Atropisomerism in some *N,N′*-diaryl-2-iminothiazoline derivatives: chiral separation and configurational stability

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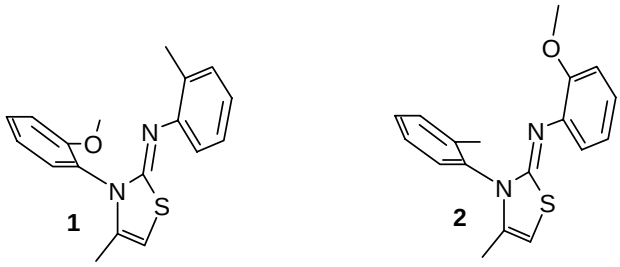
Abstract

Semi-preparative resolution of the atropisomers by chiral liquid chromatography and determination of the barriers to rotation has allowed an unequivocal identification of the regioisomers produced by the reaction between *N*-(2-methoxyphenyl)-*N*'-(2-methylphenyl)thiourea and α-chloroacetone. Attention is drawn on the potential use of these optically pure atropisomers as new non-biaryl ligands for enantioselective metal catalysis.

Keywords: Atropisomerism, chiral HPLC, enantiomerization barrier

Introduction

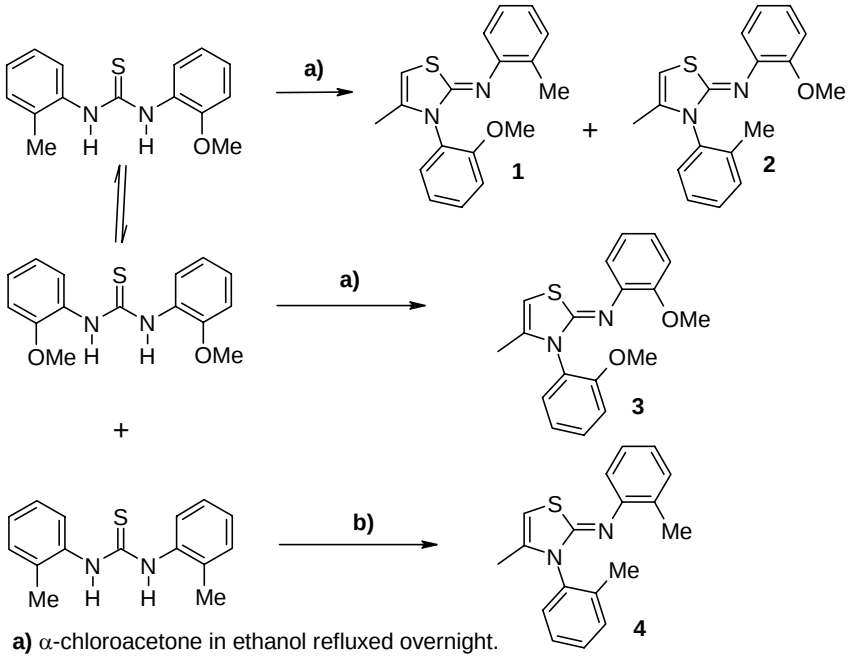
N,N′-Diaryl-2-iminothiazoline derivatives are readily available by a time-honored reaction between an α-halogenoketone and a *N,N′*-diaryl thiourea.[1] The synthesis is easy, general and straightforward when symmetrical thioureas are used since the same substituent is located on the exocyclic imino group and on the intracyclic nitrogen atom. However, when an unsymmetrical thiourea is used, two regioisomers may be formed depending on the difference in electronic and steric contributions affecting the reactivity of the nitrogen atoms in the thiourea.[1,2] We are interested in the unequivocal identification of the two regioisomers **1** and **2** formed in the reaction between *N*-(2-methoxyphenyl)-*N*'-(2-methylphenyl)-thiourea and α-chloroacetone (Scheme 1). Examination of molecular models showed that these compounds were good candidates for showing atropisomerism.[3] The resolution of these atropisomers may afford new leads for chiral non-biaryl bidentate ligands in two very different topographic relationships.[4]



Scheme 1. Structure of the atropisomers **1** and **2**.

Results and Discussion

The reaction between *N*-(2-methoxyphenyl)-*N*'-(2-methylphenyl)thiourea and α-chloroacetone afforded the two regio-isomers **1** and **2** in similar amounts according to the NMR spectra, and two by-products were obtained in small amount (5% each). The by-products were identified by comparison with authentic samples (*vide infra*) as being the symmetrical compounds **3** and **4** which resulted from the scrambling of the substituents in the starting thiourea during reaction. Compounds **1** and **2** were isolated by careful chromatography on silica, but on the basis of their NMR data it was not possible to safely identify **1** or **2** as the fast or slow eluting isomers.



Scheme 2. Three thioureas in equilibrium lead to the regioisomers **1** and **2** and the by-products **3** and **4**.

Our first idea for the identification of the isomeric forms was to hydrolyse the imino bond to obtain the corresponding thiazoline-2-one analogues which are well known in our laboratory.[5] To our surprise, these compounds resisted all our hydrolysis attempts, being either unchanged or destroyed.[6]

The mixture of compounds **1** and **2** was then injected onto a CHIRALCEL OD-H column, cellulose *tris*-(3,5-dimethylphenyl carbamate) coated on silica, and four well-resolved peaks were observed at room temperature. The retention factors and the associated signs from polarimetric detection were 1.42 (-); 1.87 (+); 2.65 (-); 3.19 (+) respectively, corresponding to two pairs of enantiomers in the original mixture. The inner pair of peaks was assigned to one of the regioisomers and the outer pair to the other (Figure 1). This first result showed that both compounds **1** and **2** afforded atropisomers which were stable enough at room temperature to withstand a chiral resolution by liquid chromatography on a chiral stationary phase.

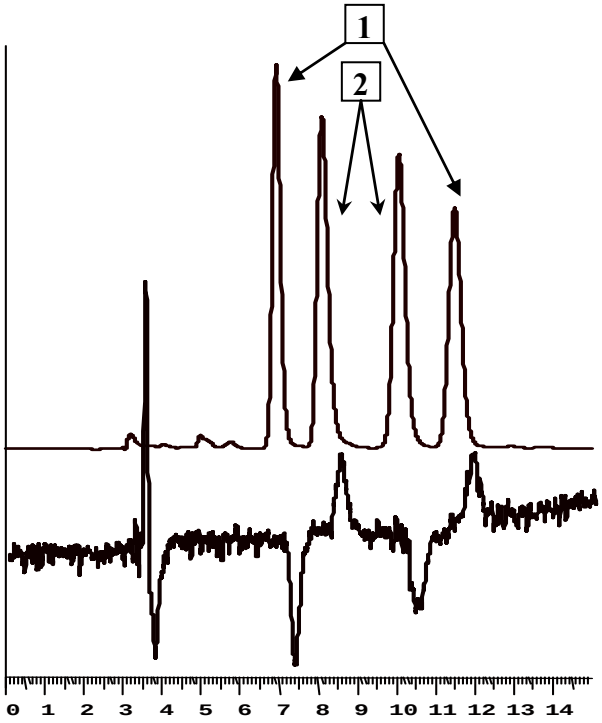


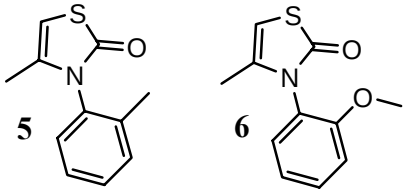
Figure 1. Chromatography on CHIRALCEL OD-H (hexane–propan-2-ol, 95:5, flow rate = 1 mL/min), showing the UV at 254 nm and the corresponding polarimetric trace of the regioisomers **1** and **2**.

Furthermore, the absence of a detectable plateau between the peaks in the chromatograms indicated that these atropisomers have barriers to rotation which, at room temperature, are high enough to allow off-line determination of the enantiomerization barriers on the isolated enantiomers. Collection of each of the enantiomers using a semi-preparative column under the same conditions as before, evaporation of the solvent under vacuum, and analytical checking of

the *ee* of the collected fractions showed that, for the outer pair of enantiomers, extensive racemization (up to 15%) had occurred during processing, whereas in the inner pair very high *ee* were maintained. This experimental observation indicated that the barriers to rotation in **1** and **2** were significantly different, and might thus provide the key for the identification. The barriers to enantiomerization were quantitatively determined in EtOH for the enantiomers of the outer pair ($\Delta G^{\neq}$ = 109.7 kJ/mol at 58°C; $t_{1/2}$= 2.82 hrs at this temperature), and for the enantiomers of the inner pair ($\Delta G^{\neq}$ = 121.8 kJ/mol at 78°C; $t_{1/2}$= 17.5 hrs at this temperature). On the basis of data in the literature, the apparent size of a methyl group is larger than the apparent size of a methoxy group in rotational processes in biphenyl.[7,8] It can thus be inferred that the regioisomer with the low barrier is **1**, and the one with the high barrier is **2**.

In order to gain definitive proof, compounds **3** and **4** were prepared from the respective symmetrical thioureas as standards for the identification of **1** and **2**. We anticipated that compounds **3** and **4** should be good mimics, in terms of the rotational barriers around the pivot *N*-aryl bond, for what was encountered in **1** and **2** respectively. In compounds **1** and **3** the barrier to rotation should result mainly from the through-space interaction between the methoxy group of the *N*-anisyl and the imino- nitrogen or (and) the 4-methyl group of the heterocycle. The same holds true for the rotation of the tolyl group in compounds **2** and **4**, respectively. In all cases, the barriers to rotation should not be affected by the *N*-imino aryl group which is located away from the rotation pathway and should not interfere, on steric grounds.

Chromatographic chiral separations of compounds **3** and **4** were attempted on various chiral stationary phases. Several chiral selectors and eluting conditions allowed a very clean separation of the enantiomers, showing that compounds **3** and **4** give stable atropisomers at room temperature. The barriers to rotation obtained in EtOH from the isolated enantiomers were 107.2 kJ/mol (58°C) for **3**, and 122.3 kJ/mol (78°C) for **4**. These results confirmed nicely the identification of **1** and **2.**



Scheme 3

It is worth noting that the barriers to enantiomerization in **2** and **4** were very similar to that already determined for 3-(2-methylphenyl)-4-methyl-thiazoline-2-one **5** ($\Delta G^{\neq}$ = 122 kJ/mol),[5b] indicating that carbonyl- and imino- groups exhibit the same steric requirement in the thiazoline framework. This was confirmed by the determination of the barrier to rotation in the 3-(2-methoxyphenyl)-4-methylthiazoline-2-one atropisomers **6** ($\Delta G^{\neq}$ = 110.5 kJ/mol at 58°C), which was found to be very close to those observed in **1** and **3**.

Conclusions

The conjunction of semi-preparative resolution of the atropisomers in **1** and **2** by chiral liquid chromatography and determination of the barriers to rotation allowed an unequivocal identification of these regioisomers. The method is appropriate for the identification of other pairs of regioisomers issuing from the reaction of an *ortho–ortho'*- dissymmetrically substituted thiourea with α-chloroacetone. More interestingly, the barriers to rotation are high enough in the aryl-iminothiazolines **1**, **2** and **3** to produce rather stable atropisomers which were easily resolved by chiral liquid chromatography under various analytical and semi-preparative conditions. We plan to apply these atropisomeric imino thiazolines in screening experiments aiming to the design of new non-biaryl ligands for enantioselective metal catalysis.

Experimental Section

General Procedures. Melting points are uncorrected. ^{1}H- and ^{13}C- NMR spectra were recorded in $CDCl_3$ at 200 and 50 MHz, respectively. Chemical shifts are reported in ppm with the signal for residual $CHCl_3$ in the $CDCl_3$ solvent as internal standard (the singlet at 7.26 ppm for ^{1}H and the center line of the triplet at 77.0 ppm for ^{13}C). Flash column chromatography was performed with silica gel 60 (230–400 mesh). TLC was on Merck $60F_{254}$ silica plates (UV 254 nm), with CH_2Cl_2–EtOAc 90:10 as eluent.

The chiral HPLC experiments were performed on a screening unit composed of a Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven which accommodates 12 chiral columns connected to a Valco 12 positions valve, Merck-Lachrom L-7400 UV-detector, and Jasco OR-1590 polarimeter detector. Hexane, propan-2-ol and ethanol were of HPLC grade, and were degassed and filtered on a 0.45 μm membrane before use. A CHIRALCEL OD (250x10 mm) was used for semi-preparative separation.

Synthesis of *N*-[(2Z)-3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3H)-ylidene]-*N*-(2-methyl-phenyl) amine (1) and *N*-(2-methoxyphenyl)-*N*-[(2Z)-4-methyl-3-(2-methylphenyl)-1,3-thiazol-2(3H)-ylidene]amine (2). *o*-Toluidine (50.2 g, 0.47 mol) was added with stirring at 0 °C to CS_2 (52.8 mL, 0.88 mol) in 70 mL of NH_4OH (32%).[9,10] The stirring was continued for 0.5 h at r.t., $Pb(NO_3)_2$ (156.4 g, 0.47 mol) added in 800 mL of water, and the mixture stirred for 2 h, then steam distilled. The organic phase was separated and dried ($CaCl_2$) to give 1-isothiocyanato-2-methylbenzene (35.7 g, 51 %): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.10–7.30 (m, 4H), 2.39 (s, 3H). The product could be distilled under reduced pressure: b.p. = 120–123 °C / 11 mm Hg (lit. 126–129 °C / 12 mm Hg).[11]

o-Anisidine (25.8 mL, 0.23 mol) was added with stirring at r.t. to 1-isothiocyanato-2-methylbenzene (34.3 g, 0.23 mol) in 50 mL of absolute ethanol, to give 1-(2-methoxyphenyl)-3-*o*-tolyl-thiourea (39.5 g, 64%): m.p. 137–138 °C (lit. 126 °C);[12] ^{1}H- NMR (200 MHz, $CDCl_3$) δ

8.40–7.60 (m, 2H), 7.30–6.85 (m, 8H), 3.74 (s, 3H), 2.34 (s, 3H). The ^{1}H-NMR and TLC also show 5% of 1,3-*bis*-(2-methoxyphenyl)- thiourea and 5% of 1,3-di-*o*-tolylthiourea.

α-Chloroacetone (6.8 mL, 85 mmol) was added with stirring at r.t. to 1-(2-methoxyphenyl)-3-*o*-tolyl-thiourea (20.0 g, 73.5 mmol) in 340 mL of absolute ethanol. The mixture was refluxed overnight, then cooled to r.t., evaporated, and dissolved in 120 mL of CH_2Cl_2. The organic phase was washed with Na_2CO_3 (1*M*) and water, dried ($MgSO_4$) and evaporated to give a mixture of **(1)** and **(2)** (22.7 g, 99%), with traces of **(3)** and **(4)**.

The mixture was separated by flash chromatography on silica gel (CH_2Cl_2/EtOAc 90:10) to give **(1)**; m.p. 143–144 °C; R_f = 0.78; ^{1}H- NMR (200 MHz, $CDCl_3$) δ 7.45–6.85 (m, 8H), 5.58 (q, 1H, *J* = 1.2 Hz), 3.87 (s, 3H), 2.11 (s, 3H), 1.80 (d, 3H, *J* = 1.2 Hz); ^{13}C- NMR (50 MHz, $CDCl_3$) δ 159.7, 155.9, 150.9, 135.5, 130.9, 130.4 (2), 130.2, 126.6, 126.3, 122.9, 121.2, 120.7, 112.4, 92.7, 55.8, 17.4, 14.8; MS (EI) *m/z* 310 (M+), 279, 204, 148. Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02. Found: C, 69.49; H, 5.97; N, 8.94%.

Chiral chromatography on CHIRALCEL OD-H (250 x 4.6 mm): hexane–propan-2-ol, 95:5, 1 mL/min, 25 °C, UV 254 nm and polarimeter detection, t_R(-) = 7.30 min, t_R(+) = 12.65 min, k(-) = 1.42, k(+) = 3.19, α = 2.25. (See Supporting Information for the results on the other columns).

(2): m.p. 123–124 °C; Rf = 0.65; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–6.80 (m, 8H), 5.62 (q, 1H, *J* = 1.4 Hz), 3.74 (s, 3H), 2.32 (s, 3H), 1.74 (d, 3H, *J* = 1.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.8, 151.5, 141.8, 137.4, 136.6, 134.5, 131.3, 129.2, 129.1, 127.1, 123.9, 122.7, 121.3, 112.4, 93.6, 55.8, 17.5, 15.1; MS (EI) *m/z* 310 (M+), 188, 132, 91; Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02. Found: C, 70.03; H, 5.89; N, 9.12%.

Chiral chromatography on CHIRALCEL OD-H (250x4.6 mm): hexane–propan-2-ol, 95:5, 1 mL/min, 25 °C, UV 254 nm and polarimeter detection, t_R(+) = 8.67 min, t_R(-) = 11.01 min, k(+) = 1.87, k(-) = 2.65, α = 1.42. (See Supporting Information for the results on the other columns).

Synthesis of *N*-(2-methoxyphenyl)-*N*-[(2Z)-3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amine (3). 40 mL of a solution of NaOH (40%) was added with stirring at r.t. to *o*-anisidine (42.1 mL, 0.37 mol) and CS_2 (29 mL, 0.48 mol). The mixture was refluxed for 2 h and then cooled to r.t. A precipitate formed after the addition of 80 mL of water. The precipitate was filtered, washed with 150 mL of water and dried to give 1,3-*bis*-(2-methoxyphenyl)thiourea (34.2 g, 64%) as a white solid: m.p. = 134–135 °C (lit. 132–134 °C).[13]

α-Chloroacetone (10.8 mL, 0.135 mol) was added with stirring at r.t. to 1,3-bis-(2-methoxyphenyl)-thiourea (30 g, 0.104 mol) in 375 mL of absolute ethanol. The mixture was refluxed overnight, then cooled at r.t., evaporated, and dissolved in 80 mL of CH_2Cl_2. The organic phase was washed with Na_2CO_3 (1*M*) and water, dried ($MgSO_4$) and evaporated to give **(3)** (27.9 g, 82%): m.p. 139–140 °C; R_f = 0.26; ^{1}H- NMR (200 MHz, $CDCl_3$) δ 7.45–6.80 (m, 8H), 5.60 (q, 1H, *J* = 1.3 Hz), 3.89 (s, 3H), 3.75 (s, 3H), 1.78 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.3, 155.9, 151.7, 141.9, 135.4, 130.9, 130.1, 126.4, 123.7, 122.7, 121.4 (2), 113.0, 112.9, 93.1, 56.1, 56.0, 14.8; MS (EI) *m/z* 326 (M+), 295, 206, 204, 148; Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.03; H, 5.52; N, 8.75%.

Chiral chromatography on CHIRALCEL OD-H (250x4.6 mm) : hexane/propan-2-ol 95:5, 1 mL/min, 25 °C, UV 254 nm and polarimeter detection, $t_R(-) = 9.33$ min, $t_R(+) = 15.96$ min, k(-) = 2.01, k(+) = 4.15, $\alpha = 2.06$, Rs = 6.53 (See Supporting Information for the results on the other columns).

Synthesis of *N*-[(2*Z*)-4-methyl-3-(2-methylphenyl)-1,3-thiazol-2(3H)-ylidene]-*N*-(2-methylphenyl) -amine (4).10 mL of a solution of NaOH (40%) was added with stirring at r.t. to *o*-toluidine (10 mL, 94 mmol) and CS_2 (7 mL, 116 mmol). The mixture was refluxed for 2 h and then cooled to r.t. The precipitate was filtered, washed with 40 mL of water and dried to give 1,3-di-*o*-tolyl-thiourea (6.7 g, 56%) as a white solid, m.p. = 187–188 °C.

α-Chloroacetone (1.75 mL, 21.5 mmol) was added with stirring at r.t. to 1,3-di-*o*-tolyl-thiourea (5 g, 19.5 mmol) in 70 mL of absolute ethanol. The mixture was refluxed for 7 h, then cooled at r.t., evaporated and dissolved in 20 mL of CH_2Cl_2. The organic phase was washed with Na_2CO_3 (1*M*) and water, dried ($MgSO_4$) and evaporated to give **(4)** (4.3 g, 75%) : m.p. 135–136 °C; R_f = 0.89; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–6.85 (m, 8H), 5.62 (q, 1H, *J* = 1.3 Hz), 2.29 (s, 3H), 2.10 (s, 3H), 1.76 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.3, 150.8, 137.2, 136.7, 134.7, 131.2, 130.5, 130.3, 129.3, 129.1, 127.2, 126.7, 123.0, 120.5, 93.2, 17.7, 17.5, 15.0; MS (EI) *m/z* 294 (M+), 279, 188, 132, 91; Anal. Calcd for $C_{18}H_{18}N_2S$: C, 73.43; H, 6.16; N, 9.51. Found: C, 73.05; H, 6.19; N, 9.69%.

Chiral chromatography on CHIRALCEL OJ (250x4.6 mm) : hexane–propan-2-ol, 80:20, 1 mL/min, 25 °C, UV 254 nm and polarimeter detection, $t_R(-) = 9.36$ min, $t_R(+) = 15.13$ min, k(-) = 2.03, k(+) = 3.90, $\alpha = 1.92$, Rs = 1.86. (See Supporting Information for the results on the other columns).

Kinetics of enantiomerization

All the reported barriers to rotation are the barriers to enantiomerization and not the barriers to racemization. An optically enriched sample is heated in ethanol at the chosen temperature. The *ee*- variation as a function of time is monitored by chiral HPLC, and the rate constant for rotation, k_{rot} , is determined by plotting the first-order kinetic line according to the equation $\ln(ee_t / ee_{t=0}) = -2k_{rot} \times t$. In all cases, R^2 is larger than 0.9999 (See Supporting Information for the range of half-lives). The $\Delta G^{\neq}$ is calculated from k_{rot} and Eyring's equation.

Supporting Information Available

^{1}H- and ^{13}C- spectra, mass spectrum, chiral HPLC screening, separation of the enantiomers by semi-preparative chiral chromatography, rotatory power and Experimental Details for the enantiomerization barrier calculation in compounds **1**, **2**, **3** and **4**.

Acknowledgments

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