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SYNTHESIS AND REACTIVITY STUDY OF TWO NEW DIHYDROISOQUINOLINE-DERIVED OXAZIRIDINES

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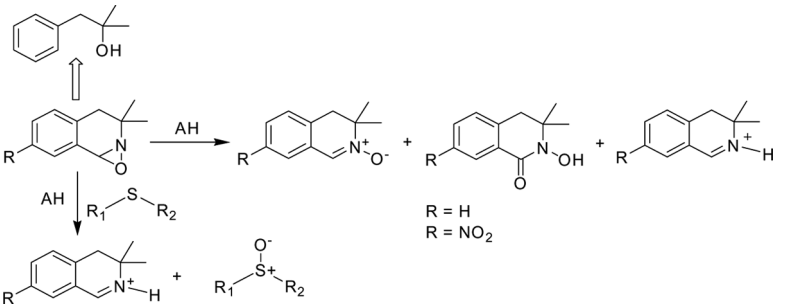
GRAPHICAL ABSTRACT



Abstract *The N-alkyl oxaziridines may be used as reagents for the oxidation of sulfides in acid-promoted reactions. The present work describes the behavior of two newly synthesized dihydroisoquinoline-derived oxaziridines with respect to methanesulfonic acid. An isomerization reaction was observed in the absence of sulfide.*

Keywords Hydroxamic acid; methanesulfonic acid; nitrone; oxaziridine; oxygen transfer

INTRODUCTION

The oxaziridine function, discovered in 1956 by Emmons,[1] contains a small three-element cycle involving a carbon atom, an oxygen atom, and a nitrogen atom. It has been extensively investigated and contains the presence of a relatively weak N-O bond into a strained ring, which endows its components with remarkably great reactivity.

Oxaziridines are usually known for their ability to react as aminating or, in some cases, oxygenating agents with nucleophiles. In fact, ordinary oxaziridines, whether (N-H oxaziridines),[2] (N-alkyl oxaziridines),[3] or (N-alkoxycarbonyl oxaziridines),[4] are electrophilic amination reagents.[5] The nitrogen transfer is thus the normal reaction of oxaziridines with nucleophiles. Nevertheless, oxygen transfer

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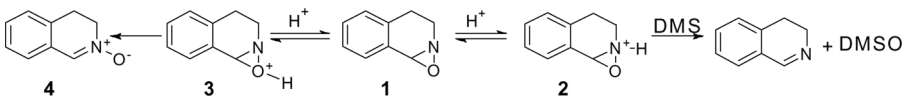


Scheme 1. Reactivity of oxaziridine **1**.

may occasionally result from hindered oxaziridines and hindered nucleophiles.[6] Sulfoxidation has been performed with oxaziridines having electron-withdrawing substituents on the nitrogen atom or on both the nitrogen and the carbon atoms of the three-membered ring.[7–9]

In this respect, the nonsubstituted dihydroisoquinoline-derived oxaziridine **1** has been reported to be an excellent agent for the transfer of oxygen on organosulfides, which are weakly basic nucleophilic substrates, if the oxygen transfer is promoted by an acid.[10] In this case, the N-protonated oxaziridine **2** plays the role of the active oxidizing species and renders the simultaneous presence of acid and sulfide necessary. Indeed, in the absence of sulfide, oxaziridine **3**, which is equally O-protonated, isomerizes into nitrone **4** (Scheme 1).

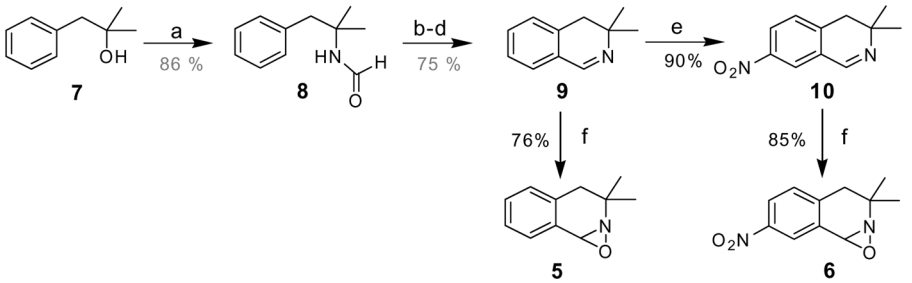
In the asymmetric field, acid-catalyzed oxidation of prochiral sulfides by a chiral N-alkyl oxaziridine has been reported.[11] More recently, acid-catalyzed enantioselective sulfoxidations using N-alkyl binaphthyl-derived oxaziridines have also been reported.[12] Also, Lewis acid–catalyzed enantioselective sulfoxidations using an otherwise inert oxaziridine have been recently reported.[13]

In the present paper, we describe the synthesis of two new ordinary oxaziridines **5** and **6** from the dihydroisoquinoline-derived family. Using this new oxidizing system, described in Scheme 1, the latter was investigated for potential reactivity to organosulfides as well as isomerization by the action of methanesulfonic acid.

RESULTS AND DISCUSSION

Synthesis of the Oxaziridines 5 and 6

The two new models presented in the current study were synthesized starting from commercial tertiary alcohol **7** (Scheme 2). The formamide **8** from step (a)[14] was cyclized to form imine **9**[15,16] after a three-step sequence.[17] The nitration of this



Scheme 2. Reagents and conditions : (a) KCN; SO_4H_2-AcOH; rt; (b) oxalyl chlorid; CH_2Cl_2; (c) $FeCl_3$; (d) MeOH; H_2SO_4; (e) KNO_3-H_2SO_4; rt 2 h, 60 °C 4 h; (f) m-CPBA; MeOH.

imine under soft conditions[18,19] selectively led to the derived **10**. The oxidation of imines **9** and **10** under conditions (f) rapidly led to oxaziridines **5** and **6**, respectively. They were isolated with overall yields of 49% and completely characterized (Scheme 2).

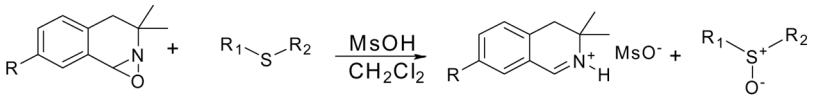
Oxygen-Atom Transfer onto Sulfides

The oxidation of sulfides with **5** and **6** were first performed under the conditions previously[10] described at room temperature in the presence of methanesulfonic acid (MsOH) in dichloromethane (Table 1).

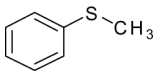
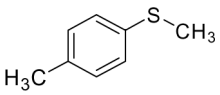
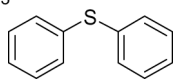
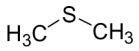
It can be noted from Table 1 that both oxaziridines **5** and **6** have equivalent behavior in the reactions under investigation, oxidize quantitatively and quickly at room temperature, and give good sulfoxide conversion with no overoxidation to sulfones. The reaction times were significantly shortened with oxaziridine **6**. The presence of an electron-withdrawing group (NO_2) increased the electrophile of oxaziridine and thus notably accelerated the transfer of the oxygen atom.

The reaction of oxygen transfer was slowest for both oxaziridines with diphenylsulfide (entry 3); this is attributed to the resonance effect of this reagent. Moreover, the oxidation of diphenylsulfide with oxaziridine **5** is not total; a conversion of only 80% into the corresponding sulfoxide was observed.

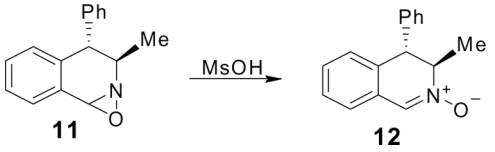
Table 1. Oxidation of sulfides[a] with **5** and **6** in the presence of methanesulfonic acid[b]



5 R = H
6 R = NO_2

Entry	Sulfides	Time[c] (min)		Yield of sulfoxides (%) (conversions)[d]	
		R=NO_2	R=H	R=NO_2	R=H
1		<2	9	82[e] (100)	84[e] (100)
2		<2	10	79[e] (100)	77[e] (100)
3		12	40	78[e] (100)	65[e] (80)
4		5	10	(100)	(100)

[a]Reaction performed at room temperature in CH_2Cl_2.
[b]0.5 mmol of sulfide (0,16 M), 2 equivalent of MsOH, and 1 equivalent of oxaziridine.
[c]Determined by TLC.
[d]Determined by ^1H NMR spectroscopy in $CDCl_3$.
[e]Isolated product.



Scheme 3. Chiral oxaziridine **11**.

The oxidation of this same reagent by oxaziridine **6** was, however, faster and more quantitative. In fact, a noticeable increase in the electrophile of oxaziridine **6** was observed. Consequently, an active oxygen loss through the isomerization of the oxaziridine into nitrone was noted with the least reactive oxaziridine **5**. In fact, and in this case, the oxygen transfer reaction was not fast enough to mask the acid-catalyzed isomerization reaction. This is consistent with a previously reported result in the literature[11] stipulating that if the nucleophilic substrate presents a steric effect, 15–20% of the chiral oxaziridine **11** of the dihydroisoquinoline-derived family isomerize into the corresponding nitrone **12** under acid catalysis.

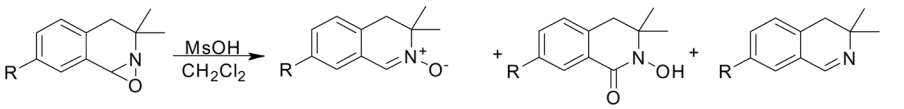
The isomerization reaction of oxaziridine **11** by a methanesulfonic acid excess in the absence of nucleophilic substrate led, rapidly and quantitatively, to nitrone **12** (Scheme 3).

The acid-catalyzed isomerization reaction of new oxaziridines **5** and **6** under these conditions is shown in Scheme 4.

With oxaziridine **5**, unsubstituted in position 7, it was found that when the latter was made to react with 2 equivalents of MsOH acid, the reaction would lead to the corresponding nitrone **13** after 30 min, with a conversion rate of 100%. The nitrone obtained, already described in the literature data,[20] was isolated in 80% yield.

With the oxaziridine **6**, the reaction was very slow. It was only after 30 h that the reagent disappeared and the reaction led to a mixture of nitrone **14** (50% of conversion), hydroxamic acid **15** (25% of conversion), and protonated imine **16** (25% of conversion). Those products were isolated with yields of 32%, 16%, and 16%, respectively. The structure of this already unknown compound (hydroxamic acid **15)** was established by x-ray diffraction[21] (Fig. 1).

It is worth noting in this respect that the oxaziridines **1, 5,** and **11** of the dihydroisoquinoline-derived family, unsubstituted in position 7, isomerized quickly and quantitatively to their corresponding nitrones whereas nitrone **14**, formed by



R	reaction time	conversion (yield)		
5 H	30 min	**13** 100% (80%)	-	-
6 NO_2	30 h	**14** 50% (32%)	**15** 25% (16%)	**10** 25% (16 %)

Scheme 4. Oxaziridines **5** and **6** under the action of methanesulfonic acid.

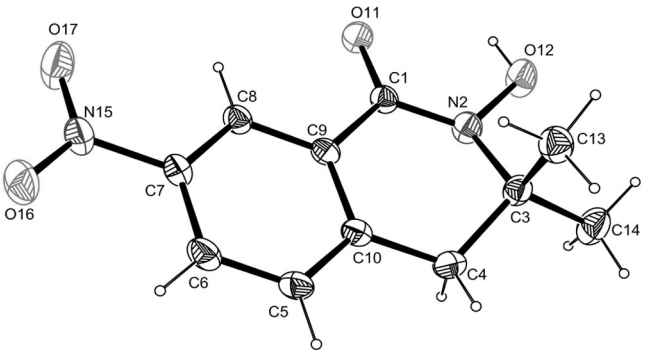
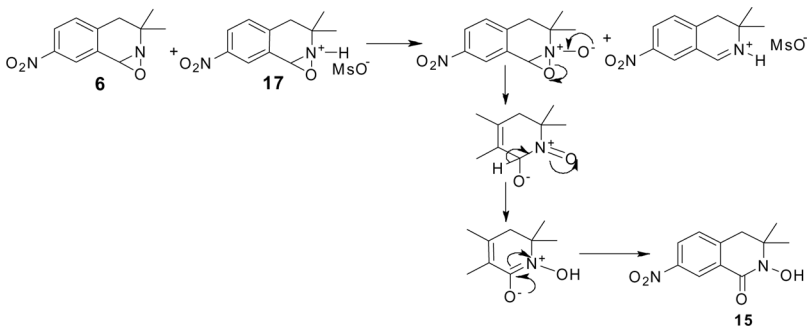


Figure 1. Molecular structure of hydroxamic acid **15**.

the isomerization of the protonated oxaziridine **6** into oxygen by the methanesulfonic acid at room temperature, was accompanied by the hydroxamic acid **15** (Scheme 4). In fact, it was previously reported[22] that the action of a peracid on steroidic oxaziridines can lead to the formation of hydroxamic acid in addition to the compounds that result from the ring opening of the oxaziridine. The action of a peracid on an oxaziridine was previously explained by an oxaziridine nucleophilic attack onto the oxidation agent.

By analogy, the present study propose that the hydroxamic acid **15** most probably came from the oxidation of the oxaziridine **6** by the N-protonated oxaziridine **6** (intermediate **17**, Scheme 5). In fact, it was noted that the introduction of the attractor grouping (nitro) in position 7 onto the dihydroisoquinoline skeleton of the function brought about a significant variation in terms of oxaziridine **6** reactivity so that the N-protonated intermediary **17** became able to oxidize oxaziridine **6**, which would play the role of a nucleophile (Scheme 5). This therefore can be considered as the first time a protonated oxaziridine is shown to be able to oxidize its precursor and to bring about a hydroxamic acid formation. The latter have always been reported as highly required products with excellent biological activities particularly in a wide range of organic syntheses and processes.[23,24]



Scheme 5. Mechanistic hypothesis of hydroxamic acid **15** formation.

CONCLUSION

The findings of the present study demonstrate the effectiveness of the new oxaziridine **6** as an oxygen-transfer agent for sulfides in acidic media and the high potential of the N-protonated intermediary to oxidize an oxaziridine and form the hydroxamic acid. This reactivity, which is actually novel for both ordinary and activated oxaziridine functions, can be considered promising because it offers interesting possibilities for future applications.

EXPERIMENTAL

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 (EI) (70 eV) on a AEI MS-50 spectrometer and in high resolution (HR) on a Kratos MS-80 spectrometer. NMR spectra were recorded at 250 or 300 MHz for ^{1}H and 62.5 or 75 MHz for ^{13}C. Chemical shifts (δ) are given in parts per million relative to tetramethylsilane (TMS), 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 ultraviolet (UV) light or stained with Draggendorf reagent. The presence of oxidizing species in the reaction mixtures was determined by potassium iodide test. All sulfides were commercially available. Formamide **8**[14] and imine **9**[15,16] were synthesized by a known procedure.

Preparation of the Imine 10

The imine **9** (6.8 g, 43 mmol) was added to 25 ml of concentrated sulfuric acid through maintaining the temperature of the reaction mixture lower than −5 °C. A solution of potassium nitrate (5.2 g, 52 mmol) in 20 ml of sulfuric acid (98%) was progressively added. The reaction mixture was stirred at room temperature for 2 h and then at 60 °C for 4 h. After returning to room temperature, the reaction mixture was poured on ice and then alkalized (ammonia). The organic phase was extracted with dichloromethane, washed with a saturated solution of sodium chloride, and dried on sodium sulfate. Removal of solvent left a solid residue. By recrystallization (hexane), the imine **10** was obtained with a yield of 90%. Mp: 105–106 °C (hexane). ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.25 s (6H $2CH_3$), 2.83 s (2H CH_2 H-4), 7.32 d (1H arom H-5, $J = 9$ Hz), 8.15 d (1H arom H-8, $J = 2.1$ Hz), 8.22 dd (1H H-6, $J = 2.1$ Hz, $J = 9$ Hz), 8.30 s (1H H-1). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 28.01 [$C(CH_3)_2$], 37.99 (CH_2 C-4), 55.15 (CMe_2 C-3), 121.77, 125.80, and 129.20 (CH arom.), 127.96, 143.06, and 147.28 (C arom.), 155.30 (CH C-1). MS (IE): 204 ($M^{+\cdot}$, base peak). Anal. calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.73; H, 6.05; N, 13.51%.

Preparation of the Oxaziridine 5

m-Chloroperbenzoic acid (357 mg, 1.78 mmol, 1 equiv of active oxygen) was added in small portions to a solution of imine **9** (283 mg, 1.78 mmol) in 10 ml of methanol under magnetic stirring. The solvent was evaporated, and the residue was taken up in dichloromethane and washed with a sodium bicarbonate solution and then with

water. The collected organic phase were dried over Na_2SO_4, filtered, and concentrated. The resulting pale yellow oil was purified by chromatography on silica gel (eluent CH_2Cl_2/Et_2O 95/5) and distilled (75–80 °C, 0.05 mmHg) to give 238 mg of colorless oil of oxaziridine **5** (yield: 76%). ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.90 s (3H CH_3), 1.50 s (3H CH_3), 2.36 d (1H H-4, $J = 15.30$ Hz), 2.74 d (1H H-4, $J = 15.30$), 4.93 s (1H H-1) 7.10 m (1H arom.), 7.29 m (1H arom.), 7.36 m (1H arom.), 7.51 m (1H arom.); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 22.67 (CH_3 C-3), 28.70 (CH_3 C-3), 36.28 (CH_2 C-4), 56.94 (CMe_2 C-3), 75.42 (CH C-1), 126.5, 134.88 (C arom.), 126.5, 128.42, 129.73 (CH arom.). MS (EI): 175 ($M^{+\cdot}$, 76%), 160 [$(M^{+\cdot} - 15)$, 87%], 159 [$(M^{+\cdot} - 16)$, 87%], 143 (base peak). Anal. calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.48; N, 7.99; O, 9.13. Found: C, 75.61; H, 7.58; N, 8.16; O, 9.07%.

Preparation of the Oxaziridine 6

m-Chloroperbenzoic acid (2.75 g, 13.7 mmol, 1 equiv of active oxygen) was added in small portions to a solution of imine **10** (2.8 g, 13.7 mmol) in 100 ml of methanol. The reaction was monitored by thin-layer chromatography (TLC). TLC that was performed after the end of peracid addition indicated that the reaction was complete. The solvent was evaporated, and the white solid residue was taken up in dichloromethane and washed with a sodium bicarbonate solution and then with water. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The resulting yellow solid was purified by recrystallization (ether) to give 2.57 g of yellow crystals of oxaziridine **6** (yield 85%). Mp 80–82 °C. ^{1}H NMR ($CDCl_3$, 250 MHz, δ): 0.91 s (3H CH_3), 1.53 s (3H CH_3), 2.5 d (1H H-4, $J = 19.25$ Hz), 2.8 d (1H H-4, $J = 19.25$ Hz), 5.04 s (1H H-1), 7.3 d (1H arom. H-5, $J = 10$ Hz), 8.24 dd (1H H-6, $J = 3$, $J = 10$ Hz), 8.43 d (1H arom H-8, $J = 3$ Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz, δ): 22.74 (1 CH_3 C-3), 28.68 (1 CH_3 C-3), 36.49 (CH_2 C-4), 57.30 (CMe_2 C-3), 74.44 (CH C-1), 124.85, 124.88, 129.66 (CH arom.), 130.5, 142.62 and 146.95 (C arom.). MS (IE): 220 ($M^{+\cdot}$, 67%), 204 [$(M - 16)^{+\cdot}$, base peak], 174 (27%), 159 (47%). Anal. calcd. for $C_{11}H_{12}O_3N_2$: C, 59.99; H, 5.49; N, 12.72; O, 21.79. Found: C, 59.78; H, 5.73; N, 12.59; O, 21.91%.

Oxygen Transfer to Sulfides with Oxaziridines 5 and 6

A solution of the oxaziridine **5** or **6** (0.50 mmol) in methylene chloride (2 ml) was added to a solution of sulfide (0.50 mmol) and methanesulfonic acid (1 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 with Na_2SO_4 and concentrated in vacuo. The sulfoxides were purified by chromatography on silica gel. The sulfoxides obtained are compared and identified with commercial samples. The various results that were obtained are presented in Table 1.

Action of the Methanesulfonic Acid on the Oxaziridine 6

Methanesulfonic acid (2.7 mmol) were added to a solution of oxaziridine **6** (300 mg, 1.35 mmol) in dichloromethane (6 ml), and the mixture was stirred at room temperature. A control of the reaction mixture by TLC indicated the disappearance

of the oxaziridine after 30 h with appearance of three products, nitrone **14**, imine **10** and another product of Rf = 0.73 (ether elution), which with acid iron (III) chloride solution gave a violet blue spot, a distinguishing attribute of the hydroxamic acid.[25]

The reaction mixture was diluted with dichloromethane and was washed with an aqueous sodium bicarbonate solution and with a saturated sodium chloride solution. The organic phase was then dried (sodium sulfate), and the solvent was evaporated. An aliquot of the crude product was analyzed by ^{1}H NMR in $CDCl_3$. A mixture of (**14, 15,** and **10**) in the molar ratio 2:1:1 was detected. These products were separated by chromatography on silica gel (ether) with the yields of 32%, 16%, and 16%, respectively.

Selected Data

Nitrone 14. Mp: 152–154 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.47 s (6H $2CH_3$), 3.19 s (2H CH_2 H-4), 7.4 d (1H arom. H-5, $J = 8.2$ Hz), 7.79 s (1H H-1), 7.97 d (1H arom. H-8, $J = 2$ Hz), 8.10 dd (1H H-6, $J = 2$, $J = 8.2$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 24.82 [$C(CH_3)_2$], 41.73 (CH_2 C-4), 67.49 (CMe_2 C-3), 119.10, 123.46 and 128.65 (CH arom.), 129.73, 131.17, 136.59 (C arom.) and 148 (CH C-1). MS (EI): 221 [$(M + H)^{+\cdot}$, base peak]. Anal. calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72; O, 21.79. Found: C, 60.07; H, 5.76; N, 12.59; O, 21.65%.

Acide hydroxamique 15. Mp: 175–176 °C. ^{1}H NMR (CD_3SOCD_3, 300 MHz, δ): 1.26 s (6H $2CH_3$), 3.23 s (2H CH_2 H-4), 7.58 d (1H arom H-5, $J = 8$ Hz), 8.33 dd (1H H-6, $J = 2.4$, $J = 8$ Hz), 8.55 d (1H arom H-8, $J = 2.4$ Hz). ^{13}C NMR (CD_3SOCD_3 75 MHz, δ): 25.24 [$C(CH_3)_2$], 41.80 (CH_2 C-4), 60.66 (CMe_2 C-3), 122.02, 126.87 and 130.41 (CH arom.), 129.91, 144.05 and 147.21 (C arom.), 160.08 [-C(O) C-1]. MS (IE): 236 ($M^{+\cdot}$), 221 [$(M - 15)^{+\cdot}$, base peak]; MS (HR): found mass: 236.0844 mass calculated for $C_{11}H_{12}N_2O_4$: 236.0875.

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