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Heterocyclizations of *N*-Boc derivatives of β-amino alcohols and thio analogs: an unusual case of the Thorpe–Ingold effect

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Summary – Enantiopure oxazolidin-2-ones were synthesized from chiral *N*-Boc β-aminoalcohols which underwent a cyclization upon treatment with tosyl chloride. This reaction was strongly accelerated in the case of carbamates derived from *N*-methylated amines. A similar heterocyclization was observed with dithiocarbamates, *ie* sulfur analogs of carbamates. The rate enhancement due to the nitrogen substitution was studied by AM1 calculations.

carbamate / dithiocarbamate / oxazolidinone / thiazolidinone / AM1 calculations

The enhancement of cyclization rates by alkyl substituents that are located between the interacting groups continues to attract considerable attention [1]. The *gem*-dialkyl substitution effect was originally described 80 years ago [2] and is known as the Thorpe–Ingold effect [3]. The origin of this classical phenomenon is still a subject of debate [4]. This effect was first ascribed to a decrease in a bond angle provoked by the repulsion between the two *gem*-substituents. However this explanation was convincingly rejected by Schleyer [5], and the suggestion of Bruice and Pandit [6] that an increase of the reactive rotamer population could account for this phenomenon is now considered as the most trustworthy [7]. We wish to report here a full account of our recent results on cyclizations involving carbamate (*N*-Boc group) and dithiocarbamate as internal nucleophilic reagents [8]. From a synthetic point of view, these cyclizations are very convenient routes to oxazolidin-2-ones and sulfur-containing analogs. Furthermore, these heterocyclizations lay emphasis on two facts, which are related to the Thorpe–Ingold effect: (i) the origin of such rate enhancements is not restricted to *gem*-disubstitution but monosubstitution may also be operative [3]; and, (ii) to our knowledge, with one exception [9], substitution of a heteroatom has not yet been reported to have any effect.

Oxazolidin-2-ones from *N*-Boc β-aminoalcohols

When treated with tosyl chloride in pyridine, *N*-Boc derivatives of β-aminoalcohols led to cyclized derivatives resulting from a nucleophilic attack by the carbamate moiety. Thus, derivatives of (1*R*,2*S*)-ephedrine **1**, (1*R*,2*S*)-norephedrine **2** and (1*S*,2*S*)-pseudoephedrine **3** afforded, respectively, oxazolidinones **4**–**6** (fig 1). This reaction occurs with inversion at the hydroxyl-bearing carbon center and this sterochemical outcome is indicative of an S_N2 process.

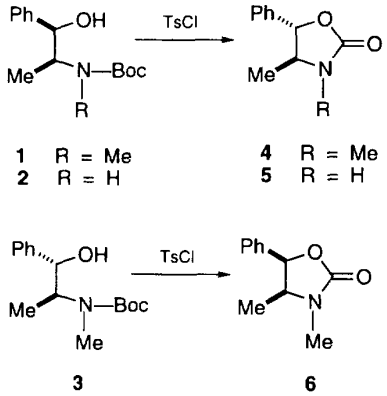

Fig 1

We have noticed that this reaction was highly favored in the case of carbamates derived from *N*-methyl secondary amines. In this respect, two series of results are especially noteworthy. First, there is a marked difference of stereoselectivity between the cyclizations of two interrelated substrates: the *N*-Boc derivatives of pseudoephedrine **3** (fig 1) and norpseudoephedrine **7** (fig 2).

* Correspondence and reprints

Whereas the cyclization using substrate **3** occurred totally stereoselectively, when its unsubstituted analog **7**, was treated under the same conditions, it reacted sluggishly with partial decomposition to yield a mixture of diastereomeric oxazolidinones **8** and **9** in a respective 80:20 ratio. Stereochemical relationships within oxazolidinones **4–6**, **8** and **9** were assigned by comparison of their ^{1}H NMR spectra with literature values [10].

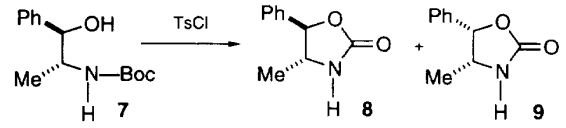

Fig 2

The beneficial outcome of *N*-methyl substitution as regards reactivity is also illustrated by the strikingly different behavior of the *N*-Boc derivatives of (*R*)-phenylglycinol **10** and its *N*-methylated analog **11** (fig 3). Reaction of substrate **11** with TsCl at 0°C directly leads to oxazolidinone **12**. However, its nor-analog **10** yields tosylate **13**. Cyclization of compound **13** required a subsequent heating at 60°C to give the corresponding oxazolidinone **14**.

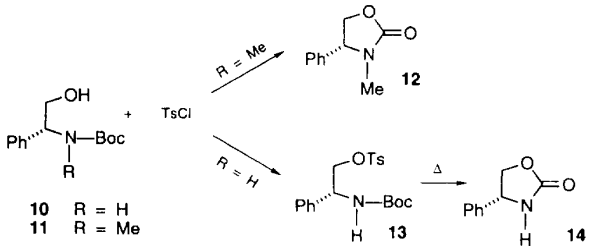

Fig 3

The above results are consistent with a nucleophilic attack by the Boc moiety (fig 4) with a displacement of the tosyloxy group, followed by loss of isobutene. Although such carbamates are widely used as nitrogen protective groups [11], it is well known that carbamates are very prone to react intramolecularly with nucleophiles, mainly alkoxy functions [12]. However, there are also some reports in which carbamates act as nucleophiles reacting with halides [13], activated carboxylic acids [14], epoxides [15] and iodonium ions in iodocyclocarbamations [16].

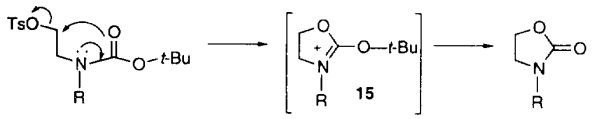

Fig 4

The prominent part of the *N*-methyl moiety, which accelerates the heterocyclization, can be ascribed to a Thorpe–Ingold-related effect (*vide infra*). The lack of stereoselectivity observed in the case of carbamate **7** (eq 2) is due to steric hindrance during the oxazolidinone formation in an S_N2 process. In the corresponding transition state, leading to oxazolidinone **9**, there is a torsional strain between the incipient heterocycle *cis*-substituents. In this case therefore, such a process is highly disfavored and an S_N1-like mechanism accounts for the production of the mixture of oxazolidinones **8** and **9**. In contrast with this result, *N*-Boc aminoalcohol **3** is much more reactive, owing to the presence of the *N*-methyl group and thus provides cleanly the *cis*-oxazolidinone **6** (eq 1) *via* the S_N2 mechanism.

Heterocyclization of thio analogs

With the aim of extending the scope of the above reaction, we next turned our attention to dithiocarbamates as internal nucleophiles (fig 5). Oxazolidinones are actually very versatile chiral inducers [17] and were also considered for their therapeutic properties [18]. Their sulfur analogs are less well studied [19] but the derived β-amino thiols were used in asymmetric synthesis [20] and their ability to inhibit aminopeptidase was described [21].

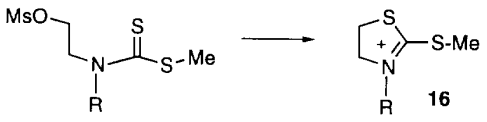

Fig 5

Dithiocarbamates **17–22** were thus prepared [22] from the corresponding β-aminoalcohols by reaction with carbon disulfide and iodomethane.

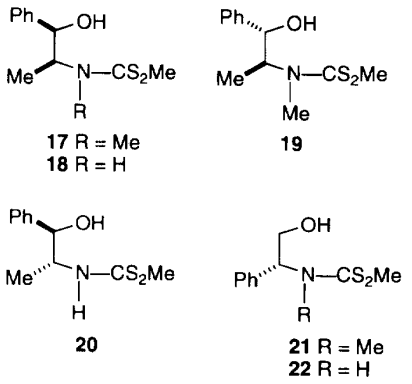

Fig 6

Primary amine derivatives **18**, **20** and **22** were treated with mesyl chloride in pyridine; it should be noted that this reagent appeared to be more reactive than tosyl chloride which was used with the previously described carbamates. In both cases an excess of the sulfonyl chloride reagent was necessary in order to complete the reaction in a reasonable time. These reactions

gave the expected thiazolines **23–25** arising from spontaneous pyridine-mediated deprotonation of thiazolinium intermediates corresponding to formula **16**. A similar cyclization was recently reported with thioamides yielding thiazol-2-ines [23]. The *cis* and *trans* relationships between the phenyl and the methyl groups in thiazolines **23** and **24** were deduced from analysis of their ^{1}H NMR spectra; owing to the magnetic anisotropy of the phenyl substituent, the methyl group in the *cis* compound **24** is more shielded (1.08 ppm) than in the *trans* isomer **23** (1.41 ppm).

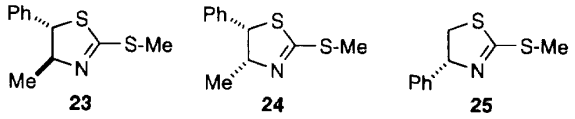

Fig 7

With the secondary amine derivatives **17**, **19** and **21**, the evolution of the cyclized products depends on the experimental procedure. Thiazolidinethiones **26** and **27** were produced when substrates **17** and **21** were refluxed in dichloromethane in the presence of mesyl chloride and pyridine. On the other hand, thiazolidinones **28–30** were obtained when the cyclization of substrates **17**, **19** and **21** was performed in two distinct steps: (i) treatment with mesyl chloride in pyridine at room temperature; and (ii) addition of 5 N aqueous NaOH.

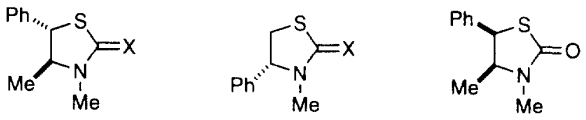

Fig 8

In each case, there is first an S_N2 process leading to the heterocyclic products. With *N*-methyl thiazolinium intermediates **31**, the formation of thiazolidinethione **32** or thiazolidinone **33**, respectively, results from the cleavage of the Me-S bond or from a basic hydrolysis of the thiazolinium moiety (fig 9).

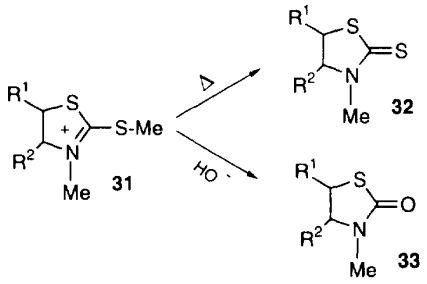

Fig 9

Intermediate **31** (R^1 = H; R^2 = Ph) results from the treatment of substrate **21** and was observed by ^{1}H NMR when the reaction (3 equiv of MsCl in pyridine-d_5, rt) was performed in an NMR tube. The hydrogen atom *gem* to the phenyl substituent resonated at 6.03 ppm in thiazolinium ion **31** whereas the corresponding signal appeared at 5.54 ppm in thiazoline **25**. It is worth mentioning that no special effect due to a methyl substituent on the nitrogen atom was observed on reactivity or on stereoselectivity (compare the non-stereoselective formation of the mixture of oxazolidinones **8** and **9** from *N*-Boc substrate **7** and the formation of thiazoline **24** as the only cyclized product from dithiocarbamate **20**). Cyclization of these compounds is actually a highly favored process because of the higher nucleophilicity of sulfur *vs* oxygen in the *N*-Boc cases and of the higher $^-$X-C=N$^+$ double bond character in sulfur (X = S) than in oxygen (X = O) derivatives [1b, 24].

The *N*-methyl effect on cyclizations that afforded oxazolidinones was scrutinized by means of AM1 calculations which were performed on model reactions starting with molecules **34** and **35** (fig 10) in their *E* reactive structures. These calculations showed that, in each case, the *E* geometry is favored ($H_{fZ} - H_{fE}$ = 1.35 and 1.75 kcal for model compounds **34** and **35**, respectively). Therefore, in the present case, the reactive rotamer hypothesis [6,7] does not seem to be in line with the observed reactivity.

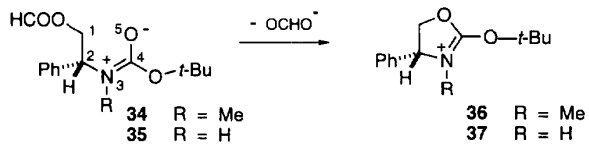

Fig 10

The only significant result is a compression of the C_2—N=C_4 valence angle in model compound **34** relative to its N-H analog **35**: 120.6°and 122.6°, respectively. In the case of open-chain amides, it has been reported [25] that the relevant angle is significantly smaller in tertiary (117.7°) than in secondary systems (122.0°). This angle effect can result from the electron-donating property of the *N*-methyl group. Such an effect has been invoked classically to explain the Thorpe–Ingold [3] effect, which is indirectly related to the effect reported here.

Experimental section

General comments

^{1}H and ^{13}C spectra ($CDCl_3$ solution unless otherwise stated) were recorded on a Bruker AC 200 spectrometer at 200 and 50 MHz; chemical shifts are reported in ppm from TMS. Mass spectra were recorded with an ion-trap mass spectrometer (Varian Saturn 3) coupled with the Varian Star 3400 gas-phase chromatograph. Optical rotations were determined with a Perkin Elmer 141 instrument. Melting points were obtained with a Reichert apparatus (hot stage provided with a microscope) and are uncorrected. Column chromatography was performed on silica gel, 230-400 mesh. TLCs were run on silica gel 60 F_{254} plates (Merck). Mention of usual workup means: (i) decantation of the organic layer; (ii) extraction of the aqueous layer with ether; (iii) drying

of the combined organic phases over $MgSO_4$; and (iv) solvent evaporation under reduced pressure. Compositions of stereoisomeric mixtures were determined by NMR analysis on crude products before any purification.

General procedure for N-*Boc derivative formation*

A solution of β-aminoalcohol (20 mmol, 1 equiv) and di-*tert*-butyl dicarbonate (10 mL, 20 mmol, 1 equiv) in ethyl acetate (40 mL) was refluxed for 12 h. The solution was cooled to rt, washed with water (30 mL), the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. These crude *N*-Boc derivatives (nearly quantitative yields) were used without further purification. The physicochemical properties of known compounds **1–3**, and **10** were identical to those described in the literature (**1** [26], **2** [27], **3** [26], **10** [28]).

• *(1*R*,2*R*)*-tert-*Butyl* N-*(2-hydroxy-1-methyl-2-phenylethyl)carbamate* **7**

According to the above procedure, and starting with (1*R*,2*R*)-norpseudoephedrine, compound **7** was obtained as an oil (95%): $[\alpha]_D^{20}$: −35.2 (*c* 0.47, $CHCl_3$).

IR ($CHCl_3$): 3 405, 1 670 cm^{-1}.

^1H NMR: 1.05 (d, J = 6.8 Hz, 3H), 1.37 (s, 9H), 3.50–3.70 (bs, 1H), 3.80–4.05 (m, 1H), 4.50 (d, J = 6.8 Hz, 1H), 4.80–5.00 (bm, 1H), 7.25–7.40 (m, 5H).

^{13}C NMR: 17.5, 26.3, 52.3, 77.3, 79.5, 126.5, 127.5, 128.1, 141.7, 156.3.

Anal calc for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.55; H, 8.31; N, 5.85.

• (R)-tert-*Butyl* N-*(2-hydroxy-1-phenylethyl)*-N-*methylcarbamate* **11**

According to the above procedure and starting with (*R*)-*N*-methyl phenylglycinol, compound **11** was obtained as an oil (90%); $[\alpha]_D^{20}$: −69.1 (*c* 1.9, $CHCl_3$).

IR ($CHCl_3$): 3 410, 1 670 cm^{-1}.

^1H NMR: 1.45 (s, 9H), 2.67 (s, 3H), 3.10 (s, 1H), 3.65–4.10 (m, 2H), 5.20–5.40 (m, 1H), 7.10–7.50 (m, 5H).

^{13}C NMR: 28.4, 60.2, 61.8, 67, 80.1, 127.4, 127.5, 128.6, 137.9, 157.

Anal calc for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.47; H, 8.50; N, 5.65.

General procedure for the preparation of oxazolidinones **4–6**, **8**, **9** *and* **12** *from the* N-*Boc derivatives* **1–3**, **7** *and* **11**

p-Toluenesulfonyl chloride (12 mmol, 3 equiv) was added to a solution of the *N*-Boc derivative of the β-aminoalcohol (4 mmol, 1 equiv) in pyridine (10 mL). The reaction was monitored by TLC until completion: 24 h at rt for **1**, 3 d at rt for **2**, 4 d at rt followed by reflux during 1 h for **3**, 3 d at rt followed by reflux during 6 h for **7**, 12 h at 0°for **11**. After cooling to rt, water (100 mL) was added and the mixture was extracted with ether. The ethereal extracts were washed with a saturated aqueous solution of $CuSO_4$, dried over $MgSO_4$ and concentrated under reduced pressure. Title oxazolidinones were obtained from this residue by flash chromatography. Following this procedure, oxazolidinones **4–6** (**8** + **9**) were obtained in 53, 52, 70 and 29% (80:20 ratio) respective yields. These yields were not optimized and refer to isolated pure compounds. The physicochemical properties of these known compounds were identical to those described in the literature [10, 29].

• (R)*3-Methyl-4-phenyloxazolidin-2-one* **12**

Following the above procedure and starting with **11**, compound **12** was obtained as a white solid (85%): mp 78°C; $[\alpha]_D^{20}$: −69 (*c* 2, $CHCl_3$).

IR ($CHCl_3$): 1 740 cm^{-1}.

^1H NMR: 2.17 (s, 3H), 4.07 (dd, J = 5.7 and 7 Hz, 1H), 4.60–4.80 (m, 2H), 7.25–7.5 (m, 5H).

^{13}C NMR: 29.4, 62.2, 69.9, 127, 129.2, 129.5, 137.8, 158.0.

Anal calc for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.58; H, 6.35; N, 7.84.

• (R)-tert-*Butyl* N-{*1-phenyl-2-[(*p*-toluenesulfonyl) oxy]ethyl}carbamate* **13**

To a solution of **10** (700 mg, 2.95 mmol) in pyridine (10 mL), *p*-toluenesulfonyl chloride (1.68 g, 8.85 mmol) was added at 0°C. The mixture was stirred overnight, poured into water (20 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with a saturated aqueous solution of $CuSO_4$ (3 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography of the residue (ether/petroleum ether: 40:60) gave compound **13** as a white solid (0.7 g, 62%): mp 160°C; $[\alpha]_D^{20}$: −2 (*c* 3, $CHCl_3$).

^1H NMR: 1.39 (s, 9H), 2.41 (s, 3H), 4.10–4.40 (m, 2H), 4.80–4.85 (m, 1H), 5.00–5.20 (m, 1H), 7.10–7.45 (m, 7H), 7.64 (d, J = 8.3 Hz, 2H).

^{13}C NMR: 21.5, 28.2, 53.6, 71.5, 79.9, 126.6, 127.8, 128.6, 129, 132.6, 137.9, 144.9, 155.0.

Anal calc for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.41; H, 6.46; N, 3.55.

• (R)*-4-Phenyloxazolidin-2-one* **14**

A solution of tosylate **13** (1 g, 2.55 mmol) and pyridine (0.24 mL, 3 mmol) in chloroform (20 mL) was refluxed for 48 h. After cooling to rt, the solution was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Oxazolidinone **14** was obtained as a white solid (346 mg, 82%). The physicochemical properties of this compound were identical to those described in the literature [30].

General procedure for the preparation of dithiocarbamates **17–22**

Carbon disulfide (2.3 mL, 38 mmol) was added dropwise to a solution of β-aminoalcohol (30 mmol) and triethylamine (5.2 mL, 37 mmol) in chloroform (50 mL). The resulting solution was stirred at rt for 15 min and iodomethane (2.3 mL, 37.5 mmol) was added. After the mixture had been stirred at rt for 3 h, the solvent was removed under reduced pressure. Usual workup and flash chromatography (elution with ether/petroleum ether) gave the following dithiocarbamates **17–22**.

• *(1*S*,2*R*)-Methyl* N-*(2-hydroxy-1-methyl-2-phenylethyl)*-N-*methyl-dithiocarbamate* **17**

Starting from (1*R*,2*S*) ephedrine, compound **17** was obtained after flash chromatography (ether/petroleum ether: 1:9) as a white solid (82%): mp 87°C; $[\alpha]_D^{20}$: −59.3 (*c* 0.83, $CHCl_3$).

IR ($CHCl_3$): 3 590, 3 400, 1 075 cm^{-1}.

^1H NMR [31]: 1.17 (d, J = 7 Hz, 3H), 2.53 (d, J = 3.8 Hz, 1H), 2.66 (s, 3H), 3.26 (s, 3H), 5.14 (m, 1H), 5.94 (m, 1H), 7.2–7.6 (m, 5H).

^{13}C NMR: 10.9, 20.1, 35.9, 63.1, 75.8, 125.6, 127.7, 128.4, 141.5, 199.9.

MS (EI): 208 (35), 207 (75), 118(100), 117 (90).

Anal calc for $C_{12}H_{17}NOS_2$: C, 56.44; H, 6.71; N, 5.48. Found: C, 56.49; H, 6.63; N, 5.33.

• *(1S,2R)-Methyl N-(2-hydroxy-1-methyl-2-phenylethyl) dithiocarbamate* **18**

Starting from (1*R*,2*S*) norephedrine, compound **18** was obtained after flash chromatography (ether/petroleum ether: 15:85) as an oil (95%): $[\alpha]_D^{20}$: −40.5 (*c* 1.08, $CHCl_3$).

IR ($CHCl_3$): 3 600, 3 380, 1 480, 1 000 cm^{-1}.

^1H NMR: 0.96 (d, *J* = 6.9 Hz, 3H), 2.54 (s, 3H), 3.85 (bs, 0.8H), 4.15 (bs, 0.2H), 4.90 (m, 1H), 5.05 (d, *J* = 2.5 Hz, 1H), 7.15–7.30 (m, 5H), 7.40 (bs, 0.8H), 8.22 (bs, 0.2H).

^{13}C NMR: 12.2, 18.1, 57.6, 74.6, 125.8, 127.7, 128.4, 140.4, 198.7.

Anal calc for $C_{11}H_{15}NOS_2$: C, 54.74; H, 6.26; N, 5.80. Found: C, 54.80; H, 6.53; N, 5.57.

• *(1S,2S)-Methyl N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-dithiocarbamate* **19**

Starting from (1*S*,2*S*) pseudoephedrine, compound **19** was obtained after flash chromatography (ether/petroleum ether: 20:80) as a white solid (82%): mp 82°C; $[\alpha]_D^{20}$: +0.92 (*c* 1.39, $CHCl_3$).

IR ($CHCl_3$): 3 580, 3 410, 1 105 cm^{-1}.

^1H NMR: 0.84 (d, *J* = 6.7 Hz, 3H), 2.54 (s, 1H), 3.12 (bs, 2H), 3.30 (bs, 2H), 3.40 (bs, 1H), 3.42 (d, *J* = 5.8 Hz, 1H), 4.50 (m,1H), 4.79 (bs, 0.3H), 6.05 (bs, 0.7H), 7.20–7.25 (m, 5H).

^{13}C NMR: 13.7, 14.1, 19.8, 33.6, 36.7, 62.6, 75, 76.6, 126.7, 127.8, 128.2, 140.5, 140.9, 198.8, 200.9.

MS (EI): 208 (40), 207 (70), 118(100), 117 (90).

Anal calc for $C_{12}H_{17}NOS_2$: C, 56.44; H, 6.71; N, 5.48. Found: C, 56.37; H, 6.62; N, 5.46.

• *(1R,2R)-Methyl N-(2-hydroxy-1-methyl-2-phenylethyl)dithiocarbamate* **20**

Starting from (1*R*,2*R*) norpseudoephedrine, compound **20** was obtained after flash chromatography (ether/petroleum ether: 5:95) as an oil (80%): $[\alpha]_D^{20}$: +16.8 (*c* 0.9, $CHCl_3$).

IR ($CHCl_3$): 3 580, 3 350, 1 480, 1 000 cm^{-1}.

^1H NMR: 1.22 (d, *J* = 6.7 Hz, 3H), 2.61 (s, 3H), 3.10 (bs, 0.8H), 4.25 (bs, 0.2H), 5.00 (m, 1H), 7.20–7.40 (m, 5.8H), 8.15 (bs, 0.2H).

^{13}C NMR: 16.4, 18.2, 57.6, 76.3, 126.5, 128.7, 140.8, 199.3.

• (R)-*Methyl N-(2-hydroxy-1-phenylethyl)-N-methyl-dithiocarbamate* **21**

Starting from (*R*)-*N*-methylphenylglycinol, compound **21** was obtained after flash chromatography (ether/petroleum ether: 1:9) as a solid (76%): mp 80°C: $[\alpha]_D^{20}$: −223.6 (*c* 0.69, $CHCl_3$).

IR ($CHCl_3$): 3 580, 1 075 cm^{-1}.

^1H NMR: 2.68 (s, 3H), 3.04 (bs, 0.3H), 3.06 (s, 3H), 3.28 (bs, 0.7H), 4.10 (dd, *J* = 12.5 and 12.8 Hz, 1H), 4.29 (dd, *J* = 7 and 13 Hz, 1H), 7.20–7.50 (m, 5H).

^{13}C NMR: 20.4, 35, 61.5, 65.4, 127.4, 128.9, 136, 201.9.

MS (EI): 194 (12), 193 (53), 104 (100), 78 (22).

Anal calc for $C_{11}H_{15}NOS_2$: C, 54.74; H, 6.26; N, 5.80. Found: C, 55.17; H, 6.33; N, 5.98.

• (R)-*Methyl N-(2-hydroxy-1-phenylethyl) dithiocarbamate* **22**

Starting from (*R*)-phenylglycinol, compound **22** was obtained after flash chromatography (ether/petroleum ether: 2:8) as an oil (73%): $[\alpha]_D^{20}$: −40 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 3 580, 3 350, 1 470, 1 060 cm^{-1}.

^1H NMR: 2.60 (s, 3H), 3.80 (bs, 1H), 3.91 (d, *J* = 4.8 Hz, 1H), 5.04 (bs, 0.2H), 5.78 (bs, 0.8H), 7.10–7.40 (m, 5.8H), 8.44 (bs, 0.2H).

^{13}C NMR: 15, 18.1, 19, 60, 61.6, 62.2, 64.7, 65.2, 65.6, 77.5, 126, 127.6, 128.6, 128.9, 129.1, 129.3, 136.8, 137.6, 189.4, 199.3, 202.6.

Anal calc for $C_{10}H_{13}NOS_2$: C, 52.83; H, 5.76; N, 6.16. Found: C, 52.79; H, 5.88; N, 6.05.

General procedure for the preparation of thiazoline **23–25**

To a solution of thionothiocarbamate (1.5 mmol) in pyridine (10 mL) was added methanesulfonyl chloride (345 μL, 4.5 mmol). The resulting solution was stirred at room temperature for 1 day, poured into water (20 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with a saturated aqueous solution of $CuSO_4$ (3 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (ether/petroleum ether) gave the compounds described hereafter.

• *(4S,5S)-2-Methylthio-4-methyl-5-phenyl-4,5-dihydrothiazole* **23**

Starting from compound **18**, thiazoline **23** was obtained after flash chromatography (ether/petroleum ether: 5:95) as an oil (60%): $[\alpha]_D^{20}$: −193.7 (*c* 1.68, $CHCl_3$).

IR ($CHCl_3$): 1 555 cm^{-1}.

^1H NMR: 1.41 (d, *J* = 6.6 Hz, 3H), 2.60 (s, 1H), 4.56 (qd, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 7.30–7.40 (m, 5H).

^{13}C NMR: 15.3, 20.0, 63.8, 80.4, 127.6, 127.9, 128.8, 140.3, 163.7.

Anal calc for $C_{11}H_{13}NS_2$: C, 59.15; H, 5.87; N, 6.27. Found: C, 58.95; H, 5.83; N, 6.23.

• *(4R,5S)-2-Methylthio-4-methyl-5-phenyl-4,5-dihydrothiazole* **24**

Starting from compound **20**, thiazoline **24** was obtained after flash chromatography (ether/petroleum ether: 5:95) as an oil (45%): $[\alpha]_D^{20}$: −20 (*c* 0.05, $CHCl_3$).

IR ($CHCl_3$): 1 555 cm^{-1}.

^1H NMR: 1.08 (d, *J* = 7 Hz, 3H), 2.61 (s, 1H), 4.66 (qd, *J* = 7.2 Hz, 1H), 5.00 (d, *J* = 7.6 Hz, 1H), 7.20–7.50 (m, 5H).

^{13}C NMR: 15.4, 16.5, 60.3, 74.24, 127.5, 128.2, 128.8, 137.5, 165.4.

Anal calc for $C_{11}H_{13}NS_2$: C, 59.15; H, 5.87; N, 6.27. Found: C, 58.98; H, 5.80; N, 6.20.

• *(4R)-2-Methylthio-4-phenyl-4,5-dihydrothiazole* **25**

Starting from compound **22**, thiazoline **25** was obtained after flash chromatography (ether/petroleum ether: 5:95) as a white solid (35%): mp 87°C; $[\alpha]_D^{20}$: −117.7 (*c* 0.95, $CHCl_3$).

IR ($CHCl_3$): 1 550 cm^{-1}.

^1H NMR: 2.66 (s, 3H), 3.34 (t, *J* = 9.6 Hz, 1H), 3.85 (dd, *J* = 9 and 8.3 Hz, 1H), 5.54 (t, *J* = 8.5 Hz, 1H), 7.20–7.50 (m, 5H).

^{13}C NMR: 15.5, 42.9, 79.5, 126.4, 127.6, 128.5, 141.6, 166.7.

MS (EI): 209 (M^+; 70), 194 (20), 148 (85), 135 (100), 121 (25), 91 (42).

Anal calc for $C_{10}H_{11}NS_2$: C, 57.38; H, 5.30; N, 6.69. Found: C, 57.41; H, 5.45; N, 6.47.

General procedure for the preparation of thiazolidine-2-thiones **26–27**

To a solution of thionothiocarbamate (4.15 mmol) and pyridine (0.65 mL, 8.04 mmol) in dichloromethane (40 mL) was added methanesulfonyl chloride (640 µL, 8.33 mmol). The resulting solution was refluxed for 1 day, poured into water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (ether/petroleum ether) gave the following compounds.

• *(4S,5S)-3,4-Dimethyl-5-phenylthiazolidine-2-thione* **26**

Starting from compound **17**, thiazolidinethione **26** was obtained after flash chromatography (ether/petroleum ether: 3:7) as a white solid (56%): mp 55–58°C; $[\alpha]_D^{20}$: −129 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$): 1 030 cm^{-1}.

^1H NMR: 1.42 (d, J = 5.1 Hz, 3H), 3.21 (s, 3H), 4.10 (qd, J = 5 Hz, 1H), 4.26 (d, J = 5 Hz, 1H), 7.28–7.30 (m, 5H).

^{13}C NMR: 18, 34.9, 54.8, 73.3, 127.6, 128.7, 129.2, 138.7, 194.9.

MS (EI): 223 (M^+; 100), 135 (20), 117 (50), 91 (20).

Anal calc for $C_{11}H_{13}NS_2$: C,59.15; H, 5.87; N, 6.27. Found: C, 58.87; H, 5.83; N, 6.36.

• *(4R)-3-Methyl-4-phenylthiazolidine-2-thione* **27**

Starting from compound **21**, thiazolidinethione **27** was obtained after flash chromatography (ether/petroleum ether: 10:90) as a white solid (60%): mp 103–105°C; $[\alpha]_D^{20}$: −135 (*c* 0.72, $CHCl_3$).

IR ($CHCl_3$): 1 095 cm^{-1}.

^1H NMR: 3.10 (s, 3H), 3.18 (dd, J = 6.2 and 11.2 Hz, 1H), 3.74 (dd, J = 8.7 and 11.2 Hz, 1H), 5.17 (dd, J = 6.3 and 8.7 Hz, 1H), 7.20–7.50 (m, 5H).

^{13}C NMR: 35.5, 35.7, 73.9, 126.6, 129.3, 129.5, 138.0, 197.0.

MS (EI): 209 (M^+; 100), 135 (40), 104 (90), 91 (25), 78 (25).

Anal calc for $C_{10}H_{11}NS_2$: C, 57.38; H, 5.30; N, 6.69. Found: C, 57.36; H, 5.27; N, 6.60.

General procedure for the preparation of thiazolidin-2-ones **28–30**

To a solution of thionothiocarbamate (4 mmol) in pyridine (20 mL) was added methanesulfonyl chloride (925 µL, 12 mmol). The resulting solution was stirred for 4 h at room temperature and made strongly basic (pH 14) by addition of an aqueous solution of NaOH (5 N). Usual workup and purification by flash chromatography or recrystallization gave the following compounds.

• *(4S,5S)-3,4-Dimethyl-5-phenylthiazolidin-2-one* **28**

Starting from compound **17**, thiazolidinone **28** was obtained after flash chromatography (ether/petroleum ether: 55:45) as an oil (69%): $[\alpha]_D^{20}$: −152 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 1 030 cm^{-1}.

^1H NMR: 1.32 (d, J = 6.4 Hz, 3H), 2.90 (s, 3H), 3.70 (dt, J = 6.4 and 7.2 Hz, 1H), 4.30 (d, J = 7.2 Hz, 1H), 7.25–7.44 (m, 5H).

^{13}C NMR: 17.7, 30.0, 53.3, 64.7, 127.8, 128.4, 128.9, 136.7, 170.9.

MS (CI, NH_3): m/z 225 (MNH_4^+; 100), 208 (MH^+; 90), 150 (20), 52 (50).

Anal calc for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.65; H, 6.31; N, 6.69.

• *(4S,5R)-3,4-Dimethyl-5-phenylthiazolidin-2-one* **29**

Starting from compound **19**, thiazolidinone **29** was obtained as white crystals after recrystallization from ethanol (70%): mp 102°C; $[\alpha]_D^{20}$: −32.1 (*c* 0.2 $CHCl_3$).

IR ($CHCl_3$): 1 660 cm^{-1}.

^1H NMR: 0.87 (d, J = 6.55 Hz, 3H), 2.83 (s, 3H), 3.95 (qd, J = 6.7 Hz, 1H), 4.90 (d, J = 6.9 Hz, 1H), 7.20–7.30 (m, 5H).

^{13}C NMR: 11.4, 27.6, 48.4, 58.7, 125.7, 126, 126.1, 133.5, 169.0.

MS (EI): 207 (M^+; 60), 192 (50), 150 (35), 135 (20), 121 (70), 58 (100).

Anal calc for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.85; H, 6.35; N, 6.79.

• *(4R)-3-Methyl-4-phenylthiazolidin-2-one* **30**

Starting from compound **21**, thiazolidinone **30** was obtained after flash chromatography (ether/petroleum ether: 1:9) as a white solid (81%): mp 77°C; $[\alpha]_D^{20}$: −158 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 1 665 cm^{-1}.

^1H NMR: 2.66 (s, 3H), 3.12 (dd, J = 8 and 10.5 Hz, 1H), 3.60 (dd, J = 8 and 10.5 Hz, 1H), 4.70 (t, J = 8 Hz, 1H), 7.30–7.60 (m, 5H).

^{13}C NMR: 30.6, 33.7, 65.2, 126.5, 128.6, 129.0, 138.8 171.9.

MS (EI): 193 (M^+; 70), 135 (100), 118 (25), 91 (38), 77 (20).

Anal calc for $C_{10}H_{11}NOS$: C, 62.14; H, 5.74; N, 7.25. Found: C, 62.12; H, 5.72; N, 7.12.

• *(4R)-2-Methylthio-3-methyl-4-phenyl-4,5-dihydrothiazol-3-ium ion* **31**

To a solution of dithiocarbamate **21** (50 mg, 0.21 mmol) in pyridine-d_5 (1 mL) was added mesyl chloride (0.048 mL, 0.63 mmol) with stirring. After 1 h, the solution was transferred to a NMR sample tube. Examination of the ^1H NMR spectra (400 MHz) showed that the starting product was completely consumed. Compound **31** displayed the following resonances: 2.69 (s, 3H), 3.47 (dd, J = 7.2 and 11.7 Hz, 1H), 3.81 (s, 3H), 4.26 (dd, J = 9.9 and 11.5 Hz, 1H), 6.03 (t, J = 8.8 Hz, 1H), 6.8–7.2 (m, 5H).

Calculation procedures

The calculations were carried out using the AM1 model [32a] as implemented in the AMPAC program[32b]. The geometries were optimized by minimizing the energy with respect to all internal coordinates by using the Davidson–Fletcher–Powell algorithm (FLEPO) incorporated in AMPAC. This work was performed at the Centre de Calcul Recherche of the Université Pierre-et-Marie-Curie on an IBM RS/6000 computer.

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