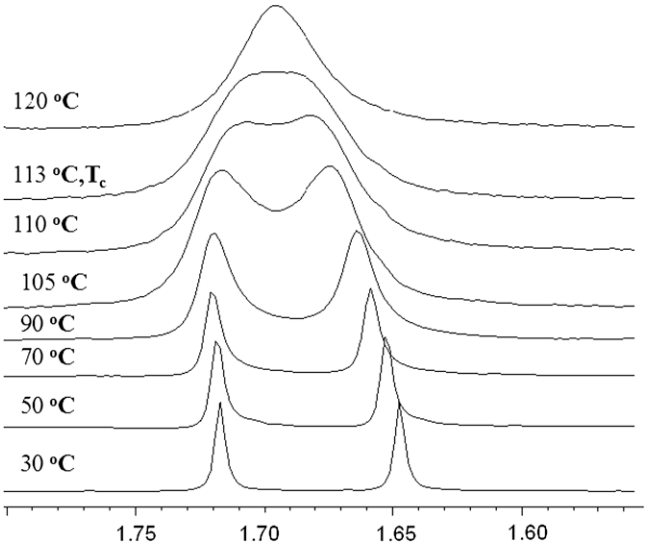


Figure 4. Temperature dependent ^{1}H NMR spectra of the diastereotopic C-5 methyl groups of compound (±)-**1** in DMSO-d_6.

corresponding arylisothiocyanates with α-hydroxy isobutyrate. The appropriate arylisothiocyanate was mixed with α-hydroxyisobutyrate in the presence of metallic sodium in toluene. The reaction mixture was refluxed for 7 h. Toluene was distilled out and the remaining crude product was purified by recrystallization from ethanol.

4.1.1.1. 5,5-Dimethyl-3-(*o*-fluorophenyl)-2-thioxo-4-oxazolidinone (±)-1. The compound was synthesized according to the general procedure using 5 g (0.033 mol) *o*-fluorophenylisothiocyanate, 4.31 g (0.033 mol) α-hydroxyisobutyrate, 0.075 g (0.0033 mol) metallic sodium and 25 ml toluene. Yield: 1 g (12.7%), mp: 82–84 °C. ^{1}H NMR (400 MHz, toluene-d_8): δ 7.20–6.60 (m, 4H), 1.16 (s, 3H), 1.14 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 188.0, 173.6, 158.2–128.3, 87.5, 25.3, 22.3 ppm. Calcd for $C_{11}H_{10}O_2NSF$: C, 55.22; H, 4.21; N, 5.85; S, 13.40. Found: C, 55.06; H, 4.25; N, 5.77; S, 13.66. IR (KBr) 1775, 1269 cm^{-1}. UV–vis (EtOH) λ_{max} 206 (logε 4.07), 272 (logε 3.86) nm, 336 (logε 1.71) nm.

4.1.1.2. 5,5-Dimethyl-3-(*o*-chlorophenyl)-2-thioxo-4-oxazolidinone (±)-2. The compound was synthesized according to the general procedure using 6.78 g (0.040 mol) *o*-chlorophenylisothiocyanate, 5.28 g (0.040 mol) α-hydroxyisobutyrate, 0.092 g (0.0040 mol) metallic sodium and 25 ml toluene. Yield: 3.05 g (29.8%), mp: 90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.26 (m, 4H), δ 1.77 (s, 3H), 1.75 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.8, 174.9, 132.2–128.3, 87.4, 24.1, 23.4 ppm. Calcd for $C_{11}H_{10}O_2NSCl$: C, 51.66; H, 3.94; N, 5.48; S, 12.54. Found: C, 51.61; H, 3.95; N, 5.51; S, 12.89. IR (KBr) 1774, 1258 cm^{-1}. UV–vis (EtOH) λ_{max} 206 (logε 3.54), 273 (logε 3.49), 331 (logε 1.71) nm.

4.1.1.3. 5,5-Dimethyl-3-(*o*-bromophenyl)-2-thioxo-4-oxazolidinone (±)-3. The compound was synthesized according to the general procedure using 2.17 g (0.01 mol) *o*-bromophenylisothiocyanate, 1.32 g (0.01 mol) α-hydroxyisobutyrate, 0.023 g (0.001 mol) metallic sodium and 25 ml toluene. Yield: 0.97 g (32.3%), mp: 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.30 (m, 4H), 1.79 (s, 3H), 1.76 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 175.8, 136.2–123.3, 88.0, 25.1, 23.2 ppm. Calcd for $C_{11}H_{10}O_2NSBr$: C, 44.01; H, 3.36; N, 4.67; S, 10.68. Found: C, 44.35; H, 3.45; N, 4.77; S, 10.50. IR (KBr) 1785, 1269 cm^{-1}. UV–vis (EtOH) λ_{max} 206 (logε 3.86), 272 (logε 3.62), 335 (logε 1.68) nm.

4.1.1.4. 5,5-Dimethyl-3-(*o*-iodophenyl)-2-thioxo-4-oxazolidinone (±)-4. The compound was synthesized according to the general procedure using 5 g (0.019 mol) *o*-iodophenylisothiocyanate, 2.5 g (0.019 mol) α-hydroxyisobutyrate, 0.043 g (0.0019 mol) metallic sodium and 25 ml toluene. Yield: 3.1 g (47%), mp: 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20–7.20 (m, 4H), 1.82 (s, 3H), 1.75 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.4, 174.6, 140.4–98.1, 87.6, 24.1, 23.7 ppm. Calcd for $C_{11}H_{10}O_2NSI$: C, 38.05; H, 2.90; N, 4.03; S, 9.24. Found: C, 38.27; H, 2.99; N, 4.01; S, 9.53. IR (KBr) 1764, 1259 cm^{-1}. UV–vis (EtOH) λ_{max} 206 (logε 3.93), 272 (logε 3.69), 334 (logε 1.53) nm.

4.1.2. General procedure for the preparation of 5,5-dimethyl-3-(*o*-aryl)rhodanines

The following is the generalized procedure used for the preparation of compounds (±)-**5**–**8**. The corresponding aryldithiocarbamates were synthesized according to a modified Kaluza synthesis[22] by using an amine, carbon disulfide and triethylamine. At the first part of the procedure, the amine was dissolved in the minimum amount of benzene and treated with carbon disulfide and triethylamine as base. The solution was cooled to 0 °C. After complete precipitation of the triethylammonium dithiocarbamate salt, the solution was filtered. The solid was washed with anhydrous ether and air dried for about 15 min. Then, the salt was dissolved in chloroform, treated with triethylamine, and cooled again to 0 °C. To this solution was added α-bromoisobutyric acid ethyl ester dropwise over a 20 min period with hand stirring. The resulting solution was stirred at 0 °C for 2 h and then heated at 50 °C for 4 h. Then, the chloroform solution was washed with 3 M HCl, twice with water and then dried over calcium chloride. The chloroform was evaporated in vacuo and the crude product was recrystallized from ethanol.

4.1.2.1. 5,5-Dimethyl-3-(*o*-fluorophenyl)rhodanine (±)-5. The compound was synthesized according to the general procedure using 14.55 g (0.15 mol) *o*-fluoro aniline, 9.9 ml (0,15 mol) carbon disulfide and 21 ml (0.15 mol, for the first part) triethylamine. 19.87 g (0.069 mol) *o*-fluorophenyl dithiocarbamate was obtained. The dithiocarbamate was dissolved in 60 ml $CHCl_3$, treated with 13.4 g (0.069 mol) α-bromoisobutyric acid ethyl ester and 9.66 ml (0.069 mol) triethylamine. Yield: 2 g (11.4%), mp: 70–72 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59–7.34 (m, 4H), 1.76 (s, 3H), 1.72 (s, 3H) ppm. ^{13}C NMR (100 MHz, benzene-d_6): δ 197.0, 177.3, 158.1–123.3, 54.1, 25.9, 24.8 ppm. Calcd for $C_{11}H_{10}ONS_2F$: C, 51.74; H, 3.94; N, 5.48; S, 25.12. Found: C, 52.12; H, 3.91; N, 5.41; S, 25.09. IR (KBr) 1747, 1247 cm^{-1}. UV–vis (EtOH) λ_{max} 300 (logε 4.28), 205 (logε 4.07), 398 (logε 1.66) nm.

4.1.2.2. 5,5-Dimethyl-3-(*o*-chlorophenyl)rhodanine (±)-6. The compound was synthesized according to general procedure using 12.75 g (0.1 mol) *o*-chloro aniline, 7.6 ml (0.1 mol) carbon disulfide and 14 ml (0.1 mol, for the first part) triethylamine. Next, 8.22 g (0.027 mol) *o*-chlorophenyl dithiocarbamate was obtained. *o*-chlorophenyl dithiocarbamate was then dissolved in 25 ml $CHCl_3$, and treated with 5.27 g (0.027 mol) α-bromoisobutyric acid ethyl ester and 3.85 ml (0.027 mol) triethylamine. Yield: 1.87 g (25.5%), mp: 74–76 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68–7.49 (m, 4H), 1.76 (s, 3H), 1.74 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 178.8, 133.3–128.1, 56.1, 28.3, 26.9 ppm. Calcd for $C_{11}H_{10}ONS_2Cl$: C, 48.61; H, 3.71; N, 5.15; S, 23.59. Found: C, 48.56; H, 3.69; N, 5.31; S, 23.26. IR (KBr) 1725, 1263 cm^{-1}. UV–vis (EtOH) λ_{max} 294 (logε 4.14), 205 (logε 3.83), 336 (logε 1.71) nm.

4.1.2.3. 5,5-Dimethyl-3-(*o*-bromophenyl)rhodanine (±)-7. The compound was synthesized according to the general procedure using 34.4 g (0.2 mol) *o*-bromoaniline, 13.2 ml (0.2 mol) carbon disulfide and 28 ml (0.2 mol, for the first part) triethylamine. Next 42.87 g (0.123 mol) *o*-bromophenyl dithiocarbamate was obtained. The dithiocarbamate was then dissolved in 90 ml $CHCl_3$, and treated with 23.9 g (0.123 mol) α-bromoisobutyric acid ethyl ester and 17.22 ml (0.123 mol) triethylamine. Yield: 11 g (25.6%), mp: 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.74–7.25 (m, 4H), 1.85 (s, 3H), 1.80 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 178.7, 134.8–123.0, 56.2, 28.3, 27.0 ppm. Calcd for $C_{11}H_{10}ONS_2Br$: C, 41.78; H, 3.18; N, 4.43; S, 20.28. Found: C, 41.86; H, 3.19; N, 4.43; S, 20.67. IR (KBr) 1729, 1245 cm^{-1}. UV–vis (EtOH) λ_{max} 295 (log ε 4.16), 205 (log ε 3.92) nm.

4.1.2.4. 5,5-Dimethyl-3-(*o*-iodophenyl)rhodanine (±)-8. The compound was synthesized according to the general procedure using 10.95 g (0.05 mol) *o*-iodo aniline, 3.8 ml (0.05 mol) carbon disulfide and 7 ml (0.05 mol, for the first part) triethylamine. Next, 8.48 g (0.021 mol) *o*-iodophenyl dithiocarbamate was obtained. The dithiocarbamate was then dissolved in 20 ml $CHCl_3$, and treated with 4.1 g (0.021 mol) α-bromoisobutyric acid ethyl ester and 3 ml (0.021 mol) triethylamine. Yield: 1 g (13.9%), mp: 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.98–7.23 (m, 4H), 1.79 (s, 3H), 1.76 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 200.2, 179.0, 140.0–100.0, 57.0, 28.0, 26.5 ppm. Calcd for $C_{11}H_{10}ONS_2I$: C, 36.37; H, 2.77; N, 3.85; S, 17.65. Found: C, 36.54; H, 2.65; N, 3.78; S, 17.87. IR (KBr) 1734, 1246 cm^{-1}. UV–vis (EtOH) λ_{max} 295 (log ε 4.04), 205 (log ε 3.88) nm.

4.1.3. General procedure for the preparation of 3-(*o*-aryl)rhodanine[11]

The 3-(*o*-aryl)rhodanines, compounds (±)-**9**–**12**, were synthesized via the reaction of the corresponding aryl isothiocyanates with thioglycolic acid ethyl ester in the presence of sodium metal in toluene. In a 100 ml round-bottomed flask, aryl isothiocyanate was mixed with thioglycolic acid ethyl ester in the presence of the small pieces of sodium metal in toluene. The reaction was refluxed for 7 h. The *N*-aryl rhodanine that formed at the end of this period, and after distillation of toluene, was purified by recrystallization from ethanol.

4.1.3.1. 3-(*o*-Fluorophenyl)rhodanine (±)-9. The compound was synthesized according to the general procedure using 3.06 g (0.02 mol) *o*-fluorophenyl isothiocyanate, 2.4 g (0.02 mol) thioglycolic acid ethyl ester and 0.046 g (0.002 mol) metallic sodium. Yield: 1.7 g (40%), mp: 103–104 °C. ^{1}H NMR (400 MHz, toluene-d_8): δ 7.2–7.09 (m, 4H), 2.82 and 2.79 (AB quartet, 1H each, J_{AB} = 18.33 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 173.6, 160.2–117.3, 37.0 ppm. Calcd for $C_9H_6ONS_2F$: C, 47.56; H, 2.66; N, 6.16; S, 28.21. Found: C, 47.71; H, 2.92; N, 6.44; S, 28.20 IR (KBr) 1727, 1238 cm^{-1}. UV–vis (EtOH) λ_{max} 300 (log ε 4.11) nm.

4.1.3.2. 3-(*o*-Chlorophenyl)rhodanine (±)-10. The compound was synthesized according to the general procedure using 3.38 g (0.02 mol) *o*-chlorophenyl isothiocyanate, 2.4 g (0.02 mol) thioglycolic acid ethyl ester and 0.046 g (0.002 mol) metallic sodium. Yield: 2.0 g (41.1%), mp: 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.15 (m, 4H), 4.25 and 4.19 (AB quartet, 1H each, J_{AB} = 17.94 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 172.6, 133.0–128.2, 36.6 ppm. Calcd for $C_9H_6ONS_2Cl$: C, 44.35; H, 2.48; N, 5.47; S, 26.31. Found: C, 44.40; H, 2.43; N, 5.71; S, 25.99. IR (KBr) 1731, 1250 cm^{-1}. UV–vis (EtOH) λ_{max} 300 (log ε 4.14) nm.

4.1.3.3. 3-(*o*-Bromophenyl)rhodanine (±)-11. The compound was synthesized according to the general procedure using 4.28 g (0.02 mol) *o*-bromophenyl isothiocyanate, 2.4 g (0.02 mol) thioglycolic acid ethyl ester and 0.046 g (0.002 mol) metallic sodium. Yield: 1.69 g (29.8%), mp: 142–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.22 (m, 4H), 4.27 and 4.21 (AB quartet, 1H each, J_{AB} = 18.33 Hz) ppm ^{13}C NMR (100 MHz, benzene-d_6): δ 199.5, 171.9, 135.8–128.5, 35.6 ppm. Calcd for $C_9H_6ONS_2Br$: C, 37.51; H, 2.09; N, 4.86; S, 22.25. Found: C, 37.53; H, 2.05; N, 4.83; S, 22.12. IR (KBr) 1730, 1230 cm^{-1}. UV–vis (EtOH) λ_{max} 301 (log ε 4.06) nm.

4.1.3.4. 3-(*o*-Iodophenyl)rhodanine (±)-12. The compound was synthesized according to the general procedure using 5.22 g (0.02 mol) *o*-iodophenyl isothiocyanate, 2.4 g (0.02 mol) thioglycolic acid ethyl ester and 0.046 g (0.002 mol) metallic sodium. Yield: 3.45 g (54%), mp: 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1–7.6 (m, 4H), 4.26 and 4.19 (AB quartet, 1H each, J_{AB} = 18.33 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 172.6, 140.3–98.4, 36.9 ppm. Calcd for $C_9H_6ONS_2I$: C, 32.25; H, 1.80; N, 4.17; S, 19.13. Found: C, 32.49; H, 1.75; N, 4.14; S, 19.09. IR (KBr) 1736, 1225 cm^{-1}. UV–vis (EtOH) λ_{max} 296 (log ε 4.17) nm.

Acknowledgment

This project has been supported by Boğaziçi University research fund (BAP) with Project No. 08B506D.

References

1. (a) Roussel, C.; Vanthuyne, N.; Bouchekara, M.; Djafri, A.; Elguero, J.; Alkorta, I. *J. Org. Chem.* **2008**, *73*, 403; (b) Vanthuyne, N.; Andreoli, F.; Fernandez, S.; Roman, M.; Roussel, C. *Lett. Org. Chem.* **2005**, *2*, 433.
2. (a) Betson, M. S.; Bracegirdle, A.; Clayden, J.; Helliwell, M.; Lund, A.; Pickworth, M.; Snape, T. J.; Worrall, C. P. *Chem. Commun.* **2007**, 754; (b) Betson, M. S.; Clayden, J.; Helliwell, M.; Johnson, P.; Lai, L. W.; Pink, J. H.; Stimson, C. C.; Vassiliou, N.; Westlund, N.; Yasin, S. A.; Youssef, L. *Org. Biomol. Chem.* **2006**, *4*, 424; (c) Adler, T.; Bonjoch, J.; Clayden, J.; Bardıa, M. F.; Pickworth, M.; Solans, X.; Solé, D.; Vallverdú, L. *Org. Biomol. Chem.* **2005**, *3*, 3173; (d) Clayden, J. *Tetrahedron* **2004**, *60*, 4335; (e) Clayden, J. *Chem. Commun.* **2004**, 127; (f) Clayden, J.; Darbyshire, M.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1997**, *49*, 8587.
3. (a) Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 494; (b) Curran, D. P.; Chen, C. H. T.; Geib, S. J.; Lapierre, A. J. B. *Tetrahedron* **2004**, *60*, 4413; (c) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130; (d) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandez, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955; (e) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, C. *J. Am. Chem. Soc.* **1994**, *116*, 3131.
4. Marelli, C.; Monti, C.; Galli, S.; Masciocchi, N.; Piarulli, U. *Tetrahedron* **2006**, *62*, 8943.
5. (a) Koide, H.; Hata, T.; Yoshihara, K.; Kamikawa, K.; Uemura, M. *Tetrahedron* **2004**, *60*, 4527; (b) Koide, H.; Hata, T.; Uemura, M. *J. Org. Chem.* **2002**, *67*, 1929.
6. Kondo, K.; Iida, T.; Fujita, H.; Suzuki, T.; Wakabayashi, R.; Yamaguchi, K.; Murakami, Y. *Tetrahedron* **2001**, *57*, 4115.
7. (a) Kitagawa, O.; Fujita, M.; Kohriyama, M.; Hasegawa, H.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 8539; (b) Kitagawa, O.; Momose, S.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 8827.
8. Kiefl, C.; Zinner, H.; Burgemeister, T.; Mannschreck, A. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 125.
9. Faigl, F.; Tarkanyi, G.; Fogassy, K.; Tepfenhardt, D.; Thurner, A. *Tetrahedron* **2008**, *64*, 1371.
10. Clayden, J. *Angew. Chem., Int. Engl.* **1997**, *36*, 949.
11. Doğan, İ.; Burgemeister, T.; İçli, S.; Mannschreck, A. *Tetrahedron* **1992**, *48*, 5157.
12. Doğan, İ.; Pustet, N.; Mannschreck, A. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1557.
13. Karataş, M.; Koni, S.; Doğan, İ. *Can. J. Chem.* **1998**, *76*, 254.
14. Demir, Ö.; Doğan, İ. *Chirality* **2003**, *15*, 242.
15. Oğuz, S. F.; Doğan, İ. *Tetrahedron: Asymmetry* **2003**, *14*, 1857.
16. Ordu, Ö. D.; Doğan, İ. *Tetrahedron: Asymmetry* **2004**, *15*, 925.
17. Aydeniz, Y.; Oğuz, S. F.; Yaman, A.; Konuklar, A. S.; Doğan, İ.; Aviyente, V.; Klein, R. A. *Org. Biomol. Chem.* **2004**, *2*, 2426.
18. Ordu, Ö. D.; Yılmaz, E. M.; Doğan, İ. *Tetrahedron: Asymmetry* **2005**, *16*, 3752.
19. Erol, Ş.; Doğan, İ. *J. Org. Chem.* **2007**, *72*, 2494.
20. Gómez, E. D.; Doğan, İ.; Yılmaz, E. M.; Ordu, Ö. D.; Albert, D.; Duddeck, H. *Chirality* **2008**, *20*, 344.
21. (a) Boyar, E. B.; Robinson, S. D. *Coord. Chem. Rev.* **1983**, *50*, 109; (b) *Multiple bonds between metal atoms*; Cotton, F. A., Walton, R. A., Eds., 2nd ed.; Clarendon: Oxford, 1993.
22. Hodgkins, J. E.; Reeves, W. P. *J. Org. Chem.* **1964**, *29*, 3098.
23. Roussel, C.; Djafri, A. *New J. Chem.* **1986**, *10*, 399.
24. Carey, A. F.; Sundberg, R. *Advanced Organic Chemistry. Part-A: Structure and Mechanism*; Plenum Press: New York, London, 1990. p 120.
25. Friebolin, H. *Basic One- and Two-dimensional NMR Spectroscopy*, 3rd revised ed.; Wiley-VCH, 1998. p 307.