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Reactivity of chlorodeoxypseudoephedrines with oxo-, thio-, and selenocyanates

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Abstract—Herein, the reactivity of chlorodeoxypseudoephedrine hydrochlorides with oxo-, thio-, and selenocyanate nucleophiles is reported. 1,3-Heterazolidine-2-iminium or ammonium salts were obtained stereoselectively in most cases. The hard–soft nature of the calcogen atom determines the mechanistic pathway via an S_N2 (X = O), aziridine intermediate (X = Se), or both (X = S). A simple method to synthesize stereoselectively the *trans*-isomer of 3,4-dimethyl-5-phenyl-oxazolidine-2-iminium chloride and the *cis*-isomer of 4-methyl-5-phenyl-oxazoline-2-ammonium chloride, was also found. In addition, heterazolidine-2-imines or amines were liberated from the corresponding salts [Cl^- or XCN^- (X = O, S, Se)] with aqueous NaOH. Finally, *cis*-3,4-dimethyl-5-phenyl-oxazolidine-2-iminium chloride, *cis*-4-methyl-5-phenyl-oxazoline-2-amine, and *trans*-4-methyl-5-phenyl-selenazoline-2-amine compounds were studied by X-ray diffraction.

1. Introduction

Ephedrines are pharmaceuticals, which have several adrenergic stimulus responses, whose use usually comes with undesirable secondary effects, mainly as a stimulant of the central nervous system (CNS) and/or cardiovascular activity. By this, ephedrine and its derivatives have been used as drugs of abuse and their prescription is restricted. Recent investigations on this topic have not been successful enough to eliminate or diminish these problems. On the other hand, the two stereogenic centers of ephedrines make them good starting materials for the synthesis of chiral inductor agents or chiral catalysts, which can be used in asymmetric synthesis to obtain optically active phamaceuticals. In this sense, the synthesis of new ephedrine derivatives is required.

One strategy to change the biological activity of ephedrine derivatives and/or the properties of a chiral inductor or catalyst based on it, is to design heterocyclic derivatives, in which ephedrine takes part. There are several reports in the literature about the synthesis of 1,3-heterazolidine-2-hetero-unsaturated compounds derived from ephedrines and norephedrines,[1] some of them have been tested for biological activity[2] and have been used as chiral inductors,[3] but many others are potential candidates to be applied in both areas. Phenmetrazine (morpholine derivative) 4-methyl-aminorex (2-amine-oxazoline), and 3,4-dimethyl-aminorex (2-imine-oxazolidine) are some examples (Fig. 1).

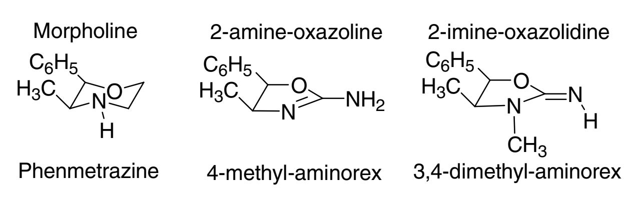

Figure 1. Ephedra heterocycles with biological activity.

The original report on aminorex and 4-methyl-aminorex, described them as potent anorectics with interesting CNS stimulus properties.[2e] Noggle et al.[1h] reported the synthesis and analytical profiles of the four stereoisomers of 3,4-dimethyl-aminorex as analogous of aminorex and 4-methyl-aminorex. The individual enantiomers of *cis*- and *trans*-3,4-dimethyl-aminorex were prepared by treating

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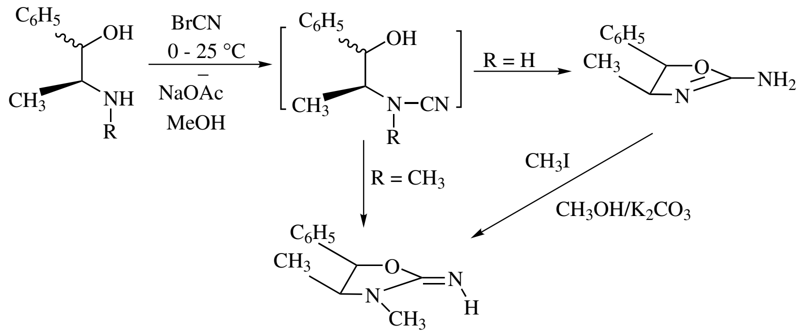


Scheme 1. Synthesis of aminorex derivatives.

ephedrines or pseudoephedrines with cyanogen bromide (Scheme 1).

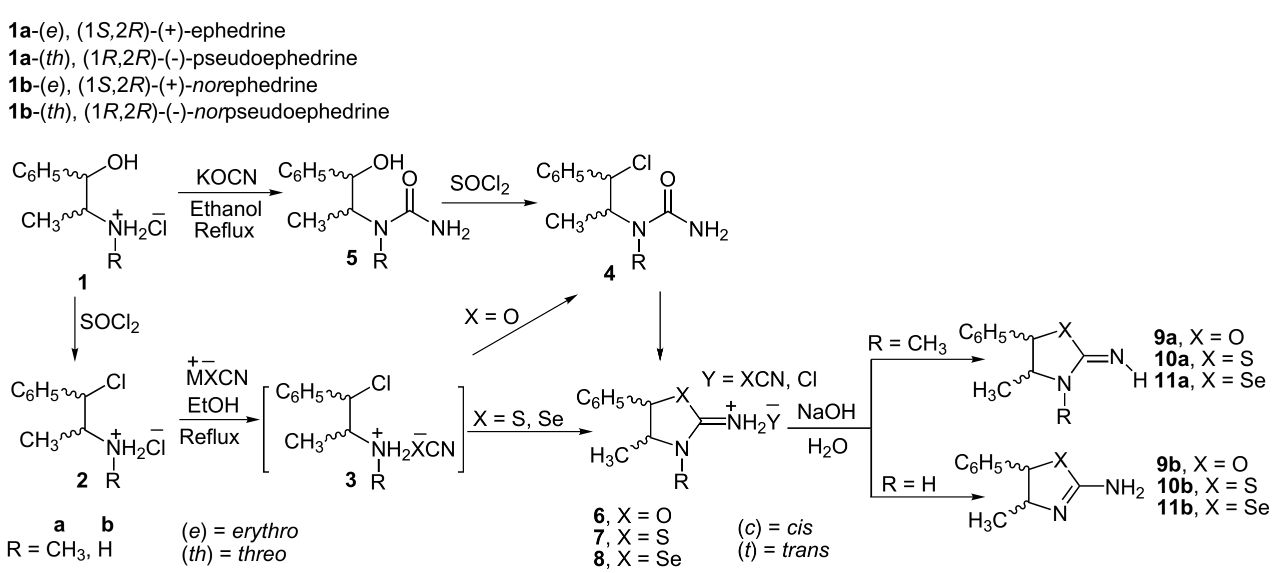
In previous work, we reported the condensation reactions of chlorodeoxypseudoephedrine hydrochloride **2a**-(*th*) with KOCN, NaSCN, and KSeCN as nucleophiles[1j] to obtain *cis*-1,3-oxazolidine-2-iminium oxocyanate **6a**-(*c*), *trans*-1,3-thiazolidine-2-iminium thiocyanate **7a**-(*t*), and *trans*-1,3-selenazolidine-2-iminium selenocyanate **8a**-(*t*), respectively (Scheme 2). In addition, each 2-iminium heterocycle could be liberated with aqueous NaOH to give the respective heterazolidine-2-imines **9a**, **10a**, and **11a**. When potassium oxocyanate was used, the *cis*-isomer of **6a** (65%), was obtained in a mixture with a secondary compound (35%), which was not identified.

In continuation with our investigations on the design of new heterocycles derived from ephedrines **1**, in this work, we revisited the cyclization reactions of chlorodeoxypseudoephedrine hydrochloride **2a**-(*th*) (R = Me) with 1 or 2 M equiv of potassium oxocyanate, sodium thiocyanate, and potassium selenocyanate nucleophiles as cyclizing agents in refluxing ethanol. In addition, the results of the reaction of chlorodeoxynorpseudoephedrine hydrochloride **2b**-(*th*) (R = H) with the above mentioned nucleophiles are reported. An interesting finding of this study was the synthesis of the *trans*-isomer of 1,3-oxazolidine-2-iminium chloride **6a**-(*t*) through the in situ chlorinated urea intermediate **4a**-(*e*) (Scheme 2).

2. Results and discussion

2.1. Condensation with potassium oxocyanate

The reaction of chlorodeoxypseudoephedrine hydrochloride **2a**-(*th*) with 2 M equiv of potassium oxocyanate with stirring ethanol at room temperature, was carried out. The reaction was monitored by ^{1}H NMR. Under these conditions, two compounds, in 80:20, 60:40, and 40:60 proportions were observed at 24, 48, and 72 h, respectively. The NMR tube of the 40:60 mixture in DMSO-d_6 was heated in a water bath at 92 °C for 1 h, to be quantitatively transformed into the 1,3-oxazolidine-2-iminium oxocyanate **6a**-(*c*). These results indicate the intermediacy of the above mentioned secondary compound, which was identified as *N*-(1-chloro-1-phenyl-2-methyl-ethyl)-*N*-methyl urea **4a**-(*th*) in the 80:20 mixture with **6a**-(*c*). Therefore, the use of 1 M equiv of potassium oxocyanate in refluxing ethanol for 16 h is required to obtain the hydrochloride of



Scheme 2. Reactivity of chlorodeoxypseudoephedrine hydrochlorides **2** with heterocyanates.

the oxazolidine-2-imine **6a**-(*c*), which was purified by crystallization in ethanol and whose X-ray structure is shown in Figure 2.

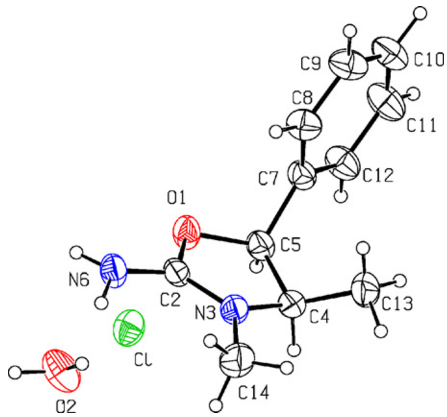


Figure 2. Molecular structure of compound **6a**-(*c*). The molecule crystallizes with one water molecule. Selected bond distances in Å are: C4–C5, 1.544(3); O1–C5, 1.472(3); O1–C2, 1.317(2); N3–C4, 1.467(3); N3–C14, 1.457(3); N3–C2, 1.311(3); N6–C2, 1.304(3). Selected torsion angles in degrees are: C13–C4–C5–C7, −7.7(3); N3–C4–C5–O1, −6.39(18); N3–C2–O1–C5, 2.9(2); O1–C2–N3–C4, −7.7(2); N6–C2–N3–C14, 3.6(3); N6–C2–O1–C5, −177.57(3); N6–C2–N3–C4, 172.85(17); C13–C4–N3–C14, −55.9(3).

The reaction is general; the analogous reaction of chlorodeoxynorpseudoephedrine hydrochloride **2b**-(*th*) (R = H) with 1 M equiv of the oxocyanate in refluxing ethanol for 8 h, resulted in the formation of the chlorourea derivative **4b**-(*th*). A mechanistic pathway to explain the inversion of the C1 configuration to form **6a**-(*c*) and **6b**-(*c*), from **4a**,**b**-(*th*) (vide infra), in the cyclization path is proposed in Scheme 3.

Compound **4b**-(*th*) was stable enough to be isolated and characterized by NMR in DMSO-d_6 solution. Two signals at 6.04 (d, $^3J = 8.5$ Hz) and 5.55 ppm (br) in a 1:2 proportion, respectively, were observed in the ^{1}H NMR spectrum and = assigned to the urea hydrogen atoms. A hydrogen bonding interaction between the NH and chlorine atom is proposed, which requires H2 and NH to be in an *anti* position, in agreement with the measured NH coupling constant value ($^3J = 8.5$ Hz). In addition, the small H1, H2 coupling constant ($^3J = 5.28$ Hz) supports this proposed interaction (Fig. 3). The ^{13}C NMR spectrum shows a carbonyl carbon signal at 159.6 ppm, according to the proposed structure.

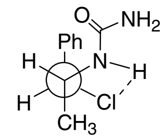
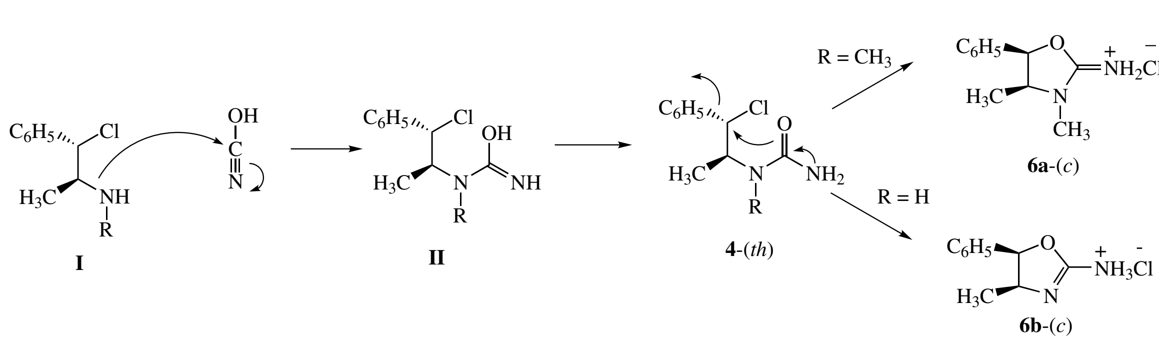


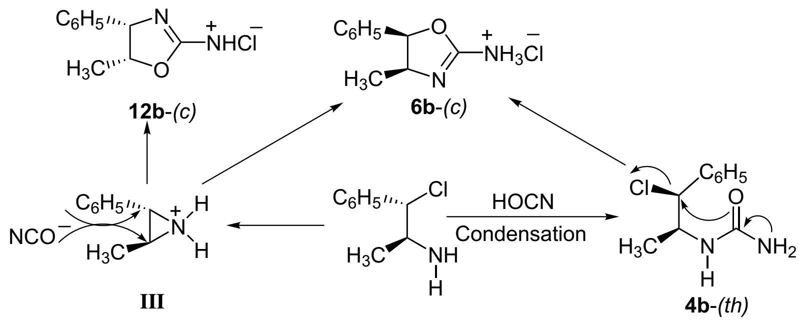
Figure 3. Hydrogen bonding interaction proposed in compound **4b**-(*th*).

Finally, the chlorourea derivative **4b**-(*th*) was refluxed in ethanol for 24 h. After cooling, a white solid precipitated, which was filtered, and washed with cool acetone. The ^{1}H NMR spectrum of the solid showed a mixture of two compounds in an 80:20 ratio. The major product was identified as *cis*-4-methyl-5-phenyloxazoline-2-ammonium chloride **6b**-(*c*). The ^{1}H NMR chemical shift of the ammonium hydrogen atoms are at 9.65 ppm as a broad signal, the signals for the methyne protons H5 (doublet) and H4 (doublet of quartet) appear at 6.49 and 4.56 ppm. The multiplicity of these signals are interchanged for the minor compound: the doublet appears at 5.26 and the doublet of the quartet at 5.41 ppm, they are correlated with ^{13}C NMR signals at 65.9 (C4) and 84.6 (C5) ppm, respectively. The same coupling constant values were measured as for **6b**-(*c*). These results allowed us to identify the formation of *cis*-5-methyl-4-phenyl-oxazoline-2-ammonium hydrochloride **12b**-(*c*), as the minor compound, whose formation can be explained due to the participation of a competitive reaction, which goes on through the aziridine intermediate **III**[1k] (Scheme 4).

The development of synthetic routes to independently obtain *cis*- and *trans*-isomers, is important in asymmetric synthesis. In a previous work we studied the chlorination reaction of ephedrine derivatives with thionyl chloride. It was found that the C1 configuration is retained through a S_Ni mechanism, when ephedrine bears an oxamide or sulfonamide group.[4] In this sense, the urea group was introduced as a bulky substituent on the nitrogen atom, by reaction of ephedrine hydrochloride **1a**-(*e*) with KOCN, to produce the *erythro*-isomer of ephedrine–urea intermediate **5a**-(*e*).[1o] This compound was isolated and subsequently reacted with thionyl chloride in $CHCl_3$ to obtain, in situ, 1-(2-chloro-1-methyl-2-phenyl-ethyl)-1-methyl-urea **4a**-(*e*). Chloroform was removed by evaporation and compound **4a**-(*e*) was refluxed in ethanol for 8 h. After solvent



Scheme 3. Mechanistic pathway involved in the synthesis of compounds **6a**-(*c*) and **6b**-(*c*).



Scheme 4. Mechanistic pathway proposed to explain the formation of compound **12b**-(*c*).

removal, a white solid was isolated whose ^{1}H and ^{13}C NMR spectroscopic data allowed us to identify the *trans*-isomer of 3,4-dimethyl-5-phenyl-oxazolidine-2-iminium chloride **6a**-(*t*). This result showed that the chlorination reaction of ephedrine–urea **5a**-(*e*) was carried out stereoselectively with retention of the C1 configuration, to obtain chlorodeoxyephedrine–urea **4a**-(*e*), which was cyclized with inversion of C1 configuration to obtain **6a**-(*t*). In a similar fashion, the reaction with norephedrine hydrochloride **1b**-(*e*), is stereoselective to give the *cis*-isomer of the oxazoline-2-ammonium chloride **6b**-(*c*). In contrast, the same procedure for pseudoephedrine **1a**-(*th*) and norpseudoephedrine **1b**-(*th*) hydrochlorides, gave a mixture of oxazolidine-2-iminium chlorides **6a** (60:40, *c*:*t*) and oxazoline-2-ammonium chlorides **6b** (75:25, *c*:*t*), respectively.

2.2. Condensation with sodium thiocyanate

It is known[1j] that the condensation reaction of chlorodeoxypseudoephedrine hydrochloride **2a**-(*th*) with 2 M equiv of sodium thiocyanate in refluxing ethanol for 8 h, affords stereoselectively the *trans*-thiazolidine-2-iminio thiocyanate **7a**-(*t*).

When the same reaction was carried out with chlorodeoxynorpseudoephedrine hydrochloride **2b**-(*th*) (R = H), the chloride was changed by thiocyanate anion to give chlorodeoxynorpseudoephedrine hydrothiocyanate **3b**-(*th*) ($v = 2057\ \mathrm{cm}^{-1}$, $^{-}$SCN). The reaction did not proceed further even after 16 h of reflux. If hydrothiocyanate **3b**-(*th*) in DMSO-d_6 is heated in a NMR tube for one hour in a water bath (90 °C), the ^{1}H NMR spectrum showed the presence of a 50:50 *cis*/*trans* mixture of 1,3-thiazoline-2-ammonium thiocyanate **7b**. However, when the reaction is heated solvent free at 170 °C for 3 h, only the *cis*-isomer of **7b** was stereoselectively produced.

2.3. Condensation with potassium selenocyanate

In contrast with the result obtained with NaSCN, when 2 equiv of KSeCN were reacted with chlorodeoxynorpseudoephedrine hydrochloride **2b**-(*th*) for 10 h in refluxing ethanol, *trans*-selenazoline-2-ammonium selenocyanate **9b**-(*t*) was obtained. This result is similar to that reported[1j] for chlorodeoxypseudoephedrine hydrochloride **4a**-(*th*). It is noteworthy that if one equivalent of KOCN, NaSCN, or KSeCN was used in the condensation reactions, the corresponding hydrochloride salts of the 2-aminoheterocycles herein reported are obtained. Both XCN^{-} (X = O, S, Se) and Cl^{-} salts could be liberated with aqueous NaOH to form the corresponding imine **9**–**11a** or amine **9**–**11b** compounds. Following this procedure, compounds **9b**-(*c*) and **11b**-(*t*) were isolated, crystallized from ethanol and chloroform, respectively, to obtain crystals suitable for X-ray analysis. The molecular structures are shown in Figures 4 and 5, respectively.

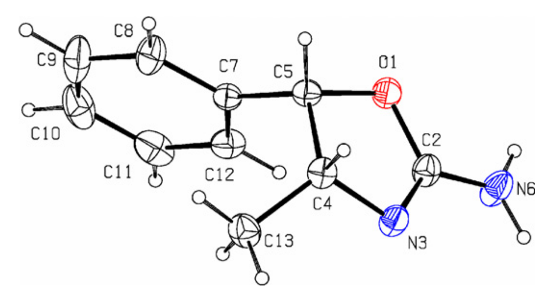


Figure 4. Molecular structure of compound **9b**-(*c*). Selected bond distances in Å are: C4–C5, 1.558(3); O1–C5, 1.450(3); O1–C2, 1.338(3); N3–C4, 1.457(4); N3–C2, 1.280(3); N6–C2, 1.327(4). Selected torsion angles in degrees are: C13–C4–C5–C7, −18.5(4); N3–C4–C5–O1, −15.9(2); N3–C2–O1–C5, −6.6(3); O1–C2–N3–C4, −4.6(3); N6–C2–N3–C4, −176.0(3); N6–C2–O1–C5, −172.8(2).

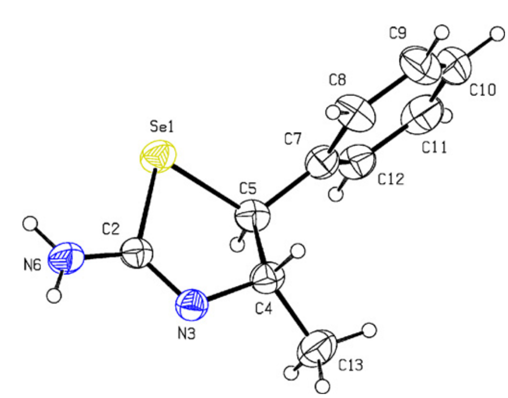


Figure 5. Molecular structure of compound **11b**-(*t*). Selected bond distances in Å are: C4–C5, 1.528(5); Se1–C5, 1.981(4); Se1–C2, 1.929(4); N3–C4, 1.472(5); N3–C2, 1.270(5); N6–C2, 1.337(6). Selected torsion angles in degrees are: C13–C4–C5–C7, −70.9(4); N3–C4–C5–Se1, 41.7(3); N3–C2–Se1–C5, 16.6(3); Se1–C2–N3–C4, 5.5(4); N6–C2–N3–C4, −177.5(4); N6–C2–Se1–C5, −160.7(3).

3. Conclusions

The condensation reaction of chlorodeoxypseudoephedrine hydrochloride **2a**-(*th*) ($R = CH_3$) or **2b**-(*th*) (R = H) with 2 M equiv of the corresponding heterocyanate nucleophiles in refluxing ethanol, afforded the corresponding 1,3-heterazolidine-2-iminium or ammonium heterocyanates **6**–**8**-(*a*,*b*), respectively. The use of 1 M equiv of the nucleophile, led to the corresponding hydrochloride salt.

The condensation reaction of chlorodeoxypseudoephedrine hydrochlorides **2a**,**b**-(*th*) with XCN^- nucleophiles proceeds through the exchange of the chloride anion by XCN^- to form intermediates **3**. The next mechanistic step is determined by the hard–soft nature of the calcogen atom X. When X = O, the intermediates **4a** and**4b** were formed and thermally cyclized via an intramolecular S_N2 mechanism to form compounds **6a**,**b**-(*c*). In the case of the Se atom, a double inversion of C1 configuration was carried out via an aziridine intermediate to obtain **8a**,**b**-(*t*). Finally, when X = S, the reaction also depends on the nature of the R group: if R = H (**3b**) the reaction proceeds through an intermolecular S_N2 mechanism, in contrast, if $R = CH_3$ (**3a**) the mechanism goes through the aziridine intermediate.

The formation of the chloroureidic derivatives **4a**,**b**-(*th*) allowed us to design an alternative method to stereoselectively synthesize the *trans*-isomer of 3,4-dimethyl-5-phenyl-oxazolidine-2-iminium chloride **6a**-(*t*) and the *cis*-isomer of 4-methyl-5-phenyl-oxazoline-2-ammonium chloride **6b**-(*c*), starting from ephedrine hydrochloride **1a**-(*e*) and norephedrine hydrochloride **1b**-(*e*), respectively. In the case of pseudoephedrine and norpseudoephedrine, this method is not stereoselective.

The heterazolidine-2-imines **9a**–**11a** or heterazoline-2-amines **9b**–**11b** were easily liberated from the corresponding salts [Cl^- or XCN^- (X = O, S, Se)] with aqueous NaOH without hydrolysis of the imine group.

The use of anhydrous ethanol is recommended to avoid the hydrolysis of the chlorodeoxypseudoephedrines **2ab** and oxocyanate.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal IA apparatus and are uncorrected. IR spectrums were recorded in a film on ZnSe using a Perkin–Elmer 16F PC IR spectrophotometer. GC/MS data were recorded on an HP 5989A, 5890 series II spectrometer [hydrochloride samples put on a non-polar column (hp1 with methylsilicon phase)]. ^{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 an internal reference following standard techniques. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC: **6a**-(*c*) (627727), **11b**-(*t*) (627726), and **9b**-(*c*) (629322). For these compounds, H atoms were treated as riding atoms, with C–H distances in the range of 0.93 ± 0.96 Å and N–H distances of 0.82 Å. For the water molecule in **6a**-(*c*), O2–H2A 0.98 Å and O2–H2B 0.87 Å. X-ray diffraction cell refinement and data collection: KappaCCD Server Software,[5] DENZO-SMN[6] for **6a**-(*c*); SMART APEX and SAINT[7] for **9b**-(*c*) and **11b**-(*t*); programs used to solve structures: SHELXS-97[8] and SHELXL-97;[8] software used to prepare material for publication: PLATON[9] and *WinGX*.[10]

4.2. (1*R*,2*R*)-1-(2-Chloro-1-methyl-2-phenyl-ethyl)-1-methyl-urea 4a-(*th*)

Chlorodeoxypseudoephedrine hydrochloride **2a**-(*th*) (1.0 g, 4.54 mmol), KNCO (0.37 g, 4.56 mmol), and 50 mL of ethanol were added into a 100 mL flask and the mixture was stirred for 12 h at room temperature. The resulting suspension was cooled in an ice bath until all the KCl was precipitated. It was then filtered and the ethanol eliminated in vacuo to obtain a gummy product: the NMR spectra data showed the urea derivative as the main product (90%): ^{1}H NMR [δ ppm, DMSO-d_6]: 7.20–7.40 (m, 5H, Ph), 5.90 (s, 2H, NH_2), 5.13 (d, 1H, $^3J = 10.27$ Hz, C1–H), 4.70 (br, 1H, C2–H), 2.70 (s, 3H, N–CH_3), 0.75 (d, 3H, $^3J = 6.75$ Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 159.5 (C=O), 140.4 (C*i*), 129.4 (C*o*), 129.2 (C*p*), 129.2 (C*m*), 65.5 (C1), 55.0 (br, C2), 30.3 (N–CH_3) 16.0 (C2–CH_3).

4.3. (1*S*,2*R*)-(−)-*cis*-3,4-Dimethyl-5-phenyl-oxazolidin-2-iminium chloride 6a-(*c*)

Chlorodeoxypseudoephedrine hydrochloride **2a**-(*th*) (1.0 g, 4.54 mmol), KOCN (0.37 g, 4.56 mmol), and 50 mL of ethanol were added into a 100 mL flask. The resulting mixture was refluxed for 16 h. The resulting suspension was cooled in an ice bath until all KCl was precipitated and filtered off. A white solid crystallized from ethanol to give 0.85 g of **6a**-(*c*) (82.5% yield), mp 198–200 °C. ^{1}H NMR [δ, ppm, DMSO-d_6]: 9.71 (br, 2H, NH_2), 7.30–7.50 (m, 5H, Ph), 6.20 (d, 1H, $^3J = 8.80$ Hz, C5–H), 4.50 (dq, 1H, C4–H); 0.74 (d, 6.8 Hz, C4–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 160.4 (C2=N), 133.3 (C*i*), 128.6 (C*o*), 129.1 (C*p*), 128.3 (C*m*), 83.9 (C5), 59.3 (C4), 29.8 (N–CH_3); 13.6 C4–CH_3. ν_{IR} (cm^{-1}, KBr) = 3374, 3320 (NH), 1708 (C=N). $Z/e = 190$ (25.6%) [M^+–HCl]. $[\alpha]_D = -105.0$ (c 2.0×10^{-4} g/mL, methanol).

4.4. (1*S*,2*R*)-(−)-*cis*-3,4-Dimethyl-5-phenyl-oxazolidin-2-imine 9a-(*c*)

cis-2-Iminium chloride **6a**-(*c*) (1.0 g, 4.42 mmol) was treated with 1 M equiv of NaOH solution and stirred for 15 min. Compound **9a**-(*c*) was extracted three times with 10 mL of $CHCl_3$. The organic phase was dried over Na_2SO_4 and the solvent evaporated in vacuo to afford 0.78 g of a white solid (93% yield), mp 96–98 °C. ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.20–7.30 (m, 5H, Ph), 5.49 (d, 1H, $^3J = 7.62$ Hz, C5–H), 3.95 (dq, 1H, C4–H); 4.82 (br, 1H, NH), 2.89 (s, 3H, N–CH_3), 0.77 (d, 3H, $^3J = 6.70$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 161.1 (C2=N), 135.7 (C*i*), 128.2 (C*o*), 128.1 (C*p*), 126.1 (C*m*), 79.7 (C5), 58.5 (C4), 29.90 (N–CH_3);

13.6 C4–CH_3. ν_{IR} (cm^{-1}, KBr): 3484 (NH), 1749, (C2=N). $Z/e = 190$ (23.0%) [M^+]. $[\alpha]_D = -120.0$ (c 2.0×10^{-4} g/mL, chloroform).

4.5. (1*R*,2*R*)-(−)-*trans*-3,4-Dimethyl-5-phenyl-oxazolidin-2-iminium chloride 6a-(*t*)

Ephedrine hydrochloride **1a**-(*e*) (1.0 g, 4.96 mmol), KOCN (0.41 g, 5.05 mmol), and 50 mL of ethanol were added into a 100 mL flask. The resulting mixture was refluxed for 10 h. The resulting suspension was cooled in an ice bath. Precipitated KCl was filtered off and ethanol eliminated in vacuo. Compound **4a**-(*t*) was crystallized from ethanol to obtain 0.93 g of ephedrine–urea **5a**-(*th*) (90% yield). Ephedrine–urea (1.0 g, 4.8 mmol), 10 mL $CHCl_3$, and $SOCl_2$ (0.686 g, 5.77 mmol) were added into a 100 mL flask, the resulting mixture was stirred for 4 h at room temperature. Chloroform was eliminated in vacuo and 5.0 mL of ethanol was added to reflux the solution for 8 h. Ethanol was removed in vacuo and the reaction mixture was suspended in ketone. The resulting suspension was cooled in an ice bath until the product was completely precipitated as a white solid. The solid was filtered off and washed three times with cold acetone. It was then crystallized from ethanol to give 0.95 g of **6a**-(*t*) (87% yield), mp 194–196 °C. ^{1}H NMR [δ, ppm, DMSO-d_6]: 9.71 (br, 2H, NH_2), 7.40–7.50 (m, 5H, Ph), 5.56 (d, 1H, $^3J = 8.79$ Hz, C5–H), 4.07 (dq, 1H, C4–H), 3.09 (s, 3H, N–CH_3), 1.30 (d, 3H, $^3J = 6.44$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 161.0 (C2=N), 135.4 (C*i*), 129.61 (C*o*), 130.6 (C*p*), 128.2 (C*m*), 88.38 (C5), 63.6 (C4), 30.2 (N–CH_3), 16.0 (C4–CH_3). ν_{IR} (cm^{-1}, KBr): 3339 (NH), 1719 (C2=N). $Z/e = 190$ (33.9%) [M^+–HCl]. $[\alpha]_D = -15.0$ (c 2.0×10^{-4} g/mL, methanol).

4.6. (1*R*,2*R*)-(−)-*trans*-3,4-Dimethyl-5-phenyl-oxazolidin-2-imine 9a-(*t*)

trans-2-Iminium chloride **6a**-(*t*) (1.0 g, 4.41 mmol) was liberated with NaOH aqueous solution as **6a**-(*c*) to get (0.79 g, 95% yield) of the corresponding 2-imine compound **9a**-(*t*) as a viscous liquid. ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.10–7.30 (m, 5H, Ph), 4.62 (d, 1H, $^3J = 8.50$ Hz, C5–H), 3.21 (dq, 1H, C4–H), 4.33 (br, 1H, NH), 2.68 (s, 3H, N–CH_3), 1.09 (d, 3H, $^3J = 6.15$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 161.4 (C2=N), 137.4 (C*i*), 128.9 (C*o*), 129.1 (C*p*), 126.4 (C*m*), 84.4 (C5), 63.2 (C4), 30.1 (N–CH_3), 16.5 (C4–CH_3). ν_{IR} (cm^{-1}, KBr), 3491.2 (NH), 1748.5 (C=N). $Z/e = 190$ (44.1%) [M^+]. $[\alpha]_D = -5.0$ (c 2.04×10^{-4} g/mL, chloroform).

4.7. (1*R*,2*R*)-(−)-(2-Chloro-1-methyl-2-phenyl-ethyl)-urea 4b-(*th*)

Chlorodeoxynorpseudoephedrine hydrochloride **2b**-(*th*) (1.0 g, 4.85 mmol), KNCO (0.40 g, 4.93 mmol), and 50 mL of ethanol were added into a 100 mL flask and the mixture refluxed for 8 h. The resulting suspension was cooled in an ice bath. KCl was filtered off and ethanol eliminated in vacuo. Chloroform was added and chlorourea **4b**-(*th*) precipitated. The solid was filtered and washed with cold chloroform to obtain 0.91 g (88.3% yield) of white crystals, mp 125–127 °C. ^{1}H NMR [δ ppm, DMSO-d_6]: 7.30–7.40 (m, 5H, Ph), 6.04 (d, 1H, $^3J = 8.51$ Hz, NH), 5.55 (s, 2H, NH_2), 5.16 (d, 1H, $^3J = 5.28$ Hz, C1–H), 4.11 (dq, 1H, C2–H), 1.00 (d, 3H, $^3J = 6.75$, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 158.6 (C=O), 139.6 (C*i*), 128.8 (C*o*), 128.8 (C*p*), 128.5 (C*m*), 65.4 (C1), 51.06 (C2), 19.0 (C2–CH_3). ν_{IR} (cm^{-1}, KBr) 1658.1 (C=O). $[\alpha]_D = -45.0$ (c 2.02×10^{-4} g/mL, methanol).

4.8. (1*S*,2*R*)-*cis*-4-Methyl-5-phenyl-oxazoline-2-ammonium chloride 6b-(*c*)

Following the same procedure as the synthesis of **6a**-(*t*) for 1.0 g, (5.33 mmol) of pseudoephedrine hydrochloride **2b**-(*th*). The solid was crystallized from ethanol to get 0.82 g (72.5%) of **6b**-(*c*). Mp 134–136 °C; $Z/e = 176$ (42.3%) [M^+]; $[\alpha]_D = -200$ (c 2.0×10^{-4} g/mL, chloroform). ^{1}H NMR, δ (ppm), DMSO-d_6: 9.50 (br, 3H, NH_3), 7.30–7.40 (m, 5H, Ph), 6.18 (d, 1H, $^3J = 8.50$ Hz, C5–H), 4.53 (dq, 1H, C4–H), 0.71 (d, 3H, $^3J = 6.44$, C2–CH_3). ^{13}C NMR: 162.2 (C2=N), 134.0 (C*i*), 129.3 (C*o*), 129.6 (C*p*), 126.9 (C*m*), 86.1 (C5), 55.0 (C4), 17.0 (C4–CH_3).

4.9. (1*S*,2*R*)-*cis*-4-Methyl-5-phenyl-oxazoline-2-ammonium chloride 6b-(*c*) (80%) and (1*R*,2*S*)-*cis*-5-methyl-4-phenyl-oxazoline-2-ammonium chloride 12b-(*c*) (20%)

Following the same amount of substances for **4b**-(*th*) and refluxing for 24 h, 0.72 g (70% yield) of white crystals were obtained. The NMR spectra showed a mixture of compounds **6b**-(*c*)/**12b**-(*c*) in a 80:20 proportion, respectively. For **12b**-(*c*): ^{1}H NMR [δ, ppm, DMSO-d_6]: 9.46 (br, 3H, NH_3), 7.20–7.50 (m, 5H, Ph), 5.42 (dq, 1H, C4–H), 5.31 (d, 1H, $^3J = 8.50$ Hz, C5–H), 0.87 (d, 3H, $^3J = 6.44$, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 163.0 (C2=N), 135.9 (C*i*), 129.4 (C*o*), 129.6 (C*p*), 127.8 (C*m*), 83.9 (C5), 61.2 (C4), 16.3 (C4–CH_3).

4.10. (1*S*,2*R*)-(−)-*cis*-4-Methyl-5-phenyl-oxazoline-2-amine 9b-(*c*) (80%) and (1*R*,2*S*)-*cis*-5-methyl-4-phenyl-oxazoline-2-amine 13b-(*c*) (20%)

The mixture of compounds **6b**-(*c*) and **12b**-(*c*) were liberated as described for **6a**-(*c*) to give a mixture of **9b**-(*c*) and **13b**-(*c*) as a white solid. For **9b**-(*c*): ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.20–7.4 (m, 5H, Ph), 5.58 (d, 1H, $^3J = 8.79$ Hz, C5–H), 4.95 (br, 2H, NH_2), 4.35 (dq, 1H, C4–H), 0.72 (d, 3H, $^3J = 6.74$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 160.4 (C2=N), 137.3 (C*i*), 128.5 (C*o*), 128.0 (C*p*), 126.2 (C*m*), 84.7 (C5), 63.1 (C4), 18.7 C4–CH_3. ν_{IR} (cm^{-1}, KBr): 3429 (NH), 1698.5 C=NH_2. $Z/e = 176$ (42.3%) [M^+]. For **13b**-(*c*): ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.20–7.4 (m, 5H, Ph), 5.11 (d, 1H, $^3J = 8.79$ Hz, C5–H), 4.95 (br, 1H, NH), 4.95 (dq, 1H, C4–H), 0.85 (d, 3H, $^3J = 6.44$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 162.0 (C2=N), 139.9 (C*i*), 128.3 (C*o*), 127.4 (C*p*), 127.7 (C*m*), 80.3 (C5), 70.0 (C4), 17.0 (C4–CH_3). $Z/e = 176$ (42.3%) [M^+].

4.11. (1*R*,2*R*)-*trans*-4-Methyl-5-phenyl-oxazoline-2-ammonium chloride 6b-(*t*)

Following the same procedure as for **6a**-(*t*) by using (1.0 g, 5.27 mmol) of norpseudoephedrine to give a 75:25 mixture of *trans*:*cis*-isomers. For compound **6b**-(*t*): ^{1}H NMR [δ, ppm, DMSO-d_6]: 10.33 (br, 3H, NH_3), 7.20–7.30 (m, 5H, Ph), 5.66 (d, 1H, $^3J = 7.91$ Hz, C5–H), 4.16 (dq, 1H, C4–H), 1.39 (d, 3H, $^3J = 6.15$ Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 161.9 (C2=N), 135.9 (C*i*), 129.6 (C*o*), 129.2 (C*p*), 127.6 (C*m*), 90.0 (C5), 59.2 (C4), 19.0 (C4–*C*H_3).

4.12. (1*S*,2*R*)-*cis*-4-Methyl-5-phenyl-thiazoline-2-ammonium chloride 7b-(*c*)

Chlorodeoxynorpseudoephedrine hydrochloride **2b**-(*th*) (1.0 g, 4.85 mmol) and NaSCN (0.4 g, 4.94 mmol) were added into a 100 mL flask. The resulting mixture was heated solvent free at 170 °C for 3 h. The resulting mixture was cooled and 10 mL of ethanol added. The resulting suspension was poured onto an ice bath. NaCl was filtered off and washed with cold ethanol, which was eliminated in vacuo to give 0.91 g (82% yield) of **7b**-(*c*) as a gummy product. ^{1}H NMR [δ, ppm, DMSO-d_6]: 9.90 (br, 3H, NH_3), 7.30–7.40 (m, 5H, Ph), 5.27 (d, 1H, $^3J = 7.03$ Hz, C5–H), 4.55 (dq, 1H, C4–H), 0.84 (d, 3H, $^3J = 6.44$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 172.1 (N=C2), 135.9 (C*i*), 129.3 (C*o*), 129.2 (C*p*), 126.0 (C*m*), 61.1 (C4), 54.5 (C5), 16.1 (C4–*C*H_3). ν_{IR} (cm^{-1}, KBr): 3427.2 (NH), 1654.0 (C=N), and $Z/e = 192$ (42.3%) [M$^+$–HCl].

4.13. (1*S*,2*R*)-(−)-*cis*-4-Methyl-5-phenyl-thiazoline-2-amine 10b-(*c*)

cis-Thiazoline-2-iminium chloride **7b**-(*c*) (1.0 g, 4.37 mmol) was liberated as described for **6a**-(*c*) to get 0.79 g (94% yield) of the corresponding 2-amine compound **10b**-(*c*) as an amber solid, mp 90–93 °C. ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.20–7.40 (m, 5H, Ph), 5.28 (br, 2H, NH_2), 4.88 (d, 1H, $^3J = 7.32$ Hz, C5–H), 4.49 (dq, 1H, C4–H), 0.93 (d, 3H, $^3J = 6.74$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 161.3 (C2=N), 138.4 (C*i*), 128.6 (C*o*), 128.0 (C*p*), 128.5 (C*m*), 70.8 (C4), 60.6 (C5), 17.6 (C4–CH_3). $Z/e = 192$ (100%) [M$^+$]. $[\alpha]_D = -75.0$ (c 2.0×10^{-4} g/mL, chloroform).

4.14. (1*R*,2*R*)-(−)-*trans*-4-Methyl-5-phenyl-thiazoline-2-ammonium chloride 7b-(*t*)

Following the same amount of substances for **7b**-(*c*) and refluxing for 4 h in DMSO on a water bath gave a 50:50 mixture of *cis*/*trans*-isomers, for *trans*-isomer: ^{1}H NMR [δ, ppm, DMSO-d_6]: 10.11 (br, 3H, NH_3), 7.30–7.40 (m, 5H, Ph), 4.95 (d, 1H, $^3J = 7.03$ Hz, C5–H), 4.31 (dq, 1H, C4–H), 1.25 (d, 3H, $^3J = 6.15$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 170.9 (N=C2), 137.5 (C*i*), 129.3 (C*o*), 129.2 (C*p*), 128.5 (C*m*), 64.7 (C4), 57.7 (C5), 18.9 (C4–*C*H_3).

4.15. (1*R*,2*R*)-*trans*-4-Methyl-5-phenyl-thiazoline-2-amine 10b-(*t*)

Compound **10b**-(*t*) was assigned from a mixture of amines liberated form the *cis*/*trans* mixture of **7b** with NaOH as the same procedure described for **6a**-(*c*). ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.20–7.40 (m, 5H, Ph), 5.28 (br, 2H, NH_2), 4.56 (d, 1H, $^3J = 7.25$ Hz, C5–H), 4.28 (dq, 1H, C4–H), 1.27 (d, 3H, $^3J = 6.74$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 159.5 (C2=N), 140.3 (C*i*), 128.7 (C*o*), 127.9 (C*p*), 128.5 (C*m*), 76.1 (C4), 64.6 (C5), 20.7 (C4–*C*H_3).

4.16. (1*S*,2*S*)-(−)-*trans*-4-Methyl-5-phenyl-selenazoline-2-ammonium chloride 8b-(*t*)

Chlorodeoxynorpseudoephedrine hydrochloride **2b**-(*th*) (1.0 g, 4.85 mmol) and KSeCN (0.7 g, 4.86 mmol) were added into a 100 mL flask and refluxed in ethanol for 12 h, or stirring for 2 weeks, to give 0.98 g (73.3% yield) of an amber solid: ^{1}H NMR [δ, ppm, DMSO-d_6]: 9.80 (br, 3H, NH_3), 7.30–7.40 (m, 5H, Ph), 4.90 (d, 1H, $^3J = 7.62$ Hz, C5–H), 4.37 (dq, 1H, C4–H), 1.39 (d, 3H, $^3J = 6.45$, C4–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 171.2 (C2=N), 137.7 (C*i*), 129.4 (C*o*), 129.0 (C*p*), 128.3 (C*m*), 65.2 (C4), 55.3 (C5), 19.0 (C4–*C*H_3). ν_{IR} (cm^{-1}, KBr): 1658.1 (C2=N).

4.17. (1*S*,2*S*)-(−)-*trans*-4-Methyl-5-phenyl-selenazoline-2-amine 11b-(*t*)

trans-Selenazoline-2-ammonium chloride **8b**-(*t*) (1.0 g, 3.63 mmol) was liberated as described for **6a**-(*c*) to give 0.82 g (94.5% yield) of the corresponding 2-amine compound **10b**-(*c*) as an amber solid, mp 137–138 °C. ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.20–7.50 (m, 5H, Ph), 5.00 (br, 2H, NH_2), 4.95 (d, 1H $^3J = 7.32$ Hz, C5–H), 4.36 (dq, 1H, C4–H), 1.27 (d, 3H, $^3J = 6.44$ Hz, C4–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 154.3 (C2=N), 140.9 (C*i*), 129.0 (C*o*), 127.8 (C*p*), 128.2 (C*m*), 76.9 (C4), 64.4 (C5), 20.1 (C4-*C*H_3). ν_{IR} (cm^{-1}, KBr), 3427.2 (NH), 1625.8 (C=N), and $[\alpha]_D = -120.0$ (c 2.0×10^{-4} g/mL, chloroform).

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