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Chlorination reactions of ephedrines revisited. Stereochemistry and functional groups effect on the reaction mechanisms †

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Abstract

The stereochemistry of the chlorination reactions with $SOCl_2$ of free ephedrine and pseudoephedrine and their hydrochlorides, oxamides and sulfonamides was analyzed. Chlorination of free and hydrochloride erythro isomers occurs with 100% inversion of configuration at C-1 (S_N2 mechanism). Chlorination of oxamides and sulfonamides of erythro isomers occurs with retention of the configuration at C-1, (S_Ni mechanism). Chlorination reactions in all threo isomers and derivatives hydrochlorides, oxamides or sulfonamides gave the same ratio of erythro (40%) and threo isomers (60%) (S_N1 mechanism). Treatment of the isomeric mixture of the chlorodeoxyephedrine and chlorodeoxypseudoephedrine hydrochloride in DMSO with HCl changes the isomeric ratio, increasing the erythro isomer content (65%). Using the erythro ethanolamines it is possible to arrive stereoselectively at the erythro chloroamines if the compound is previously tosylated or converted to the amide, or to the threo chloroamines if the compound is directly chlorinated with $SOCl_2$.

1. Introduction

Ephedrines are very important substances in asymmetric synthesis; they are also widely used as building elements for heterocycles and, as organometallic or metallic complexes, used as reagents or catalytic agents in organic chemistry.[1–3] We are currently studying the synthesis of ligands derived from ephedrines which are used for the preparation of optically active boron or phosphorous derivatives.[4–22] We are especially interested in the synthesis of ligands bearing amide groups, which have an acidic N–H

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† Dedicated to the memory of Professor Sir Derek H. R. Barton.

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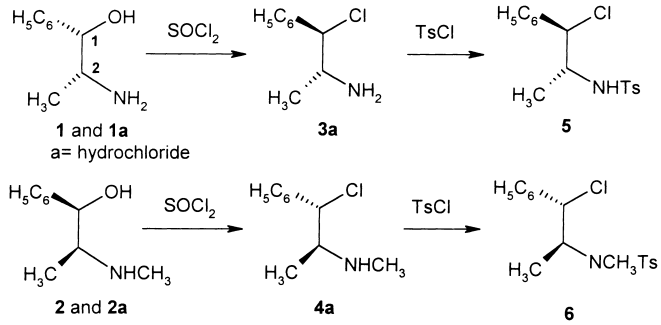


Fig. 1.

proton, easily substituted by hetero- or metallic atoms to give heterocycles.[17,19,23] Herein, we describe the stereochemistry of the synthesis of a series of chlorodeoxyephedrines, chlorodeoxysulfonamides and bis-chlorodeoxyephedrine oxamides, which are versatile intermediates for many other optically active ligands. During the preparation of these compounds, we discovered that chlorination reactions with thionyl chloride gave different results depending on the isomer used, pseudoephedrine or ephedrine, and on the nitrogen substitution.[24–26] Herein, we discuss our results which attempt to give some explanation of the mechanisms.

It has been reported that chlorination reactions of aliphatic alcohols with $SOCl_2$ in the presence of a base afford the corresponding chlorides with inversion of configuration, this fact has been explained by an S_N2 mechanism,[27] whereas in the absence of base, the configuration of the carbon atom is retained, and an S_Ni mechanism has been proposed.[27] Chlorination reactions with $SOCl_2$ of the ephedrines are reported,[24–26,28] but a clear picture of the behavior of these isomers in the reaction has not yet emerged. Therefore, we decided to investigate the behavior of the ephedrine isomers and the nitrogen substitution effect under comparable conditions.

2. Results and discussion

We have reacted free norephedrine **1**, its hydrochloride **1a** (1*S*,2*R*), ephedrine **2** and its hydrochloride **2a**[21] (1*S*,2*R*) with $SOCl_2$ in the absence of solvent and base: the corresponding chlorodeoxynorpseudoephedrine **3a** (1*R*,2*R*) or chlorodeoxypseudoephedrine **4a** (1*R*,2*R*) hydrochlorides were formed with 100% inversion at C-1 (Fig. 1). The X-ray diffraction structures of **3a** and **4a**[21] confirmed the stereochemistry (Fig. 2). Compounds **3a** and **4a** were tosylated to give **5** and **6**, respectively; their structures were determined by X-ray methods (Fig. 3).

In the molecular structure of compound **3a**, we have found that the molecule adopts the staggered conformation and the dihedral angle H1–C1–C2–H2 is 177.9°. The chlorine and nitrogen atoms are present in a gauche position due to hydrogen bonding between the N–H and the chlorine atom, Cl1–H distance is 2.54 Å. In the lattice there are intermolecular hydrogen bonds between the N–H atoms and the chloride as shown in Fig. 2b.

Compound **5** presents a staggered conformation, the chlorine and the nitrogen atoms are in gauche positions and the dihedral angle H1–C1–C2–H2 is 64.6° (Fig. 3a). This conformation is stabilized by five hydrogen bonds in five-membered rings (H17–C17–C12–C1–Cl1, H17–Cl1 distance is 2.47 Å; Cl1–C1–C2–N4–H4, Cl1–H4 distance is 2.89 Å; H2–C2–N4–S1–O1, H2–O1 distance is 2.59 Å; O1–S1–C5–C10–H10, O1–H10 distance is 2.61 Å; O2–S1–C5–C6–H6, O2–H6 distance is 2.66 Å).

Compound **6** was crystallized from chloroform and its structure was determined by X-ray diffraction.

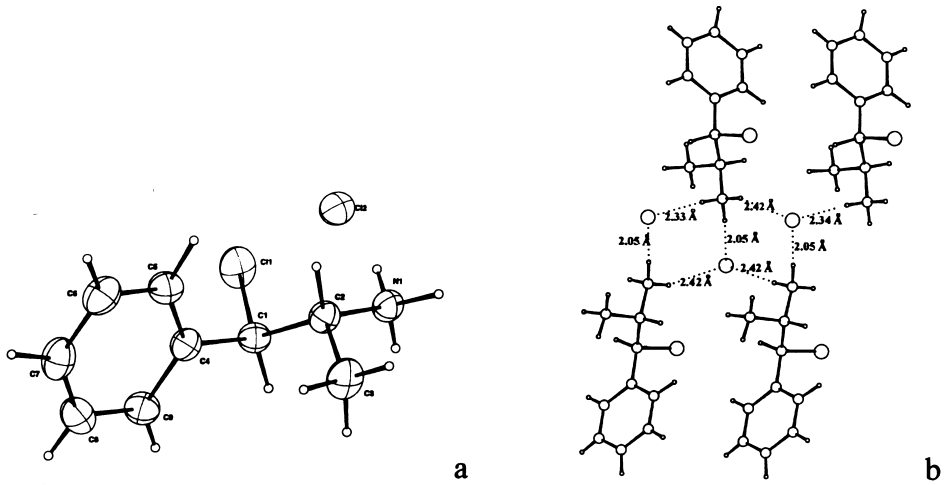


Fig. 2. (a) Molecular structure of **3a**; (b) intermolecular hydrogen bonds of **3a**

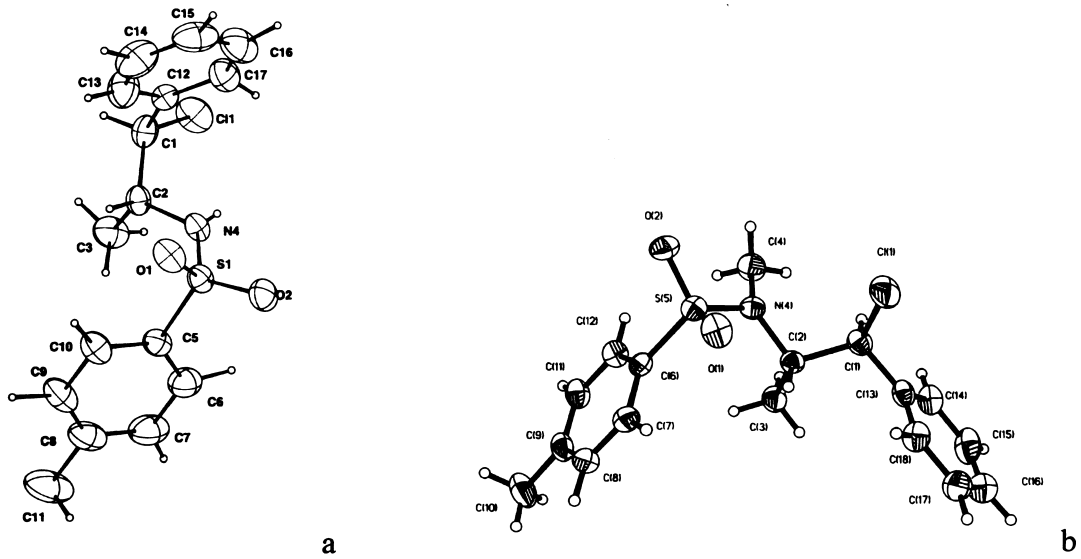


Fig. 3. Molecular structure of (a) compound **5**; (b) compound **6**

It is present in the lattice as a staggered conformer with a gauche conformation of Cl1–C1–C2–N4. The dihedral angles are Cl–C1–C2–N4 54.79° and H1–C1–C2–H2 179.76°. There are four hydrogen bond interactions: H2–C2–N4–S5–O1, H2–O1 distance is 2.49 Å; O1–S5–C6–C7–H7, O1–H7 distance is 2.50 Å; O2–S5–N4–C4–H4, O2–C4 distance is 2.58 Å; O2–S5–C6–C12–H12, O2–H12 distance is 2.83 Å (Fig. 3).

Chlorination of pseudoephedrine **7** and pseudoephedrine hydrochloride **7a** (1*S*,2*S*) with $SOCl_2$ afforded an isomeric mixture: 40% of the chlorodeoxyephedrine hydrochloride **8a** (1*R*,2*S*) and 60% of chlorodeoxypseudoephedrine hydrochloride **4a** (1*S*,2*S*) (Fig. 4). If this mixture of **4a** and **8a** is acidified (50 mg of the ephedrine mixture in 0.5 ml of DMSO-d_6 and 1 ml of concentrated HCl), after five hours the isomer ratio has changed to 65:35 of **8a**:**4a** respectively, and no additional change was noted after one week.

We have looked for an explanation of these apparently contradictory results and, therefore, we have

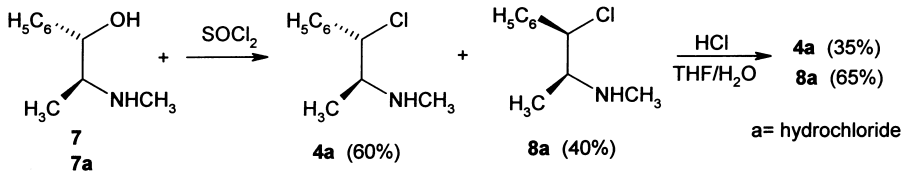


Fig. 4.

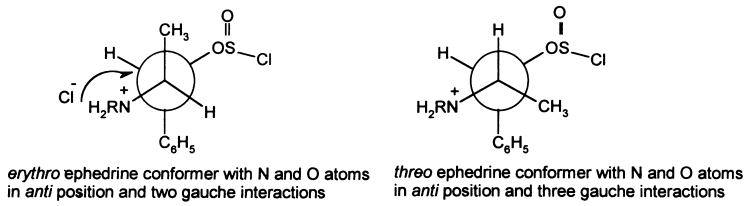


Fig. 5.

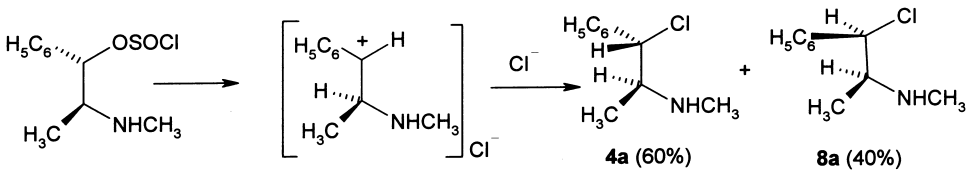


Fig. 6.

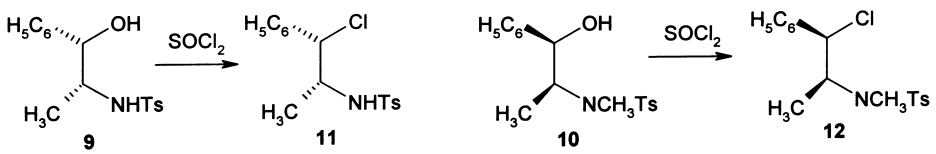


Fig. 7.

analyzed the conformers of the chlorosulfite ester intermediates resulting from the reaction of the ephedrines and $SOCl_2$. It has been found that for the ephedrine isomer the conformer that has the ammonium group *anti* to the sulfite is the more stable one with only two gauche interactions. In this conformer, the ammonium protons give assistance to the chloride approach in an S_N2 mechanism leading to a total inversion at C-1. An aziridine intermediate can be ruled out because it is not a basic medium, and we have not observed the isomeric mixture which could come from the chloride attack on C-1 or C-2 carbon atoms of the aziridine.[28] In the pseudoephedrine family the conformer with the nitrogen atom *anti* to the sulfite is not the most stable and an S_N2 mechanism is therefore not favored (Fig. 5).

The constant isomeric ratio found in the chlorination reactions of different pseudoephedrine derivatives (*vide infra*) indicates that dissociation into a carbonium ion and the sulfite anion occurs prior to the chloride attack. Under these conditions, the chloride can attack either of the two faces of the benzylic carbonium group affording the two isomers **4a** and **8a** (Fig. 6).

2.1. Chlorination of amides derived from ephedrine

An interesting fact is that the chlorination reaction by $SOCl_2$ of the tosylamide derived from the (+)-norephedrine **9** (1*S*,2*R*) or (−)-ephedrine **10** (1*R*,2*S*) produces the corresponding chlorides **11** and **12** respectively with 100% retention of configuration. The S_N2 mechanism does not work here because there is no assistance to the chloride approach, but an S_Ni chlorination is possible (Fig. 7).

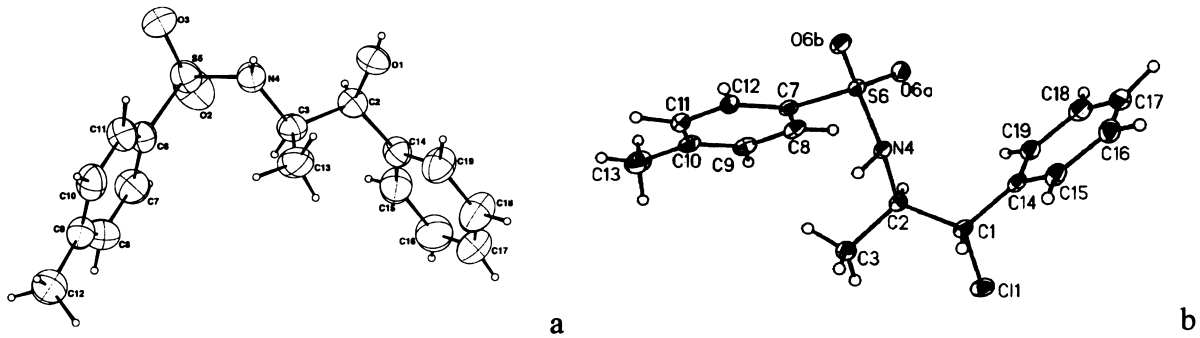


Fig. 8. Molecular structure of (a) compound **9**; (b) compound **11**

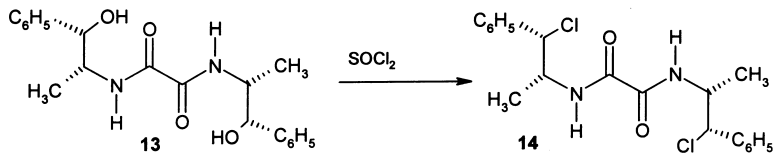


Fig. 9.

Figure 8a presents the molecular structure of the erythro compound **9**. The conformer in this structure has the O1 and N4 and phenyl and methyl groups in gauche positions, respectively. The dihedral angles O1–C2–C3–N4 and H3–C3–C2–H2 are 57.5° and 58.0°. The structure is stabilized by six hydrogen bonds in five-membered rings O1–C2–C3–N4–H4, O1–H4 distance is 2.71 Å; O1–C2–C14–C19–H19, O1–H19 distance is 2.44 Å; O1–C2–C3–C13–H13, O1–H13 distance is 2.62 Å; O2–S5–N4–C3–H3, O2–H3 distance is 2.64 Å; O2–S5–C6–C7–H7, O2–H7 distance is 2.40 Å; O3–S5–C6–C11–H11, O3–H11 distance is 2.76 Å.

Compound **11** was crystallized from MeOH and its structure was determined by X-ray diffraction (Fig. 8b). Compound **11** in the solid state shows a different conformation to compound **9**. The staggered conformer has the chloride and the nitrogen atoms in anti-positions, the torsion angle for Cl–C1–C2–N4 is 175.2° and for C3–C2–C1–C14 is 174.9°. The structure has four hydrogen bonds H12–C12–C7–S6–O6b, H12–O6b distance is 2.60 Å; H8–C8–C7–S6–O6a, H8–O6a distance is 2.55 Å; Cl1–C1–C14–C19–H19, Cl1–H19 distance is 2.34 Å and Cl1–C1–C2–C3–H3, Cl1–H3 distance is 2.78 Å.

The same stereochemical behavior of the chlorination with $SOCl_2$ in CH_2Cl_2 at rt, was found in the bis-ephedrine oxamide **13** derived from norephedrine which gave the bis-chloro derivative **14** with total retention of configuration at C-1 (Fig. 9).

2.2. Chlorination of amides derived from pseudoephedrine

Pseudoephedrine **7** (1*S*,2*S*) has been tosylated to give compound **15**. The chlorination reaction of pseudoephedrine N-tosylate **15** (1*S*,2*S*) with $SOCl_2$ in the absence of base, gave 40% of the same isomeric ratio of the corresponding chloro isomers: chlorodeoxypseudoephedrine **6** (1*S*,2*S*, 60%) and compound **16** (1*R*,2*S*, 40%) (Fig. 10).

Figure 11 presents the molecular structure of compound **15**. The staggered conformation has O1 and N atoms in gauche positions and the dihedral angles are O1–C1–C2–N4 75.63° and H1–C1–C2–H2 50.83°. This molecule is also stabilized by hydrogen bonds, there is one hydrogen bond in a six-membered ring O1–C1–C2–N4–C5–H5, bond distance O1–H5 is 2.25 Å, and five hydrogen bonds in five-membered

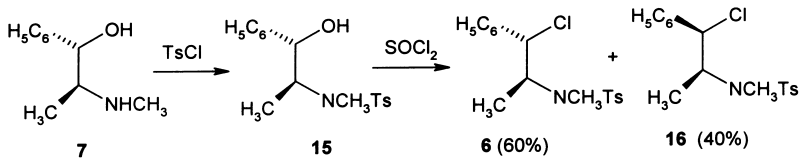


Fig. 10.

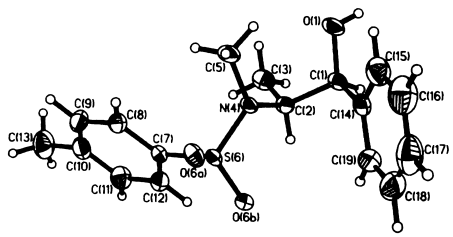


Fig. 11. Perspective representation of compound **15**

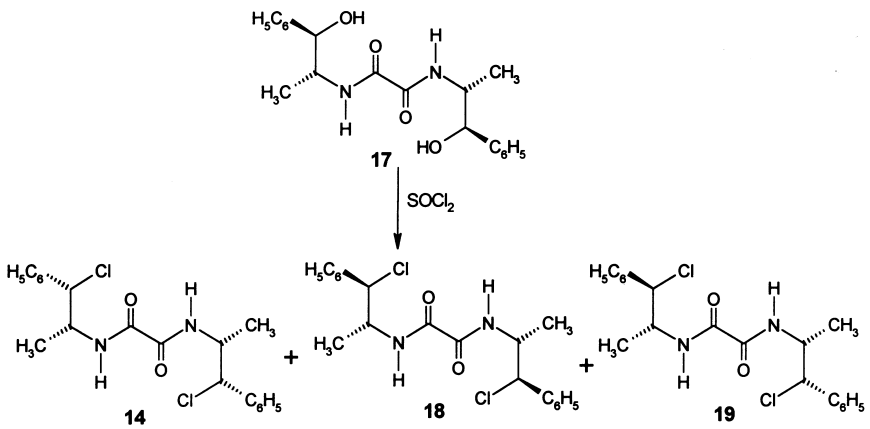


Fig. 12.

rings: O1–C1–C14–C15–H15, distance O1–H15 is 2.39 Å; O6b–S6–N4–C2–H2, distance is 2.35 Å; O6b–S6–C7–C12–H12, distance O6b–H12 is 2.53 Å; O6a–S6–N4–C5–H5 distance O6a–H5 is 3.09 Å; O6a–S6–C7–C8–H8, distance O6a–H8 is 2.69 Å.

The same stereochemical behavior of the chlorination as in pseudoephedrine was observed for bis-pseudoephedrine oxamide **17** with $SOCl_2$ in CH_2Cl_2 at rt which gave a mixture of three compounds: **14**, **18** and **19**. Under these reaction conditions the inversion at C-1 was about 40% (Fig. 12).

Compound **18** was crystallized from methanol–acetone, yielding crystals suitable for an X-ray diffraction study, Fig. 13. The structure found shows the threo configuration for the ethylenic chain fragment. The oxamide group has a planar arrangement as is deduced from the dihedral angle of O16–C5–C7–O8, −179°. There are hydrogen bonds between H4–O8 (2.35 Å), H9–O6 (2.28 Å), H3–O6 (2.41 Å) and H10–O8 (2.46 Å). The chain has an alternating conformation. The chlorine atoms are not forming a hydrogen bond with the acidic N–H proton as was found for ephedrine,[19] the dihedral angles between the chlorine and nitrogen atoms are Cl1–C2–C3–N4 53.9°, Cl12–C11–C10–N9 57.8°.

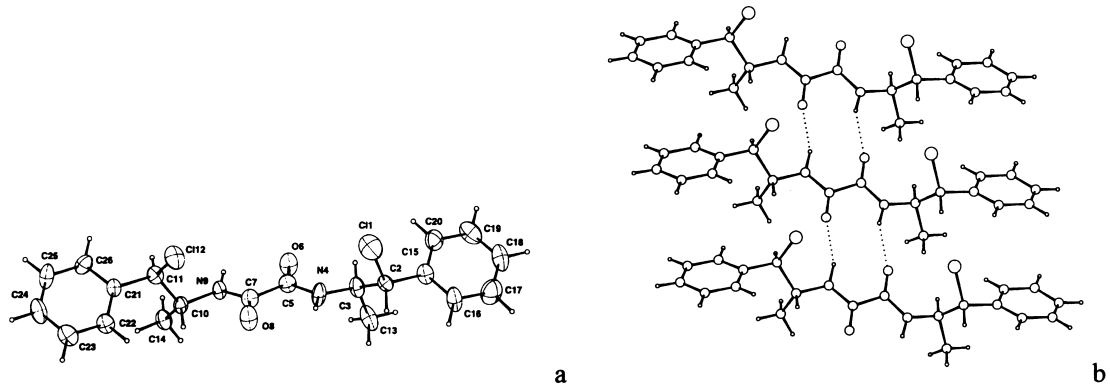
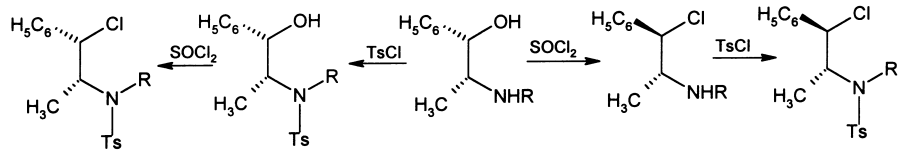


Fig. 13. (a) Molecular structure of compound **18**; (b) view of intermolecular hydrogen bonds in **18**. Each molecule presents four intermolecular hydrogen bonds between N–H and the carbonyl groups, the bond distances marked are around 2.14 Å

3. Conclusions

By analyzing the stereochemistry of the chlorination products important conclusions are evident. If chlorination is performed in the erythro ephedrine series by $SOCl_2$ in the absence of pyridine, a 100% stereoselective formation of the chlorodeoxypseudoephedrine occurs. But if the sulfonamide of the erythro ephedrine is chlorinated configuration at C-1 is retained. When the stereoisomer employed is the pseudoephedrine, the reactions are not selective but it is possible to obtain the chlorodeoxyephedrine as the predominant compound if the chlorinated compounds mixture is treated with HCl.



The X-ray diffraction structures of compounds **3a**, **5**, **6**, **9**, **11**, **15**, and **18** present several hydrogen bonds between the heteroatoms with lone pairs and nonacidic hydrogen atoms which determine the conformer in the lattice. The O–S–O angle in compounds **5** (119.9), **6** (119.3), **9** (119.5), **11** (119.9), **15** (119.2) is very open, and the oxygen atoms approach the phenyl plane favoring hydrogen bonding with *ortho* aromatic protons.

4. Experimental section

^1H and ^{13}C NMR spectra were recorded on a JEOL GXS-270 spectrometer in DMSO-d_6 and $CDCl_3$ solution with TMS as an internal reference. The IR spectra were taken as KBr discs using a Perkin–Elmer 16 F PC IR spectrometer. Mass spectra were obtained on an HP 5989A. Elemental analyses were performed by Oneida Research Services. The optical rotation were obtained on a Perkin–Elmer 241 polarimeter. Melting points were measured on a Gallenkamp apparatus and are uncorrected. Solvents were dried according to literature procedures. The X-ray diffraction experimental data has been deposited at the Cambridge Crystallographic Database.

4.1. Chlorination reactions

4.1.1. (−)-1R,2R-1-Chloro-1-phenyl-2-aminepropane hydrochloride **3a**

To the (+)-1*S*,2*R*-norephedrine **1** (1 g, 6.61 mmol), $SOCl_2$ (1.43 ml, 19.8 mmol) was added. After stirring for 5 h at rt the excess of $SOCl_2$ was removed under vacuum. The white solid obtained was washed with acetone, filtered and recrystallized from CH_3OH (0.76 g, 74%). Mp 205–207°C. IR (KBr, ν cm^{-1}): 3420, 3058, 2996, 2974, 2958, 716, 692. $[\alpha]_D^{33}=-10.4$ (H_2O, c=0.1). ^{13}C NMR ($CDCl_3$): δ=16.1 (C-3), 52.4 (C-2), 64.1 (C-1), 126.1 (C*m*), 127.5 (C*p*), 128.3 (C*o*), 137.3 (C*i*). ^1H NMR ($CDCl_3$): δ=1.13 (d, *J* 6.20, 3H, H-3), 3.91 (qd, *J* 6.2 and 6.6, 1H, H-2), 5.45 (d, *J* 6.6, 1H, H-1), 7.47 (m, 5H). Calcd for $C_9H_{13}NCl_2$, C (52.47), N (6.79), H (6.31); found: C (53.12), N (7.55), H (6.49).

4.1.2. (+)-1S,2S-1-Chloro-1-phenyl-2-(N-methyl)aminepropane hydrochloride **4a**

The same general procedure of chlorination was used for (−)-1*R*,2*S*-ephedrine **2** (3.0 g, 18.1 mmol). The white solid obtained was washed with acetone, filtered and recrystallized from CH_3OH (3.7 g, 94%). Mp 198–200°C. $[\alpha]_D^{30}=+10.5$ (CH_3OH, c=0.1). ^{13}C NMR (DMSO-d_6): δ=13.37 (C-3), 29.68 (CH_3–Ts), 58.78 (C-2), 62.78 (C-1), 128.44 (C*m*), 129.46 (C*p*), 129.74 (C*o*), 137.70 (C*i*). ^1H NMR (DMSO-d_6): δ=1.04 (d, *J* 6.2, 3H, H-3), 2.59 (s, 3H, CH_3–Ts), 3.95 (quint, *J* 6.2 and 9.5, 1H, H-2), 5.46 (d, *J* 9.5, 1H, H-1), 7.5–7.4 (m, 5H), 9.51 (s, br, NH).

4.1.3. N[(+)-1R,2R-1-Chloro-1-phenyl-2-propyl]-p-toluensulfonamide **11**

The same procedure of chlorination was used for **9** (0.6 g, 1.96 mmol). The brown solid obtained was recrystallized from THF/ethanol (0.61 g, 96%). Mp 135–136°C. $[\alpha]_D^{33}=+51.0$ (THF, c=0.1). ^{13}C NMR ($CDCl_3$): δ=15.29 (C-3), 21.62 (CH_3–Ts), 55.44 (C-2), 68.04 (C-1), 127.05, 127.36, 128.41, 128.56, 129.90, 137.64 (C*i*), 137.94 (C*p*–Ts), 143.68 (C*i*–Ts). ^1H NMR ($CDCl_3$): δ=1.0 (d, *J* 6.5, 3H, H-3), 2.39 (s, 3H, CH_3–Ts), 3.71 (dq, *J* 6.5 and 3.4, 1H, H-2), 7.27 (s, 7H, arom.) 7.75 (d, *J* 8.6, 2H, Ts).

4.1.4. N[(−)-1R,2S-1-Chloro-1-phenyl-2-propyl]-N-methyl-p-toluensulfonamide **12**

The same procedure of chlorination was used for **10** (1.0 g, 3.3 mmol). A brown viscous liquid was obtained (1.1 g, 100%). Mp 119–120°C. $[\alpha]_D^{33}=-56.6$ (THF, c=0.1). ^{13}C NMR ($CDCl_3$): δ=135.02 (C-3), 21.53 (CH_3–Ts), 29.67 (NCH_3), 58.17 (C-2), 67.42 (C-1), 127.16 (C*m*–Ts), 127.55 (C*o*), 128.46 (C*p*), 128.59 (C*m*), 129.72 (C*p*–Ts), 137.19 (C*i*), 139.05 (C*p*–Ts), 143.41 (C*i*–Ts). ^1H NMR ($CDCl_3$): δ=1.12 (d, *J* 6.7, 3H, H-3), 2.33 (s, 3H, CH_3–Ts), 2.66 (s, 3H, NCH_3), 4.45 (quint, *J* 6.7, 1H, H-2), 4.97 (d, *J* 6.7, 1H, H-1), 7.1–7.5 (m, 9H, arom).

4.1.5. N[1R,2S-1-Chloro-1-phenyl-2-propyl]-N-methyl-p-toluensulfonamide **16**

The same procedure of chlorination was used for **15** (1.0 g, 3.13 mmol). To the reaction mixture, acetone was added and the mixture was precipitated and filtered. The solution was evaporated and a brown viscous liquid was obtained [0.67 g, **6** (60%) and **16** (40%)]. Data for compound **16**: ^{13}C NMR ($CDCl_3$): δ=12.91 (C-3), 21.54 (CH_3–Ts), 58.13 (C-2), 67.47 (C-1). ^1H NMR ($CDCl_3$): δ=1.50 (d, *J* 7.3, 3H, H-3), 2.38 (s, 3H, CH_3–Ts), 4.08 (dd, *J* 7.3 and 6.6, 1H, H-2), 5.02 (d, *J* 6.6, 1H, H-1).

4.2. Synthesis of oxamides

4.2.1. *N,N′-Bis[1*S*,2*R*-norephedrine]oxamide **13**

A mixture of (+)-1*S*,2*R*-norephedrine (9.8 g, 64.8 mmol) and diethyl oxalate (4.4 ml, 32.4 mmol) was refluxed in 60 ml of toluene for 3 hours. A white solid was formed which was separated by filtration (11.4 g, 98%). $[\alpha]_D$=−39.7 (DMSO, c 1.4).

4.2.2. *N,N′-Bis[1*R*,2*R*-norpseudoephedrine]oxamide **17**

$[\alpha]_D$=−47.8 (DMSO, c 1.6).

4.2.3. *N,N′-Bis[1-chloro-1-phenylpropyl]oxamide **14***

A solution of **13** (5 g, 14 mmol) and $SOCl_2$ (3.1 ml, 42 mmol) in CH_2Cl_2 (70 ml) was stirred for 48 h. The reaction afforded a white solid which was washed with acetone/hexane (5 g, 91%). Mp 215–216°C. $[\alpha]_D$=+67.6 (DMSO, c 1.4). IR (KBr, ν cm^{-1}): 3442, 3308, 3192, 2936, 1656, 1508, 1208, 1130, 742, 698, 668. ^{13}C NMR (DMSO-d_6, 50°C): 65.1 (C-1), 50.2 (C-2), 158.2 (C-3), 17.0 (CH_3), 138.3 (C*i*), 127.9 (C*o*), 127.2 (C*m*), 128.0 (C*p*), ^{1}H NMR (DMSO-d_6, rt): 5.06 (d, 2H, *J* 8.3, H-1), 4.30 (m, 2H, H-2), 1.27 (d, 6H, *J* 6.2, CH_3), 8.56 (d, 2H, *J* 9.0, NH), 7.30 (m, 10H, C_6H_5). M^+ (%): 357.20 (1), 91.15 (28), 117.25 (44), 125.15 (36), 231.25 (22), 267.25 (65), 44.0 (100). Calcd for $C_{20}H_{22}O_2N_2Cl_2$, C (61.08), N (7.12), H (5.63); found: C (60.85), N (6.98), H (5.59).

4.2.4. *N,N-Bis-[1-chloro-1-phenylpropyl]oxamides **14**, **18**, **19***

Oxamide **17** (2 g, 5.6 mmol) was mixed with $SOCl_2$ (1.2 ml, 16.8 mmol) and stirred for 15 h, acetone was added (20 ml) and the mixture was stirred for 15 minutes, then the solvent was evaporated under vacuum. The reaction product was a mixture of diastereoisomers **14** 18%, **18** 33% and **19** 49%, their ratio was calculated from the NMR spectra (2.2 g, 100%). After 7 h standing with NaOH (0.3 g), the reaction mixture gave crystals of compound **18**, which were recrystallized from methanol acetone to give suitable crystals for an X-ray diffraction structure.

*Compound **18***: Mp 211–213°C. IR (KBr, ν cm^{-1}): 3408, 3306, 2940, 1664, 1512, 1456, 736, 700, 676, 1210, 1144, 1242. $[\alpha]_D$=−174.6 (DMSO, c=11.7). ^{13}C NMR (DMSO-d_6): 65.9 (C-1), 51.1 (C-2), 159.2 (C-3), 18.0 (CH_3), 138.9 (C*i*), 128.7 (C*o*), 127.5 (C*m*), 128.6 (C*p*). ^{1}H NMR (DMSO-d_6): 5.26 (d, 2H, *J* 9.2, H-1), 4.44 (m, 2H, H-2), 0.96 (d, 6H, *J* 6.6, CH_3), 8.92 (d, 2H, *J* 9.2, NH) 7.41 (s, C_6H_5) M^+ (%): 357.25 (2), 44.15 (100), 91.20 (24), 117.30 (41), 125.20 (33), 231.25 (25), 267.20 (92), 269.20 (34). Calcd for $C_{20}H_{22}O_2N_2 \cdot 1/8H_2O$, C (60.74), N (7.08), H (5.60); found: C (60.71), N (7.03), H (5.58).

*Compound **19***: ^{13}C NMR (DMSO-d_6): 65.6 (C-1), 50.9 (C-2), 158.8 (C-3), 17.8 (CH_3–C-2), 138.8 (C*i*), 65.3 (C-1′), 50.3 (C-2′), 158.5 (C-3′), 17.4 (CH_3–C-2′), 138.7 (C*i*). ^{1}H NMR (DMSO-d_6): 5.18 (d, 1H, *J* 8.6, H-1), 4.43 (m, 1H, H-2), 0.89 (d, 3H, *J* 7.3, CH_3), 8.76 (d, 1H, *J* 9.2, NH), 5.12 (d, 1H, *J* 9.3, H-1′), 4.3 (m, 1H, H-2′), 1.36 (d, 3H, *J* 6.6, CH_3-2′), 8.73 (d, 1H, *J* 9.24, NH-2′), 7.33 (C_6H_5).

4.3. Tosylation reactions

4.3.1. *N[(−)-1*R*,2*R*-1-Chloro-1-phenyl-2-propyl]*-p-*toluensulfonamide **5***

General procedure: A solution of **3a** (0.5 g, 2.44 mmol) and Na_2CO_3 (0.61 g) in a mixture of $CHCl_3$/ethanol (70/30, 10 ml) tosyl chloride (0.46 g, 2.43 mmol) was added. The reaction mixture was stirred for 5 h. Then, 10 ml of H_2O was added and the product extracted with $CHCl_3$ (50 ml). The combined extracts were dried with Na_2SO_4 and concentrated under vacuum. The yelow solid was recrystallized from a mixture of $CHCl_3$/hexane (25/75) (0.76 g, 90%). Mp 119–121°C. $[\alpha]_D^{33}$=−40.3

(THF, c=0.1). IR (KBr, ν cm^{-1}): 3236, 3056, 2978, 2934, 2872, 1334, 668. ^{13}C NMR ($CDCl_3$): δ=18.2 (C-3), 21.5 (CH_3–Ts), 55.4 (C-2), 65.9 (C-1), 128.0 (C*o*) 127.0 (C*m*), 126.1 (C*p*), 137.0 (C*p*–Ts), 137.6 (C*i*), 143.3 (C*i*–Ts). ^1H NMR ($CDCl_3$): δ=1.82 (d, *J* 6.7, 3H, H-3), 2.39 (s, 3H, CH_3–Ts), 3.76 (qd, *J* 6.7 and 4.9, 1H, H-2), 4.90 (d, *J* 4.9, 1H, H-1), 7.26 (m, 5H, Ar), 7.86 (d, *J* 8.4, 4H, Ts). M^+ (%): 324 (1), 288 (1), 198 (100), 155 (58), 125 (16), 91 (55). Calcd for $C_{16}H_{19}SO_2N$, C (59.40), N (4.32), H (5.56), S (9.98); found: C (62.27), N (5.13), H (5.66), S (9.66).

*4.3.2. N[(+)-1*R,*2*R*-1-Chloro-1-phenyl-2-propyl]-N-methyl*-p-*toluensulfonamide* ***6***

The same tosylation procedure was used for **4a** (2 g, 9.1 mmol). The solution was filtered and the solvent was evaporated. The white solid was obtained from a mixture of $CHCl_3$/hexane (25/75) (3 g, 98%). Mp 118–120°C. $[\alpha]_D^{30}$=+69.1 ($CHCl_3$, c=0.1). IR (KBr, ν cm^{-1}): 3236, 3056, 2978, 2934, 2872, 1334, 668. ^{13}C NMR ($CDCl_3$): δ=14.69 (C-3), 21.44 (CH_3–Ts), 58.47 (C-2), 63.97 (C-1), 127.41 (C*m*–Ts), 128.26 (C*m*), 128.53 (C*p*), 129.22 (C*o*), 130.18 (C*o*–Ts), 136.96 (C*i*), 139.43 (C*p*–Ts), (C*i*–Ts). ^1H NMR ($CDCl_3$): δ=0.58 (d, *J* 6.9, 3H, H-3), 2.35 (s, 3H, CH_3–Ts), 4.41 (qd, *J* 6.9 and 9.9, 1H, H-2), 5.16 (d, *J* 9.9, 1H, H-1), (m, 5H, Ar), (d, *J* 8.4, 4H, Ts).

*4.3.3. (+)-1*R,*2*S*-1-Chloro-1-phenyl-2-(N-methyl)amine*propane *hydrochloride* ***8a***

The same tosylation procedure was used for **7a**. The reaction afforded a mixture of compounds **4a** (60%) and **8a** (40%), which was analyzed by NMR. Data for **8a**: ^{13}C NMR (DMSO-d_6): δ=10.41 (C-3), 59.47 (C-2), 63.25 (C-1), 31.06 (N–CH_3). ^1H NMR ($CDCl_3$): δ=1.13 (d, *J* 6.6, 3H, H-3), 3.50 (N–CH_3), 3.71 (qd, *J* 6.6 and 2.6, 1H, H-2), 5.98 (d, *J* 2.6, 1H, H-1).

*4.3.4. N[(+)-1*S,*2*R*-1-Hydroxy-1-phenyl-2-propyl]*-p-*toluensulfonamide* ***9***

General procedure: To a solution of (+)-1*S*,2*R*-norephedrine **1** (1.0 g, 6.6 mmol) and triethylamine (1.0 ml, 6.7 mmol) in THF (10 ml), tosyl chloride (1.26 g, 6.63 mmol) was added. The reaction mixture was stirred for 12 h. Then, 10 ml of H_2O was added and the product was extracted with $CHCl_3$ (50 ml). The combined extracts were dried with Na_2SO_4 and concentrated under vacuum. The white solid was recrystallized from $CHCl_3$/MeOH (25/75) (1.94 g, 96%). Mp 103–105°C. $[\alpha]_D^{33}$=+21.9 (THF, c=0.1). IR (KBr, ν cm^{-1}): 3440, 3306, 3040, 3022, 2926, 2856, 1398. ^{13}C NMR ($CDCl_3$): δ=14.2 (C-3), 21.4 (CH_3–Ts), 55.0 (C-2), 75.5 (C-1), 125.9 (C*o*) 126.9 (C*m*), 127.3 (C*p*), 129.7 (C*o*–Ts), 128.1 (C*m*–Ts), 137.7 (C*i*), 140.4 (C*p*–Ts), 143.3 (C*i*–Ts). ^1H NMR ($CDCl_3$): δ=0.8 (d, *J* 7.3, 3H, H-3), 2.38 (s, 3H, CH_3 Ts), 3.50 (qd, *J* 3.3 and 7.3, 1H, H-2), 4.78 (d, *J* 3.3, 1H, H-1), 7.23 (m, 5H), 7.75 (d, *J* 8.6, 4H, H–Ts). M^+ (%): 288 (5), 198 (100), 155 (72), 107 (38), 91 (92), 44 (23). Calcd for $C_{16}H_{19}N_SO_2$, C (62.94), N (4.58), H (6.26), S (10.49), O (17.72); found: C (62.56), N (4.58), H (6.33), S (9.98).

*4.3.5. N[(−)-1*R,*2*S*-1-Hydroxy-1-phenyl-2-propyl]-N-methyl*-p-*toluensulfonamide* ***10***

The same tosylation procedure was used for (−)-1*R*,2*S*-ephedrine **2** (5 g, 30.2 mmol). The white solid was recrystallized from a mixture of $CHCl_3$ (8.6 g, 90%). Mp 60–61°C. $[\alpha]_D^{30}$=−63.9 (THF, c=0.1). ^{13}C NMR ($CDCl_3$): δ=11.00 (C-3), 21.56 (CH_3–Ts), 30.54 (NCH_3), 57.98 (C-2), 77.17 (C-1), 126.31 (C*m*–Ts), 127.10 (C*o*), 127.71 (C*p*), 128.36 (C*m*), 129.73 (C*o*–Ts), 136.33 (C*i*), 141.69 (C*p*–Ts), 143.26 (C*i*–Ts). ^1H NMR ($CDCl_3$): δ=0.85 (d, *J* 7.2, 3H, H-3), 2.37 (s, 3H, CH_3 Ts), 2.66 (s, 3H, NCH_3), 4.13 (qd, *J* 7.2 and 4.2, 1H, H-2), 4.79 (t, *J* 4.2, 1H, H-1), 7.21 (d, *J* 7.22, 2H, Ts), 7.2–7.4 (m, 5H, arom), 7.54 (d, *J* 7.22, 2H, Ts).

*4.3.6. N[(+)-1*S*,2*S*-1-Hydroxy-1-phenyl-2-propyl]-N-methyl*-p-*toluensulfonamide* ***15***

The same tosylation procedure was used for (+)-1*S*,2*S*-pseudoephedrine **7** (2 g, 9.13 mmol). The white solid was recrystallized from $CHCl_3$ (g, 87%). Mp 70–71°C. $[\alpha]_D^{33}$=+30.3 (THF, c=10^{-2}). IR (KBr, ν cm^{-1}): 3440, 3306, 3040, 3022, 2926, 2856, 1398. ^{13}C NMR ($CDCl_3$): δ=12.8 (C-3), 21.3 (CH_3–Ts), 28.6 (NCH_3), 59.1 (C-2), 74.9 (C-1), 127.2 (C*o*), 127.3 (C*m*), 128.2 (C*p*), 129.8 (C*o*–Ts), 128.5 (C*m*–Ts), 136.1 (C*i*), 140.8 (C*p*–Ts), 143.6 (C*i*–Ts). ^1H NMR ($CDCl_3$): δ=0.50 (d, *J* 6.9, 3H, H-3), 2.32 (s, 3H, CH_3–Ts), 2.69 (NCH_3), 3.99 (qd, *J* 6.9 and 8.9, 1H, H-2), 4.34 (d, *J* 8.9, 1H, H-1), 7.25 (m, 7H), 7.60 (d, *J* 8.2, 2H, H*o*–Ts). M^+ (%): 288 (5), 198 (100), 155 (72), 107 (38), 91 (92), 44 (23).

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References

1. Ager D. J.; Prakash I.; Schaad D. R. *Chem. Rev*. **1996**, *96*, 835.
2. Kagan H. B. In *Asymmetric Synthesis*; Morrison J. D., Ed.; Academic Press, 1985; Vol 5.
3. Pfaltz A. *Acc. Chem. Res*. **1993**, *26*, 339; Frump J. A. *Chem. Rev*. **1971**, *71*, 485; Müller D.; Umbricht G.; Weber B.; Pfaltz A. *Helv. Chim. Acta* **1991**, *74*, 232.
4. Contreras R.; Brazier J. F.; Klaébé A.; Wolf R. *Phosphorus* **1972** *2*, 67.
5. Contreras R.; Wolf R.; Sánchez M. *Synth. Inorg. Metal–Org. Chem*. **1973**, *3*, 37.
6. Klaébé A.; Brazier J. F.; Cachapuz Carrelhas A.; Garrigues B.; Marre M. R.; Contreras R. *Tetrahedron* **1982**, *38*, 2111.
7. Mancilla T.; Santiesteban F.; Contreras R.; Klaébé A. *Tetrahedron Lett*. **1982**, *23*, 1561.
8. Santiesteban F.; Mancilla T.; Klaébé A.; Contreras R. *Tetrahedron Lett*. **1983**, *24*, 759.
9. Santiesteban F.; Grimaldo C.; Contreras R.; Wrackmeyer B. *J. Chem. Soc., Chem. Commun*. **1983**, 1486.
10. Santiesteban F.; Campos M. A.; Morales H., Contreras R.; Wrackmeyer B. *Polyhedron* **1984**, *3*, 589.
11. Contreras R; Santiesteban F.; Paz-Sandoval M. A.; Wrackmeyer B. *Tetrahedron* **1985**, *40*, 3829.
12. Paz-Sandoval M. A.; Santiesteban F.; Contreras R. *Magn. Reson. Chem*. **1985**, *23*, 428.
13. Farfán N.; Contreras R. *Heterocycles* **1985**, *23*, 2989.
14. Farfán N.; Cuéllar L.; Aceves J. M.; Contreras R. *Synthesis* **1987**, 927.
15. Mancilla T.; Contreras R. *J. Organomet. Chem*. **1987**, *321*, 191.
16. Farfán N.; Mancilla T.; Castillo D.; Uribe G.; Carrillo L; Joseph-Nathan P.; Contreras R. *J. Organomet. Chem*. **1990**, *381*, 1.
17. Tlahuext H.; Contreras R. *Tetrahedron: Asymmetry* **1992**, *3*, 727.
18. Tlahuext H.; Contreras R. *Tetrahedron: Asymmetry* **1992**, *3*, 1145.
19. Martínez-Martínez F. J.; Ariza-Castolo A.; Tlahuext H.; Tlahuextl M.; Contreras R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1481.
20. Tlahuext H.; Santiesteban F.; García-Báez E.; Contreras R. *Tetrahedron: Asymmetry* **1994**, *5*, 1579.
21. Cruz, A.; Flores-Parra A; Tlahuext H.; Contreras R. *Tetrahedron: Asymmetry* **1995**, *6*, 1933.
22. Tlahuextl M.; Martínez-Martínez F. J.; Rosales-Hoz M. J.; Contreras R. *Phosphorus, Sulfur and Silicon* **1998**, in press.
23. Martínez-Martínez F. J.; León-Romo J. L.; Padilla-Martínez I. I.; Rosales Hoz M. J.; Contreras R. *Phosphorus, Sulfur and Silicum* **1996**, *115*, 217.
24. Roth H. J.; Schlump *Arch. Pharm*. **1963**, *296*, 213.
25. Bhat K. V.; McCarthy W. C. *J. Pharm. Sci*. **1965**, *54*, 225.
26. Kniezo L.; Kristian P.; Budesinsky M.; Havrilova K. *Coll. Czech. Chem. Commun*. **1981**, *46*, 717.
27. Lewis E. S.; Boozer C. E. *J. Am. Chem. Soc*. **1952**, *74*, 308. March J. *Advanced Organic Chemistry*; Wiley Interscience: New York, 1985, pp. 269.
28. Dieter R. K.; Deo N.; Lagu B.; Dieter J. W. *J. Org. Chem*. **1992**, *57*, 1663.