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Synthesis of two new oxaziridines and a nitrone from derivatives of aryl-substituted dihydroisoquinoline

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Abstract: N-alkyl oxaziridines may be used as reagents for the oxidation of sulfides in acid-promoted reactions. This study describes the synthesis of two new oxaziridines. The reactivity of the latter was investigated in acidic medium both in presence and in absence of sulfides. In the absence of sulfides, a new nitrone was produced.

Keywords: Sulfoxidation, Oxaziridine, Nitrone, Isomerization.

Introduction

Since their discovery by Emmons in 1956[1], oxaziridines have gained increasing attention[2]. In particular, the oxaziridine is of interest because of an inherently weak N–O bond due to the strained ring that makes the molecule unusually highly reactive. These heterocycles have been shown to be promising reagents with potent anti-tumour[3,4], anti-malarial[5], and antifungal activities[6], and as effective analogues for penicillin[7]. They are also widely used as reagents and intermediates in the preparation of biologically active molecules[2,8].

In their reactions with a wide variety of nucleophiles, oxaziridines can be used as both oxygenating[9] and aminating agents[10,11]. They are extensively employed in asymmetric syntheses[12] and as precursors of oxaziridinium salts[13]. Also, they possess basic properties that enhance isomerization and hydrolysis reactions in acid media. The isomerization of oxaziridines has been reported to lead to nitrones[14], which are useful and versatile intermediates for a wide array of organic syntheses. They behave as electrophiles toward organometallics and as 1,3-dipoles in cycloadditions[15]. In fact, novel reactivities of nitrones promoted by metal derivatives have been discovered, recently[16]. Nitrones also have relevant applications as spin traps in biological studies[17] and as therapeutic in age-related diseases[18].

In this work, we describe the synthesis of three new products, namely nitrone **10** and oxaziridines **5** and **6**. The latter were investigated for their potential reactivity towards organosulfide as well as their isomerisation by the action of methanesulfonic acid.

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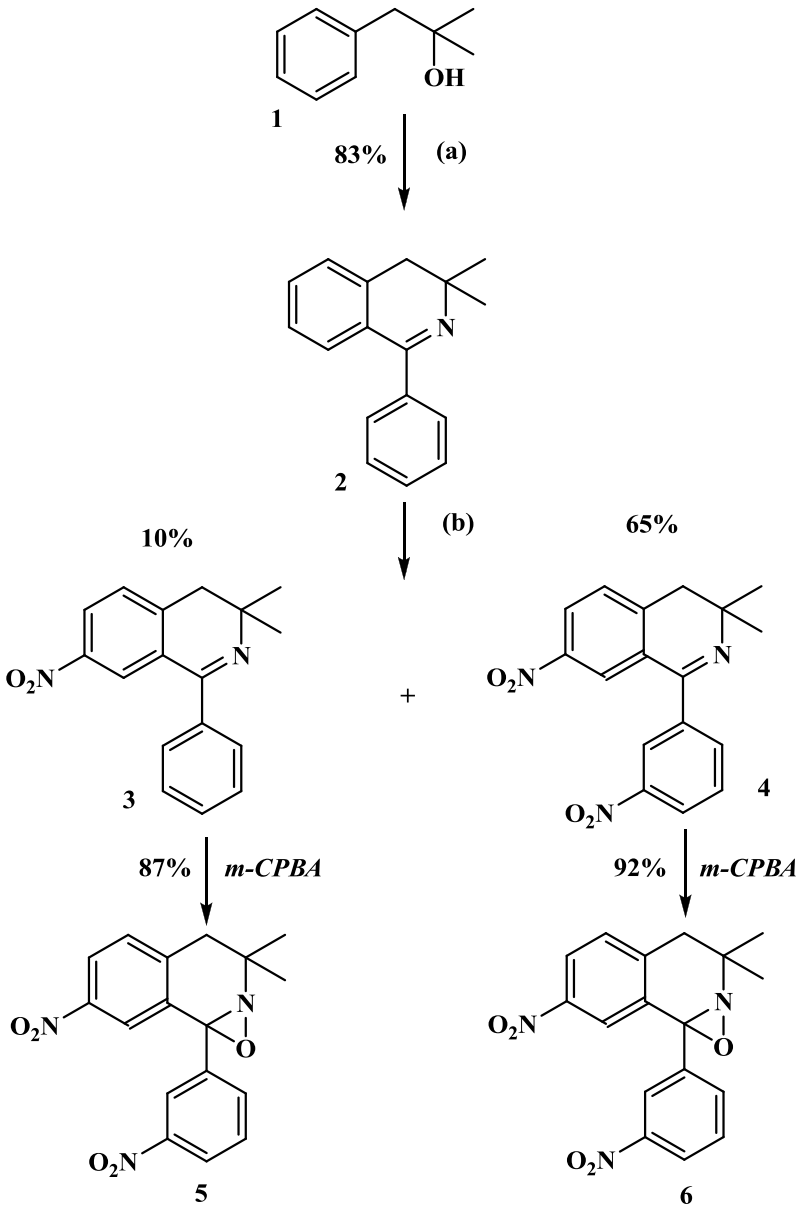
Results and Discussion

Synthesis of oxaziridines 5 and 6

The two new oxaziridines presented in this study were synthesized starting from the commercial tertiary alcohol **1** (scheme 1). Imine **2**[19] was obtained by acid catalysed reaction of 2-methyl-1-phenylpropan-2-ol (**1**) with benzonitrile. The nitration of imine **2** under mild conditions[20,21] led to a mixture of imines **3** and **4**. Those products were isolated with the respective yields of 10 % and 65 %. The peracidic oxidation of imines **3** and **4** led quickly to oxaziridines **5** and **6** in good yields. (scheme 1).



a) H_2SO_4, Ph-CN, cyclohexane / 8h at 68°C.

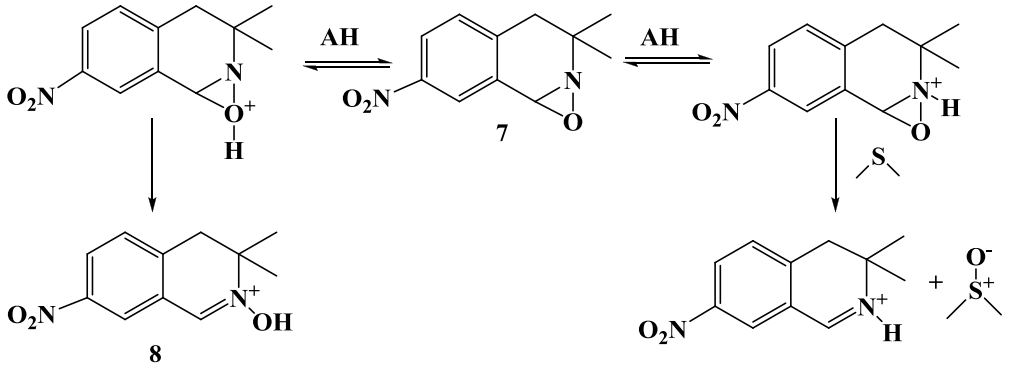
b) KNO_3, H_2SO_4 / 2h at 20°C than 4h at 60°C.

Scheme 1

Isomerization of oxaziridine 6

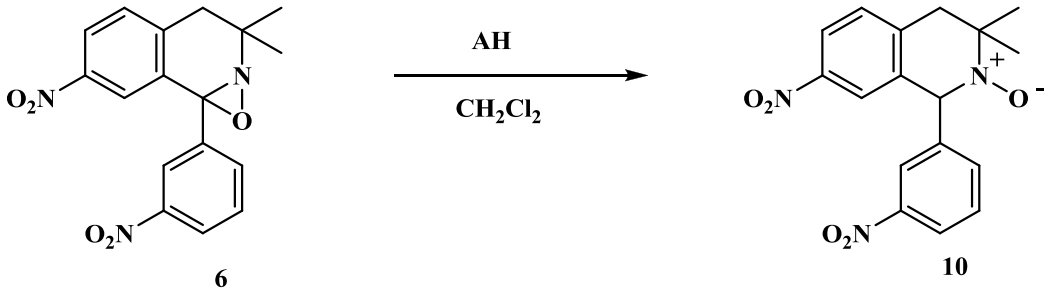
The dihydroisoquinoline oxaziridine **7** has previously been reported to be an oxygen transfer agent of organosulfides, where the oxygen transfer is promoted by an acid[22]. In this case, the N-protonated oxaziridine plays the role of the active oxidizing species that enables the transfer of its oxygen to a sulfide in the presence of an acid.

In fact, in the absence of sulfide, oxaziridine, which can be equally O-protonated, isomerizes into nitrone **8** (Scheme 2).



Scheme 2

The results of the isomerization reaction of the oxaziridine **6** (scheme 3) with various equivalents of methanesulfonic acid (CH_3SO_3H) are reported in Table 1.



Scheme 3

Table 1: Isomerization of oxaziridines **6** with the methanesulfonic acid.

Entry	AH	Time [(a)]	Yield %
1	3 eq	10 days	35
2	4 eq	5 days	60
3	5 eq	24 h	80

(a) : Reaction time followed by TLC. (b): Isolated product.

The results reported in Table 1 indicate that the isomerization of oxaziridine **6** to nitrone **10** in acidic medium (CH_3SO_3H, AH) necessitates different reaction times depending on the equivalents of methanesulfonic acid used. Nevertheless, the reaction is slow even with 5 equivalents of methanesulfonic acid (CH_3SO_3H) (entry 3). The presence of two electron

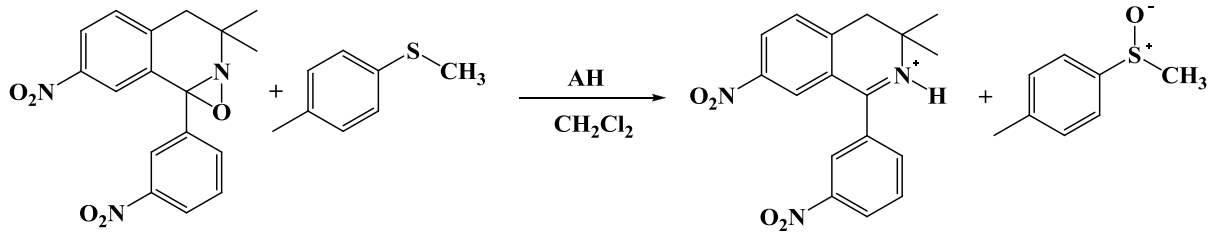
withdrawing nitro groups decreases the basicity of the substrate and slowed the reaction of isomerization.

It should be noted that the increase in the number of acid equivalents accelerates the reaction of isomerization. While with 3 equivalents of acid (entry 1), the conversion of oxaziridine **6** to the nitrone takes 10 days, with an excess of acid 5 equivalents (entry 3), one day was enough for the total isomerization of this oxaziridine into nitrone.

Finally, we can conclude that even with an excess of acid (entry 5), the isomerization of oxaziridine **6** into nitrone **10**, which promotes the reaction of oxygen transfer in the presence of a nucleophile, is slow.

Oxygen-atom transfer

We tested the ability of oxaziridine **6**, being the most electrophilic, to transfer oxygen to an organosulfur compound (p-tolylmethyl sulfide) in dichloromethane at room temperature in the presence of 3 and 4 equivalents of methanesulfonic acid (Scheme 4). The results of the oxygen transfer reaction are listed in Table 2.



6 **9**

Scheme 4

Table 2: Oxygen transfer from oxaziridine **6** to p-tolylmethyl sulfide.

Entry	AH	Time (h) [(a)]	Yield (%) [(b)]
1	3 eq	24	75
2	4 eq	15	80

(a) : Reaction time followed by C.C.M. (b): Isolated product (sulfoxide).

It can be noted from Table 2 that the presence of sulfide leads to an oxygen transfer. Oxaziridine **6** oxidizes p-tolylmethyl sulfide quantitatively and selectively to the corresponding sulfoxide at room temperature, with no over-oxidation into sulfone. We also noted that the increase in the number of acid equivalents accelerated the reaction of oxygen transfer. While with 3 equivalents of acid (entry 1), the oxidation of p-tolylmethyl sulfide to the corresponding sulfoxide takes 24 hours (entry 1), with 4 equivalents (entry 2), 15 hours are enough for the oxidation of this sulfide into sufoxide.

Conclusion

In conclusion, we demonstrated that in an acidic medium and in the absence of a nucleophile, oxaziridine isomerizes into the corresponding nitrone, in the presence of a nucleophile (organosulfur) the reaction leads selectively to the corresponding sulfoxide. The steric hindrance around the oxygen atom of the oxaziridine **6** is compatible with the oxygen transfer and does not block it. Thus, we isolated three new products, namely oxaziridines **5** and **6**, and nitrone **10**, which offer promising potential for future applications as biologically active materials and as substrates for synthetic transformations.

Experimental

General: Solvents were purified by standard methods. Melting points (mp) were determined under microscope with a Leitz Wetzlair device and are uncorrected. Mass spectra (MS) were obtained by electronic impact (70 eV) (EI) on a spectrometer AEI MS-50 or on a GC METHOD 6890 mass spectrometer operating at an ionization potential of 70 eV and in high-resolution (HR) on a GC-HRMS Micromass Autospec (IE). IR spectra were obtained in KBr disks on a UR-20 instrument. NMR spectra were recorded on an AC 300 Brüker spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts (δ) are given in ppm relative to T.M.S (tetramethylsilane) and coupling constants (J) are given in Hertz (Hz). All reactions were monitored by TLC using commercial silica gel plates and visualization was accomplished by UV light or stained with Draggendorf reagent. The presence of oxidizing species in the reaction mixtures was determined by potassium iodide test. Sulfide was commercially available.

Preparation of imine 2[19]

To a cooled (0°C) solution (10 mL) of sulfuric acid H_2SO_4 (95%) was added dropwise and under magnetic stirring, 10 mL of benzonitrile in 5 mL of cyclohexane. Then, (644 mg, 4.29 mmol) of tertiary alcohol 1 (commercial product) in 8 ml of cyclohexane was added to the solution.

After return to room temperature, the resulting mixture was stirred under reflux for 8 hours. Then, the solution is cooled at the room temperature and versed on ice-cold water (50 mL) under magnetic stirring. The solution is alkalized with ammonia. The organic layer was extracted with dichloromethane (100 mL), washed with a saturated aqueous NaCl solution, dried over sodium sulfate and filtered. The solvent was removed in vacuo.

Yield = 83%. mp : 115-116 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 1,28 (s, 6H, $2CH_3$); 2,81 (s, 2H, CH_2); de 7,19 à 7,57 (m, 9H arom). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 27.6; 38.8; 54.5; 126,4; 127,9; 128.0; 128,1; 128.2; 128,8; 128,9; 130,6; 137.5; 139.3; 164.5.

Preparation of imines 3 and 4

The imine **2** (500 mg, 2.12 mmol) is added dropwise cold on 5 mL of concentrated sulfuric acid. A solution of 280 mg potassium nitrate in 3 mL of sulfuric acid was added dropwise by maintaining the temperature at 0°C. The reactional medium was stirred at room temperature for 2 hours, then at 60°C for 4 hours. After return to room temperature the reactional medium was versed on ice-cold water (50 mL) and alkalized with ammonia. The organic phase was extracted with the dichloromethane (100 mL), washed with a saturated aqueous NaCl solution (100 mL), dried over sodium sulfate and filtered. The solvent was removed in vacuo. A

control of reaction mixture by TLC (ether / hexane: 1:1) indicated the presence of two products (Dragendorff), imines **3** and **4**. These products was separated by chromatography on silica gel (ether / hexane: 1:1) with the yields of 10 % and 65 %, respectively.

Imine 3: mp: 142°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 1.29 (s, 6H, $2CH_3$); 2.91 (s, 2H, CH_2); 7.41 (d, 1H, ^{3}J= 8.1 Hz); de 7.46 à 7.57 (m, 5H); 8,08 (d, 1H, ^{4}J= 2.1 Hz); 8.25 (dd, 1H, ^{3}J= 8.1 Hz, ^{4}J= 2.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 27.5; 38.8; 54.8; 122.5 (CH, C); 125.3; 128.5 (2 CH); 128.6 (2 CH); 129.3; 129.8; 137.8; 145.1; 146.8; 162.6. IR (KBr): ν = 727 cm^{-1} (Ar), 1756 cm^{-1} (C=N), 2683 cm^{-1} (CH_3). MS (m/z, %) : 280(M^+, 100); 253(1); 233(20); 207(5) ; 178(18) ; 151(5) ; 128(3) ; 108(10) ; 89(8) ; 63(5). M.S (HR): found mass: 280.1213 mass calculated for $C_{17}H_{16}N_2O_2$: 280.1212.

Imine 4: mp: 172°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) =1,31 (s, 6H, $2CH_3$); 2.94 (s, 2H, CH_2); 7.47 (d, 1H, ^{3}J = 8.1 Hz); 7.67 (t, 1H, ^{3}J = 8.1 Hz, ^{3}J = 7.5 Hz); 7.90 (ddd, 1H, ^{3}J = 7.5 Hz, ^{4}J = 1.8 Hz, ^{4}J = 1.2 Hz); 7,99 (d, 1H, ^{4}J = 2.1 Hz); 8,30 (dd, 1H, ^{3}J = 8.1 Hz, ^{4}J = 2.1 Hz); 8.38 (ddd, 1H, ^{3}J = 8.1 Hz, ^{4}J = 2.1 Hz, ^{4}J = 1.2 Hz); 8.48 (t, 1H, ^{4}J = 2.1 Hz, ^{4}J = 1.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 27.3; 38.6; 55.4; 121.7; 123.8; 124.6; 126.0; 127.7; 129.7 (2CH); 134.4; 139.5; 145.0; 146.9; 148.5; 160.7. IR (KBr): ν = 777 cm^{-1} (Ar), 1525 cm^{-1} (C-NO_2), 2917 cm^{-1} (CH_3). MS (m/z, %): 325(M^+, 100); 278(45); 252(3); 217(20); 176(15); 151(5); 115(10); 88(10); 63(5). M.S (HR): found mass: 325.1063 mass calculated for $C_{17}H_{15}N_3O_4$: 325.1036.

Preparation of oxaziridine 5

To a solution of imine **3** (100 mg, 0.356 mmol) in methanol (10 mL)was added in small portions, a slight excess of m-chloroperbenzoic (80 mg, 0.4 mmol, 1.12 equiv of active oxygen) under magnetic stirring and at room temperature. The reaction was followed by TLC (ether/hexane: 1:1). The solvent was evaporated and the residue obtained was taken up in dichloromethane (50 mL). The solution was washed with a solution of sodium bicarbonate and then with a saturated aqueous NaCl solution. The organic phase was dried over sodium sulfate, filtered, and concentrated.

Yield = 87%. mp : 142°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) =1.11 (s, 3H, CH_3); 1.56 (s, 3H, CH_3); 2.65 (d, 1H, ^{2}J=15.9 Hz); 2.96 (d, 1H, ^{2}J=15.9 Hz); 7.34 (d, 1H, ^{3}J=8.4 Hz); 7.47 (m, 5H); 7.90 (d, 1H, ^{4}J=2.1 Hz); 8.19 (dd, 1H, ^{3}J=8.4 Hz and ^{4}J=2.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 23.1; 28.9; 37.7; 57.2; 81.2; 124.7; 126.1; 127.3; 129.1; 129.7; 130.0; 133.4; 135.8; 143.3; 147.1. IR (KBr): ν = 763 cm^{-1} (Ar), 3002 cm^{-1} (CH_3). MS (m/z, %): 296(M^+, 100); 270(5); 249(12); 218(22); 191 (10); 165(15); 139(5); 115(8); 77(10); 51(5). M.S (HR): found mass: 296.1166 mass calculated for $C_{17}H_{16}N_2O_3$: 296.1161.

Preparation of oxaziridine 6

To a solution of imine **4** (100 mg, 0.3 mmol) in methanol (10 mL) was added in small portions, a slight excess of m-chloroperbenzoic (79 mg, 0.39 mmol, 1.3 equiv of active oxygen) under magnetic stirring and at room temperature. The reaction was followed by TLC (dichloromethane). The solvent was evaporated and the residue obtained was taken up in dichloromethane (50 mL). The solution was washed with a solution of sodium bicarbonate and then with a saturated aqueous NaCl solution. The organic phase was dried over sodium sulfate, filtered, and concentrated.

Yield = 92%. mp: 110°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) =1.15 (s, 3H, CH_3); 1.57 (s, 3H, CH_3); 2.72 (d, 1H, ^{2}J= 15.9Hz); 2.97 (d, 1H, ^{2}J= 15.9Hz); 7.42 (d, 1H, ^{3}J=8.1 Hz); 7,71 (m, 1H); 7.80 (m, 1H); 7.83 (d, 1H, ^{4}J=2.1 Hz); 8.26 (dd, 1H, ^{3}J=8.1 Hz and ^{4}J=2.1 Hz); 8.33

(m, 1H); 8.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 23.1; 28.8; 37.6; 57.5; 80.4; 122.7; 124.8; 125.3; 125.5; 130.4; 130.5; 133.6; 133.6; 138.1; 143.3; 147.1; 148.6. IR (KBr): ν = 805 cm^{-1} (Ar), 1348 cm^{-1} (NO_2), 2930 cm^{-1} (CH_3). MS (m/z, %): 341(M^+, 100). M.S (HR): found mass: 341.1014 mass calculated for $C_{17}H_{15}N_3O_5$: 341.1012.

Preparation of nitrone 10

Methanesulfonic acid (50 mg, 0.58 mmol) was added to a solution of oxaziridine **6** (50 mg, 0.146 mmol) in dichloromethane (6 mL) and the mixture was stirred at room temperature. A control of the reaction mixture by TLC (dichloromethane) indicated the disappearance of the oxaziridine after 5 days. The solution was diluted with dichloromethane (25 mL) and washed with a solution of sodium bicarbonate. The organic phase was dried over sodium sulfate, filtered and concentrated. Yield = 60%. mp: 160°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 1.54 (s, 6H, $2CH_3$); 3.31 (s, 2H, CH_2); 7.47 (d, 1H, ^{3}J=8.1 Hz); 7.60 (d, 1H, ^{4}J=2.1 Hz); 7.72 (m, 1H); 7.84 (m, 1H); 8.15 (dd, 1H, ^{3}J=8.1 Hz and ^{4}J=2.1 Hz); 8.36 (m, 1H); 8,43 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 25.0; 41.9; 69.4; 120.0 ; 123.6; 125.9; 129.4; 130.2; 136.6; 137.6; 147.9; 132.9; 131.4; 124.9 ; 137.7; 148.8. IR (KBr): ν = 813 cm^{-1} (Ar), 1653 cm^{-1} (C=N), 2156 cm^{-1} ($N^{+-}O^-$). MS (m/z, %): 341(M^+, 100); 309(12); 281(35); 253(20); 232(8); 207(40); 176(18); 147(18) ; 115(10) ; 73(35). M.S (HR): found mass: 341.1014 mass calculated for $C_{17}H_{15}N_3O_5$: 341.1012.

Oxygen transfer to p-tolylmethyl sulfide with Oxaziridines 6

A solution of the oxaziridine **6** (170 mg, 0.50 mmol) in methylene chloride (2 ml) was added to a solution of sulfide (69 mg, 0.50 mmol) and methanesulfonic acid (1.5 or 2 mmol) in methylene chloride (2 ml). The reaction mixture was stirred at room temperature until the disappearance of the active oxygen, monitored by TLC and potassium iodide test, and then was diluted with methylene chloride and washed with an aqueous sodium bicarbonate solution. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The sulfoxide was purified by chromatography on silica gel. The sulfoxide obtained are compared and identified with commercial sample. The various results that were obtained are presented in Table 2.

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