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1,3-Heterazolidines-2-heterounsaturated compounds derived from ephedrines

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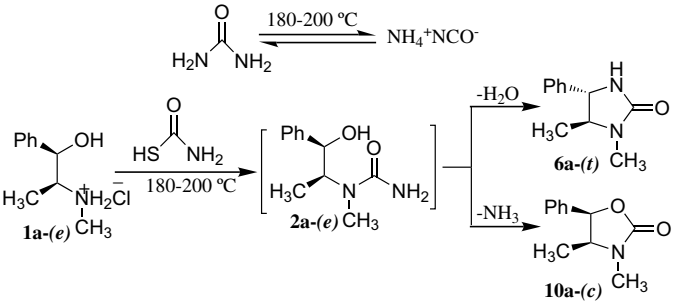
Abstract—Herein, a direct and easy method for preparing 2-oxo-, 2-thione- or 2-imine-1,3-heterazolidines derived from ephedrines and norephedrines are reported. The method is based on solvent free heating of ephedrines with oxocyanate or thiocyanate salts (180–200 °C). In the reactions with potassium oxocyanate in refluxing ethanol, it was possible to isolate ureidic derivatives. The structure and stereochemistry of the compounds were determined by ^{1}H, ^{13}C NMR, IR spectroscopies and mass spectrometry. Ureidic derivatives, *cis*-1,5-dimethyl-4-phenyl-imidazolidine-2-thione and *trans*-4-methyl-5-phenyl-thiazolidine-2-one are new compounds. Ephedrineurea, *cis*-1,5-dimethyl-4-phenyl-imidazolidine-2-thione and *trans*-4-methyl-5-phenyl-thiazolidine-2-one were also studied by X-ray diffraction.

1. Introduction

There are several reports in the literature concerning the synthesis of 1,3-heterocycles with 2-one, 2-thione and 2-imine functional groups derived from β-aminoalcohols, β-aminothiols and ethylendiamines, by the use of dialkylcarbonates,[1] phosgene,[2] urea,[3] thiophosgene and thiourea,[4] carbon disulfide[5] and cyanogen bromide.[6] In a previous work we have reported the synthesis of 1,3-thiazolidine-2-thiones,[7] 1,3-thiazolidine-2-imines,[8] 1,3-heterazaborolidines,[7–9] thiazolidines[10] and 2-imino-benzothiazolylheterazolidines[11] derived from ephedrines, which were recently reviewed.[12]

In 1950, Close[3] reported the solvent free dehydration of ephedrine hydrochloride **1a**-(*e*) in the presence of urea at 180–200 °C to afford imidazolidinone **6a**-(*t*) and oxazolidinone **10a**-(*c*) (Scheme 1). In that report it was assumed that at 180–200 °C, the urea was transformed into ammonium oxocyanate, which, in the presence of hydrochloride, transformed into ammonium chloride and oxocyanic acid. It was proposed that this reacts with free ephedrine to give ureidic intermediate **2a**-(*e*) (not isolated), which upon cyclization and dehydration, afforded the *trans*-imidazolidone **6a**-(*t*). In addition, nucleophilic attack of the oxygen atom of the ephedrine to the ureidic carbonyl and ammonia elimination, produced oxazolidone heterocycle **10a**-(*c*).



Scheme 1. Dehydration of ephedrine **1a**-(*e*) with urea according to Close.[3]

With the aim of studying the mechanistic transformation of the Close's reaction, it was revisited by the use of $K^{+}NCO^{-}$ instead of urea, and the study was extended for thiocyanates and pseudoephedrine **1a**-(*th*), norephedrine **1b**-(*e*) and norpseudoephedrine **1b**-(*th*), as chiral aminoalcohols to afford a series of optically active 1,3-heteroazolidine-2-heterounsaturated compounds **4**–**10** (Scheme 2), which are relevant because of their potential use as chiral inductors, specially those with the N–H functionality.[13]

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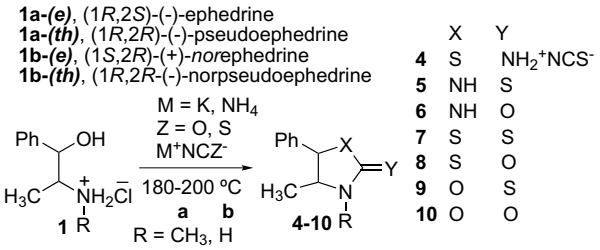
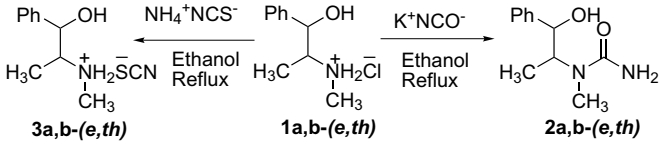


Scheme 2. 1,3-Heterazolidines-2-heterounsaturated from ephedrines.

2. Results

2.1. Reactions with oxocyanate

Urea derivative **2a**-(*e*), which in principle is formed in the Close's reaction, was isolated when ephedrine hydrochloride **1a**-(*e*) was reacted with K^+NCO^- for 72 h in refluxing ethanol (78% yield). The reaction is quite general, it was also performed with pseudoephedrine **1a**-(*th*), norephedrine **1b**-(*e*) and norpseudoephedrine **1b**-(*th*) to give, quantitatively, the ureidic derivatives **2a**-(*th*), **2b**-(*e*) and **2b**-(*th*) in 83%, 80% and 86% isolated yield, respectively (Scheme 3). On the other hand, reaction of **1a**,**b**-(*e*,*th*) with Na^+NCS^- only exchanged the chloride with a thiocyanate anion to give the corresponding hydrothiocyanates **3a**,**b**-(*e*,*th*) (Scheme 3).



Scheme 3. Reaction of ephedrines **1a**,**b**-(*e*,*th*) with K^+NCO^- and $NH_4^+NCS^-$ in refluxing ethanol.

When a racemic mixture of ephedrine hydrochloride **1a**-(*e*) was reacted with K^+NCO^-, the ureidic intermediate **2a**-(*e*) was crystallized from ethanol and its structure studied by X-ray diffraction (Fig. 1).

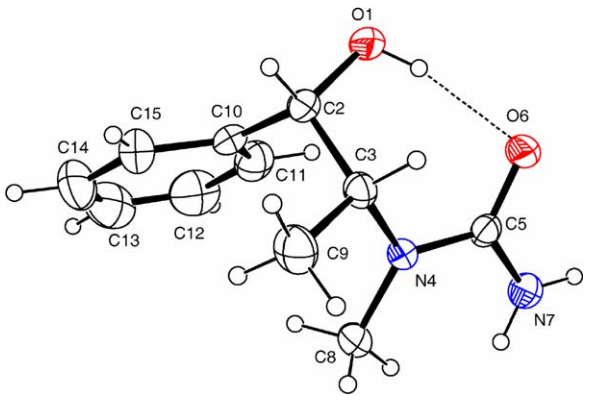


Figure 1. Molecular structure of ephedrineurea **2a**-(*e*).

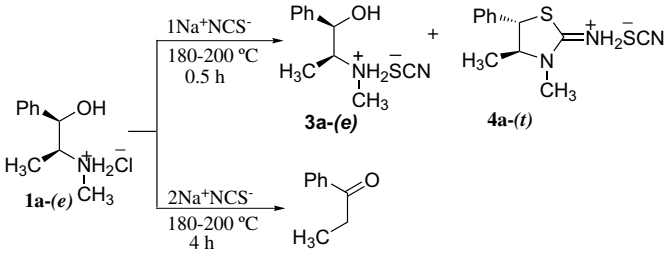
An intramolecular hydrogen bonding interaction between the hydrogen atom of the hydroxyl group and the ureidic oxygen atom to form a seven membered ring was observed. The O1H1···O6 distance of 1.820(24) Å [angle of 166.72° (2.25)] is within the range for a strong interaction.[14] The hydrogen bond formed is strong enough that it forces the NH_2 group to adopt a *syn*-conformation to the N-Me group [C8N4C5N7 angle of −6.00 (0.26)°], in spite of the steric hindance. On the other hand, both nitrogen atoms are conjugated with the carbonyl group since both N–CO bond distances are of intermediate value between a single (1.469 Å) and a double (1.279)[15] N–C bond (1.35 Å mean).

The formation of an equimolar mixture of imidazolidone **6a**-(*c*) and oxazolidone **10a**-(*c*) from intermediate **2a**-(*e*) was demonstrated when this last compound was free of solvent, heated at 180–200 °C for 1 h (Scheme 4). Imidazolidinone **6a**-(*c*) was precipitated from a $CHCl_3$ solution and was purified by recrystallization from ethanol. The analysis of ^1H and ^{13}C NMR spectra showed the formation of the *cis* (*c*) isomer instead of the expected *trans* (*t*) isomer and this was confirmed by X-ray diffraction.[9] Retention of the C1 configuration was in disagreement with the Close's mechanistic proposal. A mechanism based on an aziridine intermediacy could explain the formation of the *cis*-imidazolidone **6a**. It is known that aziridines are involved in a double inversion of the benzylic carbon atom to produce heterocycles with retention of configuration.[16] Thus, aziridine **I** and later on isocyanate **II** intermediate products would give the observed configuration for **6a**-(*c*) (Scheme 4). On the other hand, competitive attack of the hydroxy group onto the carbonyl oxygen atom with ammonia elimination explained the formation of the oxazolidone **10a**-(*c*), according to the Close's idea (Scheme 4). The results are in agreement with several reports in the literature, where the in situ generation of amide derivatives from amino alcohols are involved in oxazolidine formation.[1–3]

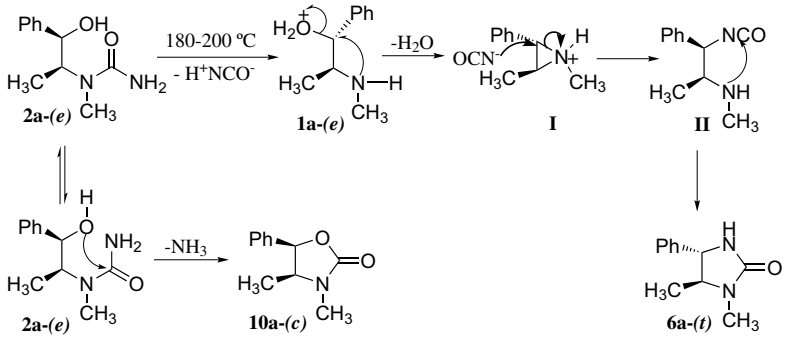
On the basis of these previous findings, the solvent free reaction of ephedrines **1a**,**b**-(*e*,*th*) were performed either with sodium or ammonium thiocyanates.

2.2. Reactions with thiocyanate

The reaction of **1a**-(*e*) with one equimolar amount of Na^+NCS^- was carried out at 180–200 °C for 0.5 h without solvent. After $CHCl_3/H_2O$ partition, the ephedrine hydrothiocyanate **3a**-(*e*) was isolated from the aqueous phase, whereas *trans*-thiazolidine-2-imino hydrothio-cyanate **4a**-(*t*) precipitated from the chloroform phase (10% yield) (Scheme 5).



Scheme 5. Reaction of ephedrine **1a**-(*e*) with NaSCN.



Scheme 4. Competitive mechanistic proposal for the cyclization of ephedrineurea **2a**-(*e*).

In order to improve the yield, the reaction time was increased to 4 h. Under these conditions, deamination of ephedrine hydrothiocyanate proceeded to give the formation of ethylphenylketone via enolate formation. The result was the same when using one or 2 M equiv of sodium thiocyanate (Scheme 5). Ethylphenylketone was identified from ^{1}H and ^{13}C NMR data [$\delta^{13}C$ in 200 ppm (C=O)], a triple and a quadruple signals in 1.2 and 2.98 ppm (CH_3CH_2)] and by mass spectrometry [(z/e) = 134 (18%), M^+].

The reaction with 2 equiv of ammonium thiocyanate for 4 h resulted in the formation of thiazolidine-2-imino hydrothiocyanate **4a**-(*t*) in 50% yield, which precipitates from a chloroform solution of the reaction mixture. The change from sodium to ammonium thiocyanate salt, avoided deamination, probably due to its lower melting point (153 °C). Compound **4a**-(*t*) was identified by comparing ^{1}H and ^{13}C NMR data with the previously reported data confirmed from an X-ray authenticated structure, obtained from chlorodeoxypseudoephedrine derivative.[8] The remaining chloroform mixture was eluted in a chromatographic column using chloroform as eluent. The analysis of the fractions by mass spectrometry showed the presence of the heterocycles as summarized in Table 1.

Pseudoephedrine **1a**-(*th*), norephedrine **1 b**-(*e*) and norpseudoephedrine **1b**-(*th*) were each reacted with 2 M equiv of $NH_4^+NCS^-$ as described above for ephedrine **1a**-(*e*). The corresponding resulting mixtures were separated by column chromatography and the fractions analyzed by ^{1}H and ^{13}C NMR and by mass spectrometry. The identified compounds are listed in Table 1.

The reaction mixture of pseudoephedrine hydrochloride **1a**-(*th*) was extracted with a 50:50 ratio of a $CHCl_3/H_2O$ mixture. The chloroform phase was separated by column chromatography, using chloroform as eluent. From the second fraction, the imidazolidine-2-thione **5a**-(*c*) was separated in 40% yield. Three remaining fractions were analyzed by mass spectrometry and imidazolidones **6a**-(*c*) and **6a**-(*t*), thiazolidinethione **7a**-(*c*), thiazolidinones **8a**-(*c*) and **8a**-(*t*) were identified in small quantities. A solid was obtained after evaporation of the aqueous phase, from which thiazolidine-2-imino hydrothiocyanate **4a**-(*c*), oxazolidinones **10a**-(*c*) and **10a**-(*t*) were identified by mass spectrometry.

Compound **5a**-(*c*) was purified and recrystallized from ethyl acetate (40% yield). NMR spectra shows a broad

Table 1. Carbonyl carbon chemical shift in parts per million, proportion (%) and mass spectrometry data [M^+ (%)] of heterocycles **4**–**10**

	Heterocycle	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Ephedrine	X	S	NH	NH	S	S	O	O
	Y	NH_2SCN	S	O	S	O	S	O
1a-(*e*)	*c*		184(2)	163(3) [190(27)]	196(7) [223(100)]	172(4)		160(2) [191(19)]
	t	168(**50**) [206(98)]	183(7)	162(7)	195(2) [223(100)]	171(7)		191(23)
1a-(*th*)	*c*	169(15) [206(15)]	184(**40**) [206(100)]	163(5) [190(27)]	196(6) [223(100)]	172 [207(64)]		160(5) [191(19)]
	t			162(2)	Traces [223(100)]	171 [207(41)]		159(**20**) [191(23)]
1b-(*e*)	*c*		Traces [192(100)]		200(5) [209(100)]	176(5) [193(16)]	189(2) [193(35)]	160(**40**) [177(8)]
	t		Traces		199(2) [209(100)]	175(**40**) [193(25)]		
1b-(*th*)	*c*	173(**40**) [192(62)]	183(10) [192(100)]		200(15) [209(100)]	175(10) [193(16)]		160(3)
	t	172(10)				174(5)		159(3)

signal at 6.32 ppm (^{1}H) and at 183 ppm (^{13}C) characteristic of the N–H and thiocarbonyl groups, respectively. The molecular ion [$z/e = 206$ (100%), M^+] supported the structure. The X-ray diffraction analysis confirmed the stereochemistry of **5a**-(*c*) (Fig. 2). The bond distances C2–N1 [1.345(14) Å] and C2–N3 [1.332(13) Å] show an intermediate value between a single (1.469 Å) and a double (1.279)[15] N–C bond, thus extensive conjugation through the N1–C2–N3 fragment is demonstrated.

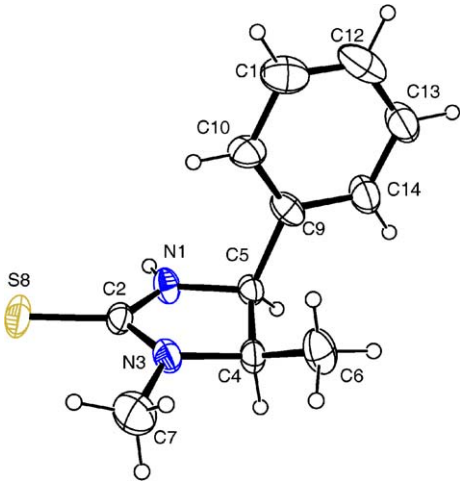


Figure 2. Molecular structure of *cis*-imidazolidinethione **5a**-(*c*).

From the reaction mixture of norephedrine hydrochloride **1b**-(*e*), four fractions were separated by column chromatography using chloroform and then ethanol as eluents, each fraction was analyzed by mass spectrometry. From the second fraction, compounds **8b**-(*c*) and **8b**-(*t*) were identified in a 1:8 ratio by ^{1}H and ^{13}C NMR. In a second column, using $CHCl_3$ as eluent, compound **8b**-(*t*) (40% yield) was separated from **8b**-(*c*). The molecular ion [$z/e =$ 193 (25%), M^+] supported the structures. Compound **8b**-(*t*) was crystallized from ethanol (40% yield) and the *trans* configuration was confirmed by X-ray diffraction (Fig. 3). The bond distances C2–N [1.332(3) Å] and C2–S [1.775(2) Å] are shorter than the single bonds C4–N [1.332(3) Å] and C5–S [1.821(2) Å], respectively, indicating an extensive conjugation through the N–C2–S fragment.

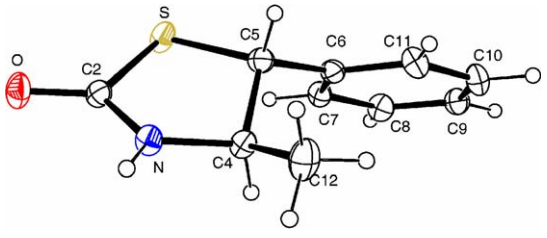


Figure 3. Molecular structure of *trans*-thiazolidinone **8b**-(*t*).

The reaction mixture of norpseudoephedrine hydrochloride **1b**-(*th*) was separated into four fractions by a chromatographic column with chloroform and then ethanol as eluents and each fraction analyzed by mass spectrometry. Thiazoline-2-amine hydrothiocyanate **4b**-(*c*) was isolated from the fourth fraction.

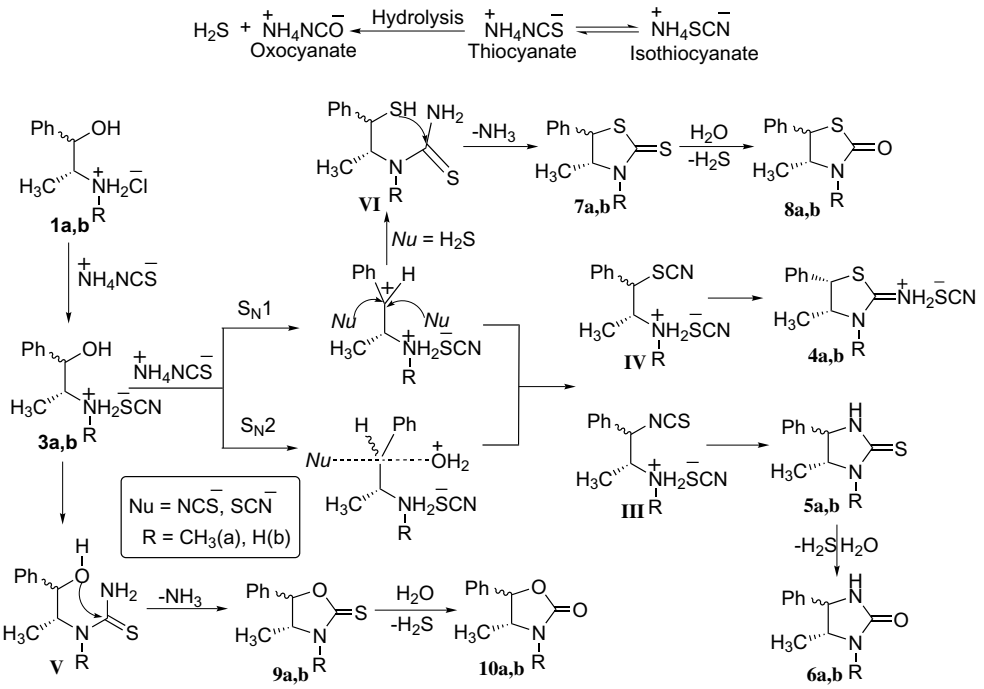
The *cis* or *trans* configuration of the heterocycles was established by the ^{1}H NMR chemical shifts of the C–CH_3 signal. The *cis* isomers showed a low frequency shift of the C–CH_3 group, which appears in the range between 0.9 and 0.7 ppm, due to the shielding effect exerted by the phenyl group. In contrast, the C–CH_3 chemical shift of the *trans* isomers is shifted to high frequency, appearing between 1.1 and 1.4 ppm.

3. Discussion

According to our results, at least four competitive mechanisms were proposed to explain the formation of heterocycles **4**–**10a**,**b** in the reaction of ephedrines **1a**-(*e*,*th*) and norephedrines **1b**-(*e*,*th*) with ammonium thiocyanate (Scheme 6). With the exception of norephedrine **1b**-(*e*), in these reactions, an S_N2 dehydration mechanism occurs due to the thiocyanate ⇌ isothiocyanate anions acting as nucleophiles and subsequent cyclization of the ephedrinethiocyanate (**IV**) and ephedrineisothiocyanate (**III**) intermediates to give the corresponding thiazolidine-2-imino hydrothiocyanates **4a**,**b** and imidazolidinethiones **5a**,**b**. For ephedrine **1a**-(*e*), the product from thiocyanate anion predominates and for pseudoephedrine **1a**-(*th*), the product from isothiocyanate gives the major product. It is noteworthy that, recently, an alkyl ephedrinethiocyanate analogue to **IV** has been isolated.[17]

In the reaction with norephedrine **1b**-(*e*), it is proposed that the H_2S generated by hydrolysis of thiocyanate, acts as the main nucleophile via competitive S_N2 and S_N1 mechanisms to form the intermediates **VI**-(*e*,*th*), which subsequently cyclize with deamination to give thiazolidinethiones **7b**-(*c*,*t*). Desulfurization by hydrolysis of the corresponding thione derivatives **7b**-(*c*,*t*), gave the thiazolidinones **8b**-(*c*,*t*). Simultaneously a mechanism through thioureidic intermediate **V** operates, which is cyclized to get the oxazolidinethione **9b**-(*c*), the subsequent desulfurization led to the oxazolidinone **10b**-(*c*). The desulfurization was demonstrated when the reaction time was decreased from 4 h to 2 h, in which case the proportion of oxazolidinethione **9b**-(*c*) increased from 10% to 40% and *cis*-oxazolidinone **10b**-(*c*) decreased by the same proportion.

The presence of oxazolidinone **10a**-(*t*) (20%) in the reaction of pseudoephedrine **1a**-(*th*), occurred via the desulfurization of oxazolidinethione **9a**-(*t*) formed by the cyclization of thioureidic intermediate **V**. As described in Scheme 6, this mechanism is favoured when 1 M equiv of $NH_4^+NCS^-$ is used. In this case, oxazolidinone **10a**-(*t*) (40%) and imidazolidinethione **5a**-(*c*) (20%) were observed as the main products. Similar results were also obtained in the reaction of norpseudoephedrine **1b**-(*th*). When the molar equivalents of $NH_4^+NCS^-$ were changed from two to one, thiazoline-2-amine hydrothiocyanates **4b**-(*c*) decreased from 40% to 15% yield, while oxazolidinone **10b**-(*t*) increased from 3% to 45% yield.



Scheme 6. Proposed mechanisms to explain the formation of heterocycles **4**–**10**.

4. Conclusions

In conclusion, from the reaction of ephedrines with potassium oxocyanate, the ureidic intermediates **2a**,**b**-(*e*,*t*) were quantitatively isolated. Compound **2a**-(*e*) was studied by X-ray diffraction. Two mechanisms are involved in the cyclization of ureaephedrine derivative **2a**-(*e*), one of which proceeds through the aziridine intermediate and the other by nucleophilic attack of the hydroxy group to the ureidic carbonyl. In both cases the heterocyclic products retain the configuration of the parent compounds. Moreover, we have described a solventless method to obtain heterazolidines-2-heterounsaturated compounds **4**–**10** from ephedrines **1a**,**b**-(*e*,*t*) and ammonium thiocyanate. Each reaction stereoselectively produced one heterocycle in 40–50% yield. Several interrelated mechanisms take place, although the proportion of the products can be manipulated by changing the reaction conditions such as stoichiometry and reaction time.

5. Experimental

5.1. General

Melting points were measured on an Electrothermal IA apparatus and are uncorrected. IR spectrum were recorded in a film on ZnSe using a Perkin–Elmer 16F PC IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz (^{1}H, 300.08; ^{13}C, 75.46 MHz). The spectra were measured with tetramethylsilane as the internal reference following standard techniques. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC: **8b**-(*t*), (601398); **2a**-(*e*), (601399) and **5a**-(*c*), (601400). X-ray diffraction cell refinement and data collection: CAD-4 EXPRESS;[18] data reduction: JANA98;[19] programs used to solve structure: SHELXS-97;[20] software used to prepare material for publication: *WinGX*.[21] Mass spectrometer HP 5989A, 5890 serie II.

5.2. Preparation of ephedrineureas 2a,b-(*e*,*t*), general method

5.2.1. (1*R*,2*S*)-(−)-1-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-1-methyl-urea 2a-(*e*). Ephedrine chlorhydrate **1a**-(*e*) (1.0 g, 4.96 mmol), $K^{+}NCO^{-}$ (0.402 g, 4.96 mmol) and 50 mL of ethanol were added into a 100 mL flask and the mixture refluxed for 72 h (96 h for ephedrine). The resulting suspension was cooled in an ice bath, until all the NaCl was precipitated, it was filtered and the ethanol eliminated in vacuo to obtain 0.8 g (78% yield) of white crystals: ^{1}H NMR, δ (ppm), DMSO-d_6: 7.15–7.30 (m, 5H, Ph), 5.64 (s, 2H, NH_2), 5.46 (d, 1H, $^{3}J = 4.7$ Hz, OH), 4.55 (dd, 1H, $^{3}J = 5.43$ Hz, C1–H), 4.23 (dq, 1H, C2–H); 2.6 (s, 3H, N–CH_3); 1.03 (d, 3H, $^{3}J = 6.75$, C2–CH_3). ^{13}C NMR: 158.9 (C=O), 144.1 (Ci), 127.7 (Co), 126.8 (Cp), 126.4 (Cm), 75.4 (C1), 55.0 (C2), 30.0 (N–CH_3); 12.9 (C2–CH_3), mp = 122–124 °C. ν_{IR} (cm^{-1}, KBr): (C=O). $[\alpha]_D = -8.1$ (c 1.6×10^{-3} g/mL, 8.9×10^{-3} M, ethanol).

5.2.2. (1*R*,2*R*)-(−)-1-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-1-methyl-urea 2a-(*t*). Following the same procedure for **2a**-(*e*), pseudoephedrine chlorhydrate **1a**-(*t*) (1.0 g, 4.96 mmol) and $K^{+}NCO^{-}$ (0.402 g, 4.96 mmol) were used to obtain 0.85 g (82.5% yield) of white crystals: ^{1}H NMR [δ, ppm, DMSO-d_6]: 7.2–7.4 (m, 5H, Ph), 5.7 (s, 2H, NH_2), 5.4 (d, 1H, $^{3}J = 3.8$ Hz, OH), 4.5 (dd, 1H, $^{3}J = 7.9$ Hz, C1–H), 4.2 (dq, 1H, C2–H), 2.6 (s, 3H, N–CH_3), 1.0 (d, 3H, $^{3}J = 6.8$ Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]:

158.9 (C=O), 144.1 (Ci), 127.7 (Co), 126.8 (Cp), 126.4 (Cm), 75.4 (C1), 55.0 (C2), 30.0 (N–CH_3), 12.9 C2–CH_3, mp = 144–147 °C. ν_{IR} (cm^{-1}, KBr): 1650 (C=O). $[\alpha]_D = -15.0$ (c 1.53×10^{-3} g/mL, 8.5×10^{-3} M, ethanol).

5.2.3. (1*S*,2*R*)-(+)-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-urea 2b-(*e*). Following the same procedure for **2a**-(*e*), norephedrine hydrochloride **1b**-(*e*) (1.0 g, 5.33 mmol) and K^+NCO^- (0.43 g, 5.33 mmol) were used to obtain 0.82 g (80% yield) of white crystals: ^{1}H NMR [δ ppm, DMSO-d_6]: 7.18–7.30 (m, 5H, Ph), 5.93 (d, 1H, $^3J = 8.5$ Hz, NH), 5.53 (d, 1H, $^3J = 4.7$ Hz, OH), 5.5 (s, 2H, NH_2), 4.61 (t, 1H, $^3J = 4.0$ Hz, C1–H); 3.78 (dq, 1H, C2–H); 0.81 (d, 3H, $^3J = 6.75$ Hz, C2–CH_3). ^{13}C NMR [δ ppm, DMSO-d_6]: 159.14 (C=O), 144.32 (Ci), 128.44 (Co), 127.22 (Cp), 126.72 (Cm), 75.47 (C1), 51.27 (C2), 14.92 (C2–CH_3), mp = 122–124 °C. ν_{IR} (cm^{-1}, KBr): 1656 (C=O). $[\alpha]_D = +3.0$ (c 1.68×10^{-3} g/mL, 8.66×10^{-3} M, ethanol).

5.2.4. (1*R*,2*R*)-(−)-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-urea 2b-(*t*). Following the same procedure for **2a**-(*e*) norpseudoephedrine chlorhydrate **1b**-(*t*) (1.0 g, 5.33 mmol) and K^+NCO^- (0.43 g, 5.33 mmol) were used to obtain 0.89 g (86% yield) of a viscous liquid: ^{1}H NMR [δ, ppm, DMSO-d_6]: 7.2–7.3 (m, 5H, Ph), 5.8 (d, 1H, $^3J = 8.2$ Hz, NH), 5.6 (broad, 1H, OH), 5.5 (s, 2H, NH_2), 4.5 (d, 1H, $^3J = 3.8$ Hz, C1–H); 3.75 (dq, 1H, C2–H); 0.95 (d, 3H, $^3J = 6.75$ Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 159.25 (C=O), 144.0 (Ci), 127.3 (Co), 127.3 (Cp), 128.2 (Cm), 75.45 (C1), 51.1 (C2), 18.5 (C2–CH_3), ν_{IR} (cm^{-1}, KBr): 1650 (C=O). $[\alpha]_D = -6.1$ (c 1.64×10^{-3} g/mL, 8.45×10^{-3} M, ethanol).

5.3. Preparation of ephedrine hydrothiocyanates 3a,b-(*e*,*t*), general method

The same procedure and quantities used for the syntheses of ephedrineureas **2a**,**b**-(*e*,*t*) were used to obtain **3a**,**b**-(*e*,*t*) in quantitative yields. The ^{1}H and ^{13}C NMR data were similar as for the corresponding **2a**,**b**-(*e*,*t*). All compounds showed the same characteristic IR signals: ν_{IR} (cm^{-1}, KBr): 3328 ($^+NH_2$), 2043 (^-SCN). Mp for **3a**-(*e*) is: 126–128 °C.

5.4. Heating of ephedrines 1a,b-(*e*,*t*) wih ammonium thiocyanate, general method

Ephedrine hydrochlorides **1a**,**b**-(*e*,*t*) (1.0 g) and 2 M equiv of $NH_4^+NCS^-$ were poured into a 100 mL flask. The mixture was heated at 180 °C without a solvent for 3 h, and then at 200 °C for 1 h. The reaction mixture was cooled and 50 mL of ethanol added. The solution was put into an ice bath for one more hour, after which the NaCl was filtered off and the ethanol evaporated. The remaining solid was dissolved in chloroform and worked up as described.

5.4.1. (1*S*,2*S*)-*trans*-3,4-Dimethyl-5-phenyl-thiazolidin-2-imine hydrothiocyanate 4a-(*t*). Ephedrine **1a**-(*e*) (1.0 g, 4.96 mmol) and $NH_4^+NCS^-$ (0.754 g, 9.92 mmol) were used. **4a**-(*t*) precipitates as a white solid from the chloroform solution, over an ice bath, the solid was filtered off and compound **4a**-(*t*) was recrystallized from ethanol to get 0.66 g of **4a**-(*t*) (50% yield): ^{1}H NMR [δ, ppm, DMSO-d_6]: 9.0 (broad, 2H, $+NH_2$), 7.30–7.45 (m, 5H, Ph), 4.9 (d, 1H $^3J = 5.0$ Hz, C5–H), 4.4 (dq, 1H, C4–H); 3.2 (s, 3H, N–CH_3), 1.4 (d, 3H, $^3J = 6.2$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 167.3 (C2=N), 138.3 (Ci), 128.95 (Co), 128.55 (Cp), 127.4 (Cm), 69.7 (C4), 53.2 (C5), 32.5 (N–CH_3); 16.5 C4–CH_3.

5.4.2. (4*S*,5*R*)-(+)-1,5-Dimethyl-4-phenyl-imidazolidine-2-thione 5a-(*c*). Pseudoephedrine **1a**-(*t*) (1.0 g, 4.96 mmol) and $NH_4^+NCS^-$ (0.754 g, 9.92 mmol) were used. The chloroform solution was extracted with water three times, dried over Na_2SO_4, filtered and purified on a silica gel chromatographic column (60, 70–230 mesh ASTM), which was eluted with a 50:50 solution of $CHCl_3$/AcOEt. The second fraction was recrystallized from ethylacetate to give 0.41 g (40% yield) of *cis*-imidazolidinethione **5a**-(*c*) suitable for X-ray analysis: ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.2–7.4 (m, 5H, Ph), 6.3 (broad, 1H, NH), 5.0 (d, 1H, $^3J = 9.4$ Hz, C4–H), 4.2 (dq, 1H, C5–H), 3.1 (s, 3H, N–CH_3); 0.8 (d, 3H, $^3J = 6.45$, C5–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 183.7 (C2=S), 136.7 (Ci), 128.85 (Co), 128.6 (Cp), 127.3 (Cm); 64.9 (C4), 61.7 (C5), 32.0 (N–CH_3); 14.3 (C5–CH_3). $z/e = 206$ (100%). ν (cm^{-1}, film): 3204.1 (NH), 1751.7 (C=S), mp = 138–140 °C, $[\alpha]_D = +34.3$ (c 1.43×10^{-3} g/mL, 7.7×10^{-3} M, $CHCl_3$).

5.4.3. (4*R*,5*R*)-(+)-4-Methyl-5-phenyl-thiazolidin-2-one 8b-(*t*). Norephedrine **1b**-(*e*) (1.0 g, 5.33 mmol) and $NH_4^+NCS^-$ (0.81 g, 10.66 mmol) were used. The chloroform mixture was eluted on a silica gel chromatographic column (60, 70–230 mesh ASTM) using chloroform as eluent. From the second fraction, *trans*-thiazolidone **8b**-(*t*) together with its *cis* isomer **8b**-(*c*) were separated in a 80/20 proportion, respectively. In a second column, compound **8b**-(*t*) was separated from its *cis* isomer, using $CHCl_3$ as eluent: The *trans*-thiazolidinone **8b**-(*t*) was recrystallized from ethanol to obtain 0.41 g of pure product (40% yield): ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.30–7.5 (m, 5H, Ph), 7.0 (broad, 1H, NH), 4.55 (d, 1H, $^3J = 8.3$ Hz, C5–H), 4.0 (dq, 1H, C4–H), 1.3 (d, 3H, $^3J = 6.2$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 175.0 (C2=O), 138.2 (Ci); 129.4 (Co), 128.9 (Cp), 128.5 (Cm), 58.1 (C5); 60.0 (C4); 19.5 (C4–CH_3). $z/e = 193$ (25.6%). ν_{IR} (cm^{-1}, KBr): 3233.6 (NH), 1678.1 (C=O), $[\alpha]_D = +33.0$ (c 2.03×10^{-3} mg/mL, $CHCl_3$), mp = 90–91 °C.

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