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Synthesis and Reactivity of Two New Trichloromethyl Substituted Dihydroisoquinoline-Derived Oxaziridines

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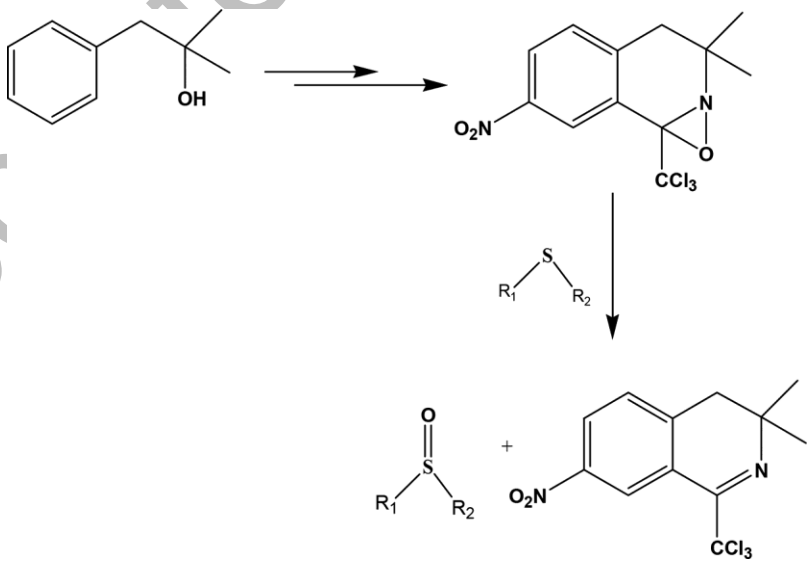
Abstract

N-alkyl oxaziridines may be used as reagents for the oxidation of sulfides in acid-promoted reactions. This paper reports on a simple and efficient synthesis of two new trichloromethyl substituted dihydroisoquinoline oxaziridines, a new family of organic oxidizing agents. Their oxygen transfer capability with respect to sulfides as model substrates and in the absence of acid is investigated.



KEYWORDS: Synthesis; Oxaziridine; Sulfoxidation.

INTRODUCTION

Oxaziridines, which were first reported in the mid-fifties by Emmons, are heterocyclic compounds containing oxygen, nitrogen and carbon atoms in a three-membered ring [1]. The literature indicates that these compounds have unusual reactivity particularly due to the presence of the strained three-membered ring and a relatively weak N-O bond.

These heterocycles have been shown to represent promising reagents for application as anti-tumour [2, 3], anti-malaria [4] and anti-fungal [5] agents and penicillin analogs [6]. They have also been widely used as reagents and intermediates in the preparation of biologically active molecules [7, 8].

Several methods have been proposed for the preparation of oxaziridines, including the oxidation of imines with cobalt-mediated molecular oxygen [9] or urea–hydrogen peroxide, [10] amination of ketenes, [11] addition of hydroxamic acid to propiolates, [12] and photolysis of nitrones.[13] The oxidation of an imine with a peracid, usually *meta*-chloroperbenzoic acid (*m*-CPBA), represents the most widely employed method for oxaziridine preparation [14].

The strained oxaziridine ring offers an unusually high reactivity due to the inherently weak N–O bond and has received considerable attention particularly due to the chirality

of the nitrogen atom, which shows an inversion barrier of 25–32 kcal/mol in N-alkyl substituted oxaziridines. [15]

Since their discovery, [1] oxaziridines have increasingly been employed as oxygen or nitrogen donors in organic synthesis, depending on their structural electronic features and the nature of the nucleophile. [16-17]

However, although N-alkyl and N-aryl oxaziridines are only weak oxidants, the analogues bearing an electron-withdrawing group, such as N-sulfonyl and N-phosphinoyl oxaziridines, react with a broad array of nucleophiles, including enolates, silyl enol ethers, organometallic compounds, alkenes, arenes, tertiary amines, thiols, thioethers, and selenides.[16] A remarkably useful property of these heterocyclic compounds is the configurational stability of the nitrogen atom, due to the combined effects of the ring strain and the presence of the electron-withdrawing oxygen atom, so that it is possible to synthesize enantio enriched oxaziridines.[18] Moreover, chiral oxaziridines, especially the N-sulfonyl derivatives commonly known as Davis reagents, have successfully been employed in several enantio-selective oxidations, such as α-hydroxylation of enolates, oxidation of sulfides, selenides, alkenes, and sulfenimines.[19-22]

The oxidation of sulfides to sulfoxides is a highly important synthetic transformation that has received much attention in recent years.[23] Asymetric sulfoxides are highly useful as synthons and chiral auxiliaries in asymmetric synthesis.[24] Some of the most successful techniques that are currently available for asymmetric sulfoxidation include the

stoicheiometric or catalytic [25] use of enantiomerically pure oxaziridine reagents and the use of oxaziridium salts,[26] which give the greatest eanatio-selectivities for the oxidation of sulfides.

The dihydroisoquinolines oxaziridines **1a-c** (Scheme 1) have previously been reported to represent promising agents for the transfer of oxygen on organosulfides if the oxygen transfer is promoted by an acid.[27,28,29] In this case, N-protonated oxaziridines play the role of the active oxidizing species, which enables the transfer of its oxygen to a sulfide in the presence of acid.

In the absence of sulfide, oxaziridine, which is equally O-protonated, isomerizes into nitrone **2a-c** (Scheme 2).

However, the structural modification of oxaziridine, most notably the substitution at position 1, can result in useful reagents for the electrophilic oxidation of nucleophiles [28].

Considering the promising opportunities that novel oxaziridines might open for the development of various applications, the present study aimed to synthesize two new oxaziridines, namely **3** and **4**. We also examine the effect of the introduction of a nitro group in position 7 and of a tichloromethyl substitute in position 1 on the oxidation of sulfides into sulfoxides.

RESULTS AND DISCUSSION

Synthesis Of Oxaziridines 3 And 4

The two new oxaziridines presented in this study were synthesized starting from the commercial tertiary alcohol **5** (Scheme 3). The imine **6** from step (a) was obtained by the cyclization of the tertiary alcohol **5** by Ritter-type procedure. The nitration of imine **6** under soft conditions [30, 31] selectively led to the derived imine **7**. The peracidic oxidation of imines **6** and **7** led to good yields of oxaziridines **3** and **4**, respectively (Scheme 3).

Oxygen Atom Transfer Onto Sulfides

In order to check the oxidizing properties of the two new oxaziridines **3** and **4**, the results of oxygen transfer of thioanisole into the corresponding sulfoxide was examined as a model reaction in the presence and absence of acid (Table 1).

The oxidation of thioanisole with **3** and **4** were first performed under the conditions previously described elsewhere [29] at room temperature in the presence of methanesulfonic acid (MSOH) in dichloromethane (entry 1).

The results presented in Table 1 revealed that the oxidation of thioanisole with oxaziridines **3** and **4** was not total; the data indicated a conversion of 65% (with **4**) and 40% (with **3**) (entry 1) into the corresponding sulfoxide, respectively.

The presence of a nitro group in position 7 increased the electrophile of oxaziridine, thus increasing the conversion rate. This is consistent with the results reported in our previously work. [28, 29]

The introduction of a nitro group onto the dihydroisoquinoline skeleton could be stipulated to induce a significant variation in the reactivity of oxaziridine. However, the oxidation of the same reagent (thioanisole) by oxaziridines **3** and **4** was performed, without acid, at reflux for 7h in different solvents (entries 2-4).

Oxaziridine **4** oxidized thioanisole quantitatively to the corresponding sulfoxide with variable yields in different solvents. The best sulfoxide production yield was obtained using chloroform as a solvent (Table 1, entry 2).

When the oxidation of thioanisole was performed using oxaziridine **3** under the same conditions, no reaction was observed and the starting reagent was recovered.

Without a nitro group (oxaziridine **3**), no oxygen transfer was observed by increasing the basicity of the function. Hence, the presence of a nitro group increased the electrophile of oxaziridine, thus making the reaction of the oxygen transfer onto sulfide easier.

It should be noted, when the oxidation of thioanisole was performed using oxaziridines **1b** [29] and **1c** [28] under the same conditions, in absence of acid and at reflux in chloroform for 7 h, no oxygen transfer was observed and the starting reagent was recovered (Table 1, entries 5 and 6).

The oxidation of other sulfides, such as *p*-tolyl methyl sulfide, dimethyl , diphenyl , dibenzyl, benzyl phenyl and aryl benzyl sulfides, was then examined using oxaziridine **4** under the optimized reaction conditions, in the absence of acid, in chloroform, and with heating at reflux for 7 h (Table 2).

The results of oxygen transfer are listed in Table 2. The results revealed that the presence of sulfide led to oxygen transfer.

Oxaziridine **4** oxidized sulfides quantitatively upon heating at reflux and in the absence of acid, giving a good sulfoxide conversion rate without over oxidation into sulfones. The reaction yield was noted to depend on the nucleophilicity of the sulfides. In fact, the yields required for the oxidation of sulfides 1 and 2 into the corresponding sulfoxides were the same.

It can be observed that the efficiency of the oxidation is related with the electronic property of substrates. Compared with the electron-withdrawing groups at *p*- position of phenyl ring, the electron-donating groups were more favorable to the conversion of sulfides (entries 1-5).

The influence of steric effects could be observed. Using diphenyl , dibenzyl, benzyl phenyl and aryl benzyl sulfides, the yields of the reaction of oxygen transfer was slightly decreased (entries 6-9).

Conversely, the best rates of dimethylsulfide oxidation were obtained by oxaziridine **4** (entry 10).

The introduction of the two attractor groupings, trichloromethyl in position 1 and nitro group in position 7, onto the dihydroisoquinoline skeleton of the function was noted to bring a significant variation in terms of oxaziridine reactivity, with the resulting oxaziridine **4** being able to oxidize sulfide into sulfoxide in the absence of acid.

Accordingly, the steric hindrance around the oxygen atom resulted from the presence of the strong electron-withdrawing trichloromethyl substitute of oxaziridine **4** was compatible with the oxygen transfer, and does not block it.

Overall, this study is the first to report on a dihydroisoquinoline-derived oxaziridine able to oxidize a sulfide into sulfoxide in the absence of acid.

CONCLUSION

The present study aimed to investigate the effect of introducing trichloromethyl and nitro groups on the dihydroisoquinoline skeleton. The results revealed that the oxaziridine became more electrophilic and that the reaction of oxygen transfer onto sulfide became possible in the absence of acid. This reactivity, which is actually novel for dihydroisoquinoline-derived oxaziridine, can be considered promising because it offers interesting possibilities for future applications.

EXPERIMENTAL

Preparation Of Imine 6

To a cooled (0°C) solution (7. 5 mL) of sulfuric acid H_2SO_4 (95%) was added dropwise and under magnetic stirring, 2 mL of trichloroacetonitrile in 28 mL of hexane. Then, (1.5 g, 9.98 mmol) of tertiary alcohol **1** (commercial product) in 15 mL of hexane was added to the solution. After return to room temperature, the resulting mixture was stirred under reflux for 2.5 h. Then, the solution is cooled at 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 and the crude material was then purified by chromatpgraphy (silica gel, eluent dichloromethane/ methanol 95:5) to afford the imine **6** as pure compound.

Yield: 90%. Mp: 74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.27 (s, 6H, 2-CH_3) ,2.74 (s, 2H , CH_2),7.22 (d, *J*= 8.7Hz ,1H),7.30 (m,1H),7.38 (m,1H), 8.11 (d, *J*= 7.8 Hz ,1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.75 (2C), 39.02, 55.74, 97.67, 122.79, 126.16, 127.60, 128.70, 131.20, 138.31, 157.90. IR (KBr): υ 2970 cm^{-1} (CH_3), 1690 cm^{-1} (C=N), 1618 cm^{-1} (Ar). HRMS-ES $[M+Na]^+$ calc for $C_{12}H_{12}NCl_3$ Na 297.9933 found 297.9929.

Preparation Of Imine 7

The cold imine **6** (980 mg, 3.56 mmol) was added dropwise to 21.5 mL of concentrated sulfuric acid. A solution of 827mg potassium nitrate in 5.5 mL of sulfuric acid is added dropwise by maintaining the temperature at less than 0°C. The reactional medium was

stirred at room temperature for 2h and then at 60°C for 4h. After return to room temperature, the reaction mixture is poured into ice-cold water and alkalized with ammonia. The organic phase was extracted with the dichloromethane, washed with brine, dried over sodium sulfate, and filtered. The solvent was removed in vacuo. The residue was purified by chromatography (silica gel, eluent dichloromethane/ methanol 95:5) to afford the imine **7** as pure compound.

Yield: 77%. Mp: 115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1,33 (s, 6H, 2-CH_3), 2.89 (s, 2H, CH_2), 7.44 (d, *J*=8.3 Hz, 1H), 8.30 (dd , *J*= 2.2, 8.3 Hz , 1H), 9.04 (d , *J*= 1.9 Hz, 1H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.77 (2C), 39.00, 55.98, 96.68, 122.79, 125.77, 126.64, 129.61,145.54, 146.45, 156.16. IR (KBr): υ 1342 cm^{-1} (NO_2), 1514 cm^{-1} (Ar), 1622 (C=N), 2966 cm^{-1} (CH_3). Anal.calc. for $C_{12}H_{11}N_2O_2Cl_3$: C, 44.82; H, 3.45; N, 8.71. Found: C, 44.88; H, 3.33; N, 8.96.

Preparation Of Oxaziridine 3

To a solution of imine **6** (300 mg, 1.09 mmol) in methanol (10 mL) was added in small portions, an excess of *m*-chloroperbenzoic acid (537.2 mg, 3.11 mmol, 2 equiv of active oxygen) under magnetic stirring and at room temperature. The reaction was followed by TLC (dichloromethane/methanol: 9:5). The solvent was evaporated and the residue obtained was taken up in dichloromethane. The solution was washed with a solution of sodium bicarbonate then with a saturated aqueous NaCl solution. The organic phase was dried over sodium sulfate, filtered, and concentrated. The residue was then purified by crystallization from ether/ hexane (1:1) to afford crystals of oxaziridine **3**.

Yield = 63%. Mp: 110°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.00 (s, 3H, CH_3),1.56 (s, 3H,CH_3), 2.49 (d, *J*=15.4 Hz,1H), 2.87 (d, *J*=15.4 Hz,1H), 7.19 (d, *J*=7.4 Hz, 1H),7.34 (m, 1H), 7.40 (m, 1H), 8.40 (dd, *J*=1.2, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.29, 28.58, 37.93, 57.41, 81.66, 99.10, 124.14, 125.96, 129.31, 129.72, 130.93,136.74. MS (EI): 291 ($M^{+\cdot}$, base peak), 174 (291- 117), 77 (291-214). IR (KBr): υ 768 cm^{-1} (C-N), 1577 cm^{-1} (Ar), 2972 cm^{-1} (CH_3). Anal. calc. for $C_{12}H_{12}NOCl_3$: C, 49.26; H, 4.13; N, 4.79. Found: C, 49.36; H, 4.10; N, 4.65.

Preparation Of Oxaziridine 4

To a solution of imine **7** (200 mg, 0.62mmol) in methanol (7 mL) was added in small portions, an excess of *m*-chloroperbenzoic acid (280 mg, 1.62 mmol, 2 equiv of active oxygen) under magnetic stirring at room temperature. The reaction was followed by TLC (dichloromethane/methanol: 9:5). The solvent was evaporated and the residue obtained was taken up in dichloromethane. 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. The residue was then purified by crystallization from ether/ hexane (1:1) to afford crystals of oxaziridine **4**.

Yield = 70 %. Mp: 127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.01 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.65 (d, *J*=15.9 Hz, 1H, CH_2), 2.93 (d, *J*=16 Hz,1H, CH_2), 7.39 (m, 1H), 8.28 (dd, *J*=2.2, *J*=8.3 Hz, 1H), 9.35 (d, J=2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 17.52, 23.60, 33.29, 52.95, 76.57, 93.34, 119.71, 121.68, 125.42, 128.99, 139.40, 141.57.

IR (KBr): υ 771 cm^{-1} (C-N), 1383 cm^{-1} (NO_2), 1521 cm^{-1} (Ar), 2871 cm^{-1} (CH_3). Anal. calc. For $C_{12}H_{11}N_2O_3Cl_3$: C, 42.69; H, 3.28; N, 8.30. Found: C, 42.40; H, 3.28; N, 8.08.

Oxygen Transfer To Sulfides With Oxaziridines 3 And 4 In Presence Of Acid

A solution of the oxaziridine **3** and **4** (0.50 mmol) in methylene chloride (2 mL) was added to a solution of thioanisole (0.50 mmol) and methanesulfonic acid (1.5 mmol) in methylene chloride (2 mL). The reaction mixture was stirred at room temperature until the disappearance of the active oxygen, as monitored by TLC and potassium iodide test, and then 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 sulfoxide was purified by chromatography on silica gel. The sulfoxide was purified by chromatography in silica gel using dichloromethane/ methanol 95:5 as eluent.

The sulfoxide obtained is compared and identified with commercial samples. The results obtained are presented in Table 1 (entry 1).

Oxygen Transfer To Sulfides With Oxaziridines In Absence Of Acid

A solution of oxaziridine **3, 4, 1b** and **1c** (1 mmol) in chloroform (20 mL) was heated at reflux in the presence of sulfide (1 mmol). The reaction was taken under magnetic stirring and heating for 7 h and monitored by TLC. Then, the reaction products were identified by ^1H NMR spectroscopic analysis. All The isolated sulfoxide compounds were purified by chromatography over silica gel using dichloromethane/ methanol 95:5

as eluent. The sulfoxides obtained are compared and identified with commercial samples. The results obtained are presented in Table 1 (entries 2, 5-6).

This reaction was carried out using also acetonitrile (20 mL) and methanol (20 mL) as solvent. The results obtained are presented in Table 1 (entries 3-4).

Characterization Data For Sulfoxides (Table 1)

Methyl phenyl sulfoxide (entry 1) [32]: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65-7.63 (m, 2H), 7.55-7.47 (m, 3H), 2.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.8, 131.2, 129.5, 123.6, 44.1.

***p*-Tolylmethyl sulfoxide (entry 2)** [32]: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (d, *J*= 8.0 Hz, 2H), 7.33 (d, *J*= 8.0 Hz, 2H), 2.69 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 142.5, 141.6, 130.2, 130.1, 123.6, 44.1, 21.5.

4-Methoxyphenyl methyl sulfoxide (entry 3) [32]: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57 (d, *J*= 8.0 Hz, 2H), 7.01 (d, *J*= 8.0 Hz, 2H), 3.82 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.0, 136.6, 125.5, 114.9, 55.6, 44.0.

***p*-Chlorophenyl methyl sulfoxide (entry 4)** [32]: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59 (d, *J*= 8.0 Hz, 2H), 7.50 (d, *J*= 8.0 Hz, 2H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 144.3, 137.3, 129.8, 125.1, 125.0, 44.1.

***p*-Nitrophenyl methyl sulfoxide (entry 5)** [33]: ^{1}H NMR (300MHz, $CDCl_3$, 278K, TMS): δ 2.56 (s, 3H, Me), 7.84 (d, 2H), 8.34(d 2H); ^{13}C NMR (75MHz, $CDCl_3$, 278K, TMS): 47.7, 124.5, 149.3, 153.1.

Diphenyl sulfoxide (entry 6) [32]: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65-7.63 (m, 4H), 7.47-7.43 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.7, 131.2, 129.4, 124.9.

Dibenzyl sulfoxide (entry 7) [34]: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.89 (d, 4H), 7.21-7.40 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 130.10, 129.01, 128.02, 57.10.

Benzyl phenyl sulfoxide (entry 8) [35]: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47-7.36 (m, 5H), 7.29-7.23 (m, 3H), 6.99 (d, *J*= 8.0 Hz, 2H), 4.12 (d, *J*= 16.0 Hz, 1H), 4.01 (d, *J*= 12.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 131.2, 130.4, 129.1, 128.9, 128.5, 128.3, 124.5.

Benzyl cyclohexyl sulfoxide (entry 9) [36]: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.29 (m, 3H), 1.51 (m, 2H)), 1.69 (m, 1H), 1.88 (m, 3H), 2.09 (m, 1H) , 2.48 (m, 1H), 3.90 (m, 2H) 7.34 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 130.85, 129.90, 128.50, 127.90, 56.98, 54.50, 26.98, 25.01, 24.87, 23.99.

Dimethyl sulfoxide (entry 10) [37]: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.62 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 40.76.

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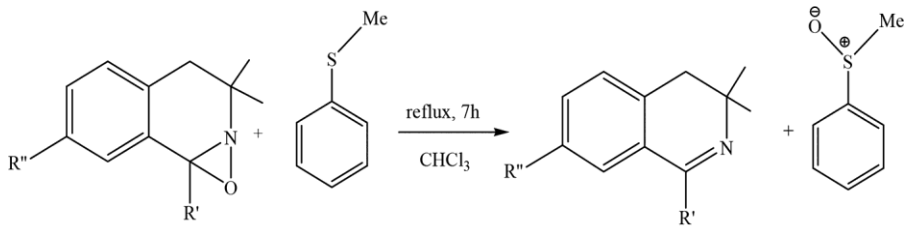
Table 1. Oxidation of thioanisole with oxaziridines **3, 4, 1b** and **1c**



3 R'= CCl_3, R''=H
4 R'= CCl_3, R''=NO_2
1b R'= H, R''=NO_2
1c R'= Me, R''=NO_2

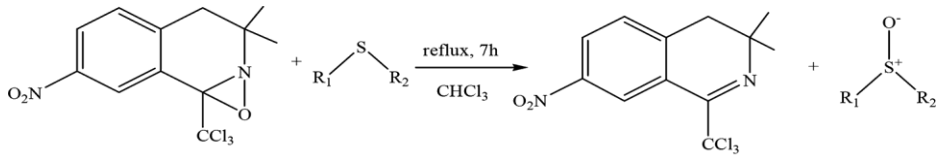
Entry	R'	Acid	Temperature (°C)	Solvent	Time[a]	Yield of thioanisole (%) (conversion)[b]	
						R''=NO_2	R''=H
1	CCl_3	MsOH	25	CH_2Cl_2	24 h	40 [c] (65)	20 (40)
2	CCl_3	No	61	$CHCl_3$	7 h	82[c] (100)	0
3	CCl_3	No	81	CH_3CN	7 h	76 [c] (100)	0
4	CCl_3	No	68	MeOH	7 h	74 [c] (100)	0
5	H	No	61	$CHCl_3$	7 h	0	-
6	Me	No	61	$CHCl_3$	7 h	0	-

[a] Determined by TLC.

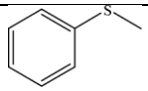
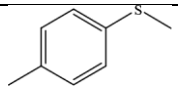
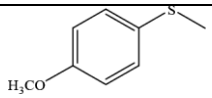
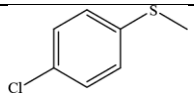
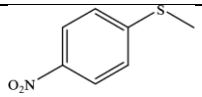
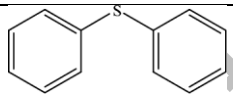
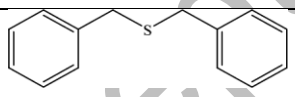
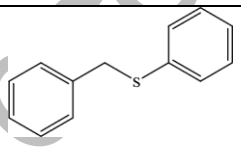
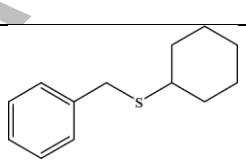
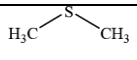
[b] Determined by ^1H NMR spectroscopy in $CDCl_3$.

[c] Isolated product.

Table 2. Oxidation of sulfides[a] with oxaziridine **4** in the absence of acid



4

Entry	Sulfides	Yield of sulfoxide (%) (conversion)[b]
1		82[c] (100)
2		80[c] (100)
3		80 [c] (100)
4		77 [c] (100)
5		75 [c] (100)
6		65 [c] (100)
7		68 [c] (100)
8		70 [c] (100)
9		72 [c] (100)
10		quantitative [d]

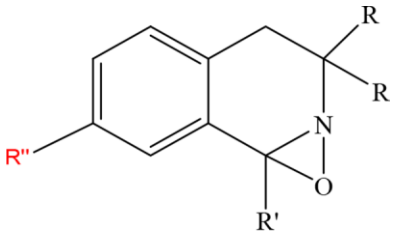
[a] Reaction performed at reflux in $CHCl_3$

[b] Determined by ^{1}H NMR spectroscopy in $CDCl_3$.

[c] Isolated product

[d] Reaction performed in $CDCl_3$

Scheme 1. Oxaziridines **1a-c**.

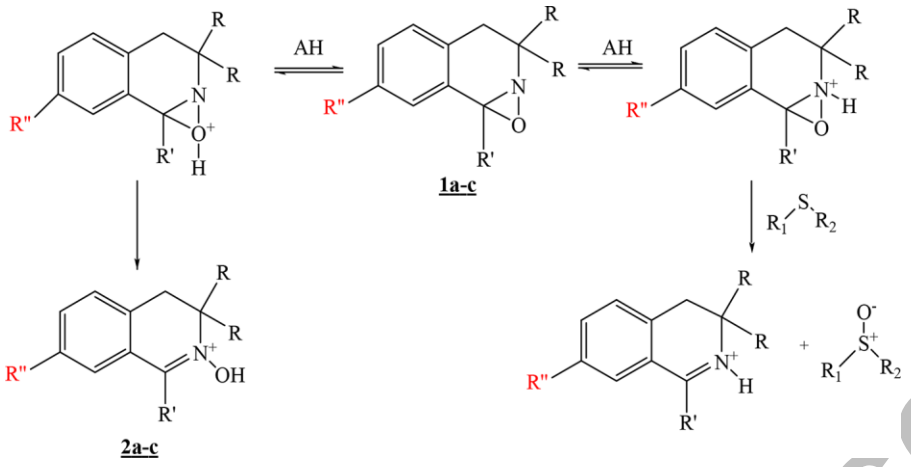


1a R=R'=R''=H

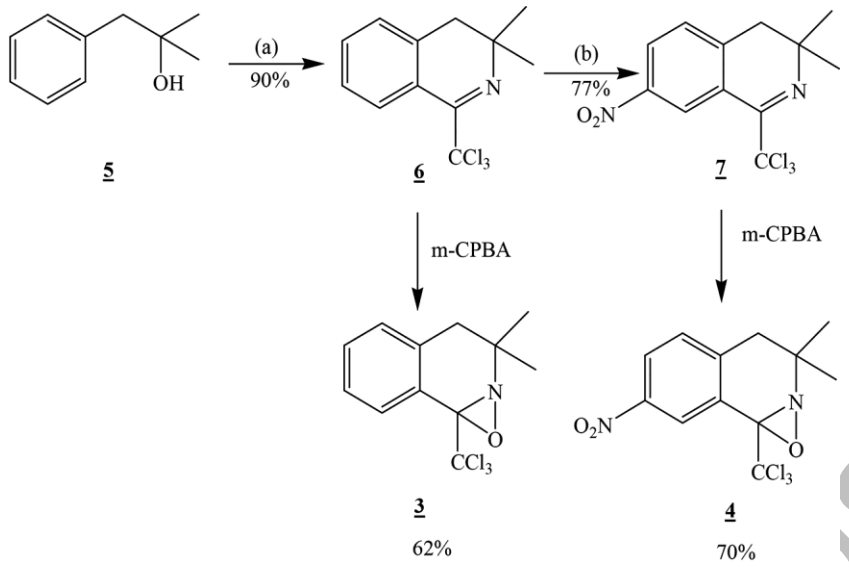
1b R=Me, R'=H, R''=NO_2

1c R=R'=Me, R''=NO_2

Scheme 2. Reactivity of oxaziridines **1a-c**



Scheme 3. Synthesis of oxaziridines **3** and **4**



[a] H_2SO_4, CCl_3CN, hexane; 68°C, 2h. 30 min.

[b] KNO_3-H_2SO_4; rt 2h; 60°C, 4h.