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► **To cite this version:**

A. Selmi, R. Aydi, Paul Mosset, R. Grée, M. Kammoun. Synthesis and reactivity of new dihydroisoquinoline-derived oxaziridines. ARKIVOC - Online Journal of Organic Chemistry, 2019, 2019 (5), pp.108-120. 10.24820/ark.5550190.p010.826 . hal-02122156

HAL Id: hal-02122156

<https://univ-rennes.hal.science/hal-02122156>

Submitted on 9 Jul 2020

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Synthesis and reactivity of new dihydroisoquinoline-derived oxaziridines

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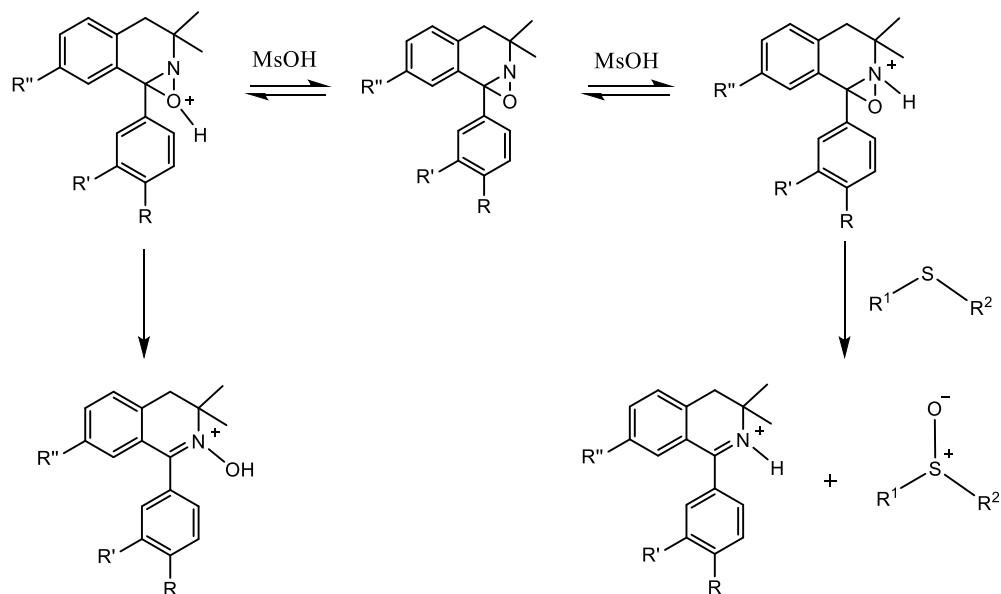
Received 11-26-2018

Accepted 02-03-2019

Published on line 03-03-2019

Abstract

N-Alkyl oxaziridines react as oxygenating reagents in the presence of a nucleophile. In this work, we describe the synthesis of new dihydroisoquinoline oxaziridines, and their reactivity in an acid-promoted reaction both in presence and in absence of sulfides. In the absence of sulfides, a new nitron is produced.



Keywords: Synthesis, oxaziridine, nitron, sulfoxidation

Introduction

Since their discovery by Emmons in 1956,¹ oxaziridines have gained increasing attention.² The oxaziridine function contains a three-membered ring with a carbon, an oxygen and a nitrogen atom. The literature indicates that these compounds have been extensively explored because of the inherently weak N-O bond due to the strained ring that makes the molecule unusually highly reactive. These heterocycles have attracted considerable attention due to various biological properties such as anti-tumor,^{3,4} anti-malarial,⁵ and antifungal⁶ to analogues of penicillin.⁷ Furthermore, they are widely used as reagents and intermediates in the preparation of biologically active molecules.^{8,9} Recently, dihydroisoquinoline oxaziridines, including those with trichloromethyl in position 1, have been shown to have potent hypolipidemic effect in high-fat diet-fed rats.¹⁰

The major routes to the synthesis of oxaziridines involve the photolysis of nitrones,¹¹ the electrophilic amination of carbonyl compounds,¹² and the double 1,4-conjugate addition of hydroxamic acids to propiolates.¹³ Oxaziridines can also be prepared by oxidation of imines with several oxidizing agents, such as cobalt-mediated molecular oxygen,¹⁴ urea-hydrogen peroxide,¹⁵ oxone,¹⁶ hydrogen peroxide,¹⁷ or a nitrile-hydrogen peroxide system.¹⁸ The oxidation of an imine with a peracid, usually *meta*-chloroperbenzoic acid (*m*-CPBA), is the most frequently employed method for oxaziridine preparation.¹⁹

Since the first discovery of this function,¹ oxaziridines are well known as both aminating and oxygenating reagents in their reactions with a wide variety of nucleophiles and their structural electronic features.²⁰⁻²² The substituents on the nitrogen atom of oxaziridines play a significant role in atom transfer reactions.^{23,24} The presence of an electron-withdrawing group on the nitrogen atom substantially increases the reactivity of oxaziridines as oxygen donors.²⁵ However, oxaziridines with small groups substituted on the nitrogen are electrophiles and they behave as amino group transfer agents to nucleophiles such as *N*-H,²¹ *N*-alkyl,²¹ and *N*-alkoxycarbonyloxaziridines.²¹

The oxidation of sulfides to sulfoxides is an important synthetic transformation that has received much attention in recent years.²⁶ Moreover, sulfoxides are useful as synthons and chiral auxiliaries in asymmetric synthesis.²⁷ Some of the most successful techniques that are currently available for asymmetric sulfoxidation include the stoichiometric or catalytic²⁸ use of enantiomerically pure oxaziridine reagents and the use of oxaziridium salts,²⁹ which give the greatest enantioselectivities for the oxidation of sulfides.

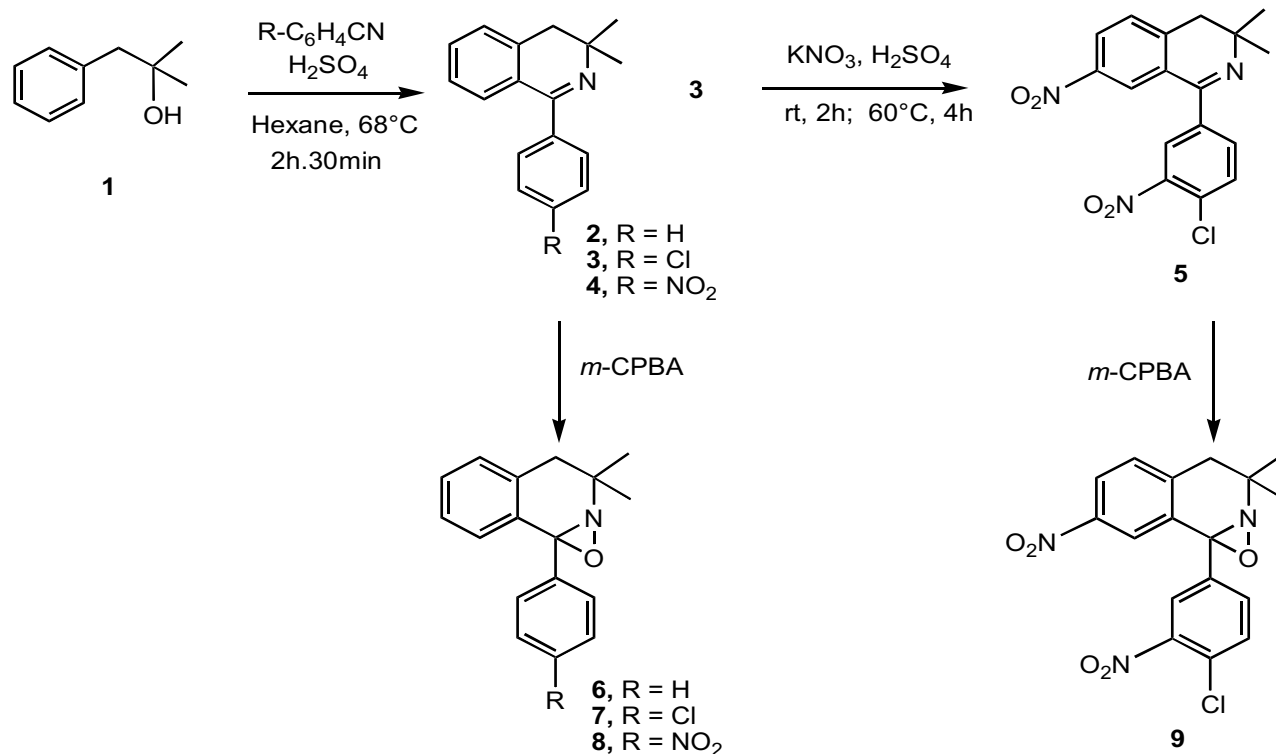
The dihydroisoquinoline oxaziridines have previously been reported to be promising agents for the transfer of oxygen to organosulfides in the presence and absence of acid.³⁰⁻³³ The substitution at position 1 onto the dihydroisoquinoline skeleton has a marked influence in the formation of sulfoxide or nitrone products from the oxidation reactions of the oxaziridines.^{31,33}

We have noted a significant variation in reaction times when we changed the structure of oxaziridine, most notably the substitution at position 1. Indeed, the unsubstituted dihydroisoquinoline oxaziridine can oxidize quickly the *p*-tolylmethyl sulfide to the sulfoxide,³² whereas oxygen transfer is slowest in the presence of steric hindrance, in position 1, of the oxaziridine.³¹

As part of our interest in the reactivity of oxaziridines and particularly in the design of a dihydroisoquinoline-derived family which is able to react in an oxygen transfer process, the present study aimed to synthesize new oxaziridines, namely **6-9**. We also examine the effect of the introduction of a *p*-chlorophenyl group substituted in position 1 and of two nitro groups, one in the phenyl ring and one in the isoquinoline skeleton, on the reaction of oxygen transfer to sulfides forming sulfoxides in an acid promoted reaction.

Results and Discussion

The new oxaziridines presented in the current study were synthesized starting from the commercial tertiary alcohol **1** (Scheme 1). The imines **2-4** from the first step were obtained by condensation of the tertiary alcohol **1** in a Ritter-type procedure. The nitration of imine **3** under mild conditions^{34,35} selectively led to the derived imine **5**. Oxidation of imines **2-5** with *m*-CPBA⁴² rapidly leads to oxaziridines **6-9** respectively, in good yields (Scheme 1).



Scheme 1. Synthesis of oxaziridines **6-9**.

We have focused on the structural modification of the oxaziridines, most notably the substitution at position 1, that can lead to useful reagents for the electrophilic oxidation of wide variety of nucleophiles.³¹ In an acidic medium and in the absence of nucleophiles, the oxaziridine can be subject to a competitive transformation which, through *O*-protonation, isomerize to a nitron. In the presence of nucleophiles, the oxaziridine can be an oxygen transfer agent to organo-sulfides, as has previously been reported.^{31,32}

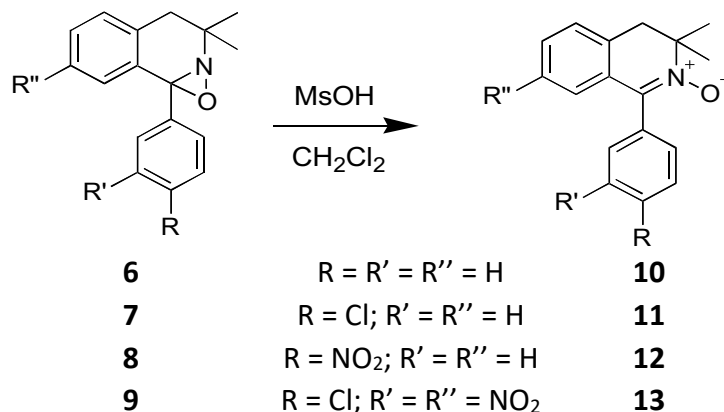
Herein, we study the isomerization reaction of new oxaziridines **6-9** with various amounts of methanesulfonic acid (MsOH) in dichloromethane as solvent at room temperature are reported in Table 1 below.

It can be noted from Table 1 that the isomerization of the oxaziridines **6-9** to nitrones **10-13** necessitates the optimization of the reaction conditions through adjusting the time for each one, which depends on the equivalents of methanesulfonic acid used [MsOH] and the different substrates employed, in particular those which are substituted at position 1.

Remarkably, we note an increase in the rate of conversion of oxaziridines into nitrones with increase in the number of equivalents of acid introduced in the reaction. Exceptional acceleration is noted for the isomerization on the addition of acid into the reaction. For example, when we change gradually the acid proportion to oxaziridine **9** we note that for 3 equivalents of acid (entry1, Table1) to transform **9** into the

nitronone **13** takes 5 days, and 2 days when 4 equivalents of acid are added (entry 2, Table1), but with 5 equivalents of acid (entry 3, Table1), 5 h are enough for the total isomerization of this oxaziridine into the corresponding nitronone in 82% yield.

Table 1. Oxaziridines **6-9** under the action of methanesulfonic acid in various concentrations



Entry	MsOH	Time ^a				Yield of nitronone ^b (%) (conversion) ^c			
		6	7	8	9	10	11	12	13
1	3 eq	12 min	5 min	3 days	5 days	80 (100)	76 (100)	60 (100)	59 (100)
2	4 eq	-	>1 min	24 h	48 h	-	78 (100)	70 (100)	72 (100)
3	5 eq	-	-	3h	5h	-	-	81 (100)	82 (100)

^a Reaction time followed by TLC. ^b Isolated product. ^c Determined by ¹H NMR spectroscopy in CDCl₃.

It is noteworthy that the reaction of oxaziridine **8**, with a *p*-nitrophenyl group in position 1, during the introduction of 3 equivalents of methanesulfonic acid (MsOH) (entry 1, Table 1) forms the corresponding nitronone **12** after only 3 days. While we were pleased to find that, with the oxaziridine **7**, the presence of *p*-chlorophenyl group in position 1 accelerates the reaction. It was only after 5min that the starting material is totally converted and the reaction led to nitronone **11** (entry 1, Table 1).

The results reported in Table 1 indicated that the presence of the withdrawing group (nitro) of the dihydroisoquinoline decreased the basicity of the substrate and slowed the isomerization reaction. In fact, the isomerizations of the oxaziridines **8** and **9** to nitrones were slower than those of oxaziridines **6** and **7** (entries 1 and 3).

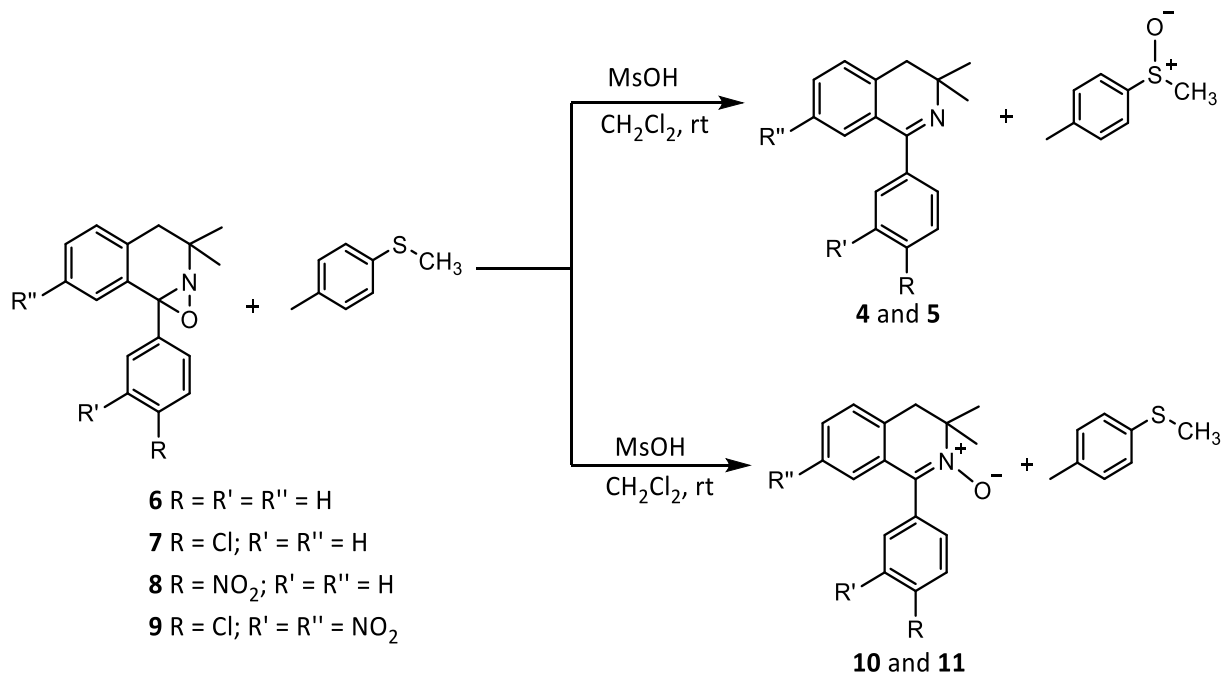
Table 2 summarizes the results of the oxidations of *p*-tolylmethyl sulfide with oxaziridines **6-9**, first performed under the conditions previously described elsewhere³² at room temperature in the presence of 3 equivalents of methanesulfonic acid (MsOH), in dichloromethane.

As shown in Table 2, the different substituents at positions 1 and 7 on the dihydroisoquinoline skeleton of the function are primarily responsible for the formation of sulfoxides or nitrones products from the oxidation reaction onto oxaziridines **6-9** (Table 2).

The oxidation of methyl *p*-tolyl sulfide to sulfoxides observed for **8** and **9** and give good sulfoxide conversion without any signs of overoxidation to the sulfones (Table 2, entries 3 and 4). When the oxidation of sulfide was performed using oxaziridines **6** and **7** under the same conditions, the reaction leads quantitatively and quickly to the corresponding nitrones **10** and **11** (Table 2, entries 1 and 2); no oxygen transfer reaction was observed.

Considering both the reaction time and yield, the best results were obtained using oxaziridine **8** and **9** (Table 2, entries 3 and 4); the reactions proceeded to completion within 15 min and 5 min respectively in high yields.

Table 2. Oxidation of methyl *p*-tolyl sulfide with oxaziridines **6-9** in the presence of methanesulfonic acid ^a



Entry	MsOH	Oxaziridine	Time ^b	Yield of sulfoxide (%) (conversion) ^d
1	3 eq	6	2 min	0
2	3 eq	7	5 min	0
3	3 eq	8	15 min	75 ^c (100)
4	3 eq	9	5 min	80 ^c (100)

^a Reaction performed at room temperature in CH₂Cl₂. ^b Reaction time followed by TLC. ^c Isolated product. ^d Determined by ¹H NMR spectroscopy in CDCl₃

The above data show that the introduction of a nitro group onto the dihydroisoquinoline skeleton could increase the electrophilicity of oxaziridines **8** and **9**, thus making the reaction of the oxygen transfer onto sulfide easier.

In our previous work,³³ 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 being able to oxidize sulfide into sulfoxide with heating at reflux for 7 h. Herein, we show that with the introduction of a *p*-chlorophenyl group in position 1 and of two electron-withdrawing nitro groups in position 7 and in the phenyl group, it was possible to oxidize the sulfide to sulfoxide at room temperature.

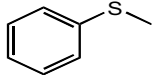
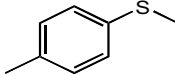
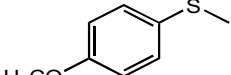
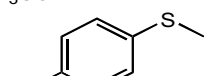
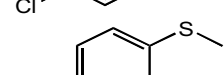
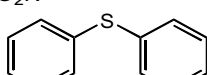
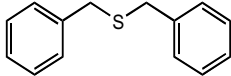
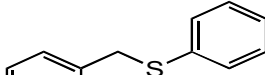
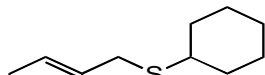
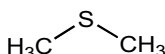
The structure of the oxaziridine C-aryl group has an effect on the oxygen transfer (Table 2). Although, the results revealed that the introduction of *p*-chlorophenyl group in position 1 and of two electron withdrawing nitro groups onto the dihydroisoquinoline skeleton of the function led to a significant variation in terms of oxaziridine **9** reactivity and thus notably accelerated the transfer of the oxygen atom (entry 4), the sulfoxide

was observed. In fact, the resulting oxaziridine **9** being able to oxidize sulfide into sulfoxide in the best time compared with the previously reported result in the literature.^{31,33}

Next, In order to check the oxidizing properties of oxaziridine **9**, the results of oxygen transfer of other sulfides into the corresponding sulfoxides was studied using a set of structurally diverse sulfides, in the presence of acid, in dichloromethane, at room temperature.

The results of oxygen transfer are shown in Table 3. It can be noted that the presence of sulfide leads to an oxygen transfer. The reaction yields and times were dependent on the nucleophilicity of the sulfides.

Table 3. Oxidation of sulfides with oxaziridine **9** in the presence of methanesulfonic acid ^a.

Entry	Sulfide	Time ^b	Yield of sulfoxide(%) (conversion) ^d
1		5 min	93 ^c (100)
2		5 min	91 ^c (100)
3		10 min	90 ^c (100)
4		10 min	80 ^c (100)
5		10 min	83 ^c (100)
6		20 min	72 ^c (100)
7		20min	75 ^c (100)
8		20 min	76 ^c (100)
9		20 min	78 ^c (100)
10		2 min	(100)

^a Reaction performed at room temperature in CH₂Cl₂. ^b Determined by TLC. ^c Isolated product. ^d Determined by ¹H NMR spectroscopy in CDCl₃.

The oxidation of sulfides by oxaziridine **9** is very efficient (Table 3). It leads to the complete conversion of sulfides to the corresponding sulfoxides in excellent yields; this conversion depends on the nucleophilicity of the different functional-group sulfides. Comparing the electron-withdrawing character of the groups on the phenyl ring, those with an electron-donating substituent showed good conversion of the sulfides (entry 1-5).

The influence of steric effects could be observed. Yields of oxygen transfer reaction are slightly decreased (entries 6–9) when diphenyl, dibenzyl, benzyl phenyl, and aryl benzyl sulfides were used. Conversely, oxidation of dimethyl sulfide by oxaziridine **9** was fastest (entry 10).

Conclusions

The present study aimed to investigate the effect of introducing a *p*-chlorophenyl group in position 1 and two nitro groups on the dihydroisoquinoline skeleton. The results revealed that the oxaziridine became more electrophilic and that the reaction of oxygen transfer to sulfide became faster.

Considering the promising properties of these new products, the three oxaziridines and their corresponding nitrones, further studies are currently under way in our laboratories to investigate their biological activities.

Experimental Section

General. Chromatography: All reactions were monitored by TLC: Merck silica gel 60 (0.25mm). Visualization of the TLC was performed by UV light or stained with Dragendorff reagent. Solvents were purified by standard methods. High resolutions (HR) were obtained on a GC-HRMS Micromass Autospec (IE). ¹H and ¹³C were recorded on a Bruker 400 and a Bruker AC 300, using CDCl₃ as solvent. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet triplet, m = multiplet), coupling constants (Hz), and integration. Melting points (mp) were determined under microscope with a Leitz Wetzlar device. All reagents and solvents were used as received. Imines, oxaziridines and nitrones were prepared according to the literature. Reference sulfoxide compounds were synthesized following procedures described in literature.

General procedure for preparation of imines 2-4. To cooled (0 °C) 95% sulfuric acid (10 ml) and under magnetic stirring, was added dropwise a benzonitrile (1.25eq). Then (500 mg, 3.33mmol) of tertiary alcohol 1,1-dimethyl-2-phenylethanol (**1**, commercial product) in cyclohexane (10 ml) was added to the solution. After return to room temperature, the resulting mixture was stirred under reflux for 2.5 hours. Then, the solution is cooled at room temperature and versed on ice-cold water 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 chromatography (silica gel) to afford the imine as pure compound.

3,3-Dimethyl-1-phenyl-3,4-dihydroisoquinoline (imine 2). Reaction of benzonitrile (429 mg, 1.25eq) according to the general procedure afforded **2** of (83%), isolated as a white solid, mp 69-71 °C; ¹H NMR (CDCl₃, 400MHz): δ (ppm) 1.34 (s, 6H, 2-CH₃), 2.86 (2H, CH₂), 7.23-7.61 (m, 9H). ¹³C NMR (CDCl₃, 75MHz): δ 27.64 (2C), 38.8, 54.5, 126.4, 127.9, 128.0, 128.1, 128.2, 128.8, 128.95, 130.7, 137.5, 139.3, 164.5. HRMS (ESI) [M + H]⁺ calc. For C₁₇H₁₈N 236.1433; found 236.1424.

1-(4-Chlorophenyl)-3,3-dimethyl-3,4-dihydroisoquinoline (imine 3). Reaction of 4-chlorobenzonitrile (572mg, 4.16mmol) according to the general procedure afforded **3** (72%), isolated as a white solid, mp 112-115 °C; ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 1.27 (s, 6H, 2-CH₃), 2.80 (2H, CH₂), 7.16 (m, 1H), 7.39 (m, 2H), 7.39 (m, 2H),

7.51 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 27.6 (2C), 38.8, 54.7, 126.6, 127.7, 128.4, 130.3, 130.95, 135.1, 137.6, 137.7, 163.6. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{17}\text{ClN}$ 270.1044; found 270.1034.

3,3-Dimethyl-1-(4-nitrophenyl)-3,4-dihydroisoquinoline (imine 4). Reaction of 4-nitrobenzotrile in 10 ml of cyclohexane (572mg, 4.16mmol) according to the general procedure afforded **4** (83%), isolated as a white solid, mp 136-138 °C; ^1H NMR (CDCl_3 , 300 MHz): δ (ppm) 1.34 (s, 6H, 2- CH_3), 2.87 (2H, CH_2), 7.11 (d, J 5Hz, 1H), 7.3 (m, 2H), 7.50 (m, 1H), 7.78 (d, J 5Hz, 2H), 8.32 (d, J 5Hz, 2H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 27.4 (2C), 38.7, 55.3, 123.5, 126.85, 127.4, 128.7, 129.9, 131.61, 131.63, 137.5, 144.9, 148.3, 163.25. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2$: 281.1284; found 281.1275.

Preparation of 1-(4-chloro-3-nitrophenyl)-3,3-dimethyl-7-nitro-3,4-dihydroisoquinoline (imine 5). The cold imine **3** (600 mg, 2.22 mmol) was added dropwise to concentrated sulfuric acid (6 ml). A solution of potassium nitrate (516 mg) in sulfuric acid (4 ml) is added dropwise, maintaining the temperature at below 0 °C. The reactional medium was stirred at room temperature for 2 h and then at 60 °C for 4 h. after return to room temperature, the reaction medium is poured on ice-cold water and alkalized with ammonia. The organic phase is extracted with the dichloromethane, washed with a solution saturated in sodium chloride, 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 **5** (93%), mp 194-196 °C; as pure compound. ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.31 (s, 6H, 2- CH_3), 2.94 (2H, CH_2), 7.49 (d, J 8.3 Hz, 1H), 7.68 (d, J 2.2 Hz, 1H), 7.74 (dd, J 8.3, 2.2 Hz, 1H), 8.04 (d, J 2.2 Hz, 1H), 8.19 (d, J 2.2 Hz, 1H), 8.32 (dd, J 8.3, 2.2 Hz, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 27.3 (2C), 38.7, 55.6, 121.5, 125.95, 126.1, 127.3, 128.5, 129.87, 132.1, 132.8, 137.8, 145.1, 147.0, 148.2, 159.75. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{15}\text{ClN}_3\text{O}_4$ 360.0745; found 360.0734.

General procedure for preparation of oxaziridines 6-9

In small portions, a slight excess of *m*-chloroperbenzoic acid (1.5 eq of active oxygen) was added to a solution of imine **2-5** in methanol (10 mL) under magnetic stirring at room temperature. The reaction was controlled by TLC (Ether/Hexane 1:1). The solvent was evaporated, and the residue obtained was taken up in dichloromethane. The solution was washed with aqueous sodium bicarbonate and then with a saturated solution of sodium chloride. The organic phase was dried on sodium sulfate, filtered, and concentrated. The residue was purified by chromatography (silica gel) to afford the oxaziridine as a pure compound.

3,3-Dimethyl-8b-phenyl-4,8b-dihydro-3H-oxazirino[2,3-*a*]isoquinoline (oxaziridine 6). Reaction of imine **2** (300 mg, 1.27 mmol) according to the general procedure afforded **6** as a white solid (85%), mp 106-108 °C; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.13 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.55 (d, J 15.4 Hz, 1H), 2.92 (d, J 15.4 Hz, 1H), 7.03 (d, J 7.3 Hz, 1H), 7.17 (m, 2H), 7.34 (m, 1H), 7.44 (m, 5H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.8, 28.8, 37.3, 56.8, 81.6, 126.3, 127.2, 128.2, 128.3, 128.5, 128.6, 129.3, 130.9, 135.4, 137.2. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{18}\text{NO}$ 252.1382; found 252.1374.

8b-(4-Chlorophenyl)-3,3-dimethyl-4,8b-dihydro-3H-oxazirino[2,3-*a*]isoquinoline (oxaziridine 7). Reaction of imine **3** (200 mg) according to the general procedure afforded **7** as a white solid (85%), mp 147-149 °C; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.13 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.55 (d, J 15.4 Hz, 1H), 2.92 (d, J 15.4 Hz, 1H), 7.02 (d, J 7.1 Hz, 1H), 7.18 (m, 2H), 7.36 (m, 1H), 7.43 (m, 4H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.8, 28.7, 37.3, 56.8, 81.2, 126.4, 128.5, 128.7, 128.8, 129.6, 130.3, 130.6, 134.5, 135.4, 135.8. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{17}\text{ClNO}$ 286.0993; found 286.0983.

3,3-Dimethyl-8b-(4-nitrophenyl)-4,8b-dihydro-3H-oxazirino[2,3-*a*]isoquinoline (oxaziridine 8). Reaction of imine **4** (200 mg, 0.71mmol) according to the general procedure afforded **8** (91%), isolated as a white solid, mp 170-173 °C; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.15 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.58 (d, J 15.5 Hz, 1H), 2.93 (d, J 15.5 Hz, 1H), 6.93 (d, J 7.7 Hz, 1H), 7.20 (m, 2H), 7.46 (m, 1H), 7.66 (d, J 8.6 Hz, 2H), 8.33 (d, J 8.6 Hz,

2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.8, 28.5, 37.0, 57.0, 81.0, 123.35, 126.6, 128.5, 129.0 (2C), 129.3, 130.3, 135.4, 144.2, 148.0. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_3$: 297.1233; found 297.1224.

8b-(4-Chloro-3-nitrophenyl)-3,3-dimethyl-7-nitro-4,8b-dihydro-3H-oxazirino[2,3-a]isoquinoline (oxaziridine 9).

Reaction of imine **5** (100 mg, 0.27 mmol) according to the general procedure afforded **9** (96%), isolated as a white solid, mp 221-223 °C; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.13 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.72 (d, J 16.0 Hz, 1H), 2.96 (d, J 16.0 Hz, 1H), 7.43 (d, J 8.3 Hz, 1H), 7.63 (dd, J 8.3, 2.2 Hz, 1H), 7.72 (d, J 8.3 Hz, 1H), 7.90 (d, J 2.2 Hz, 1H), 8.01 (d, J 2.2 Hz, 1H), 8.27 (dd, J 8.3, 2.2 Hz, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.75, 28.4, 37.2, 57.2, 79.55, 124.5, 124.9, 125.0, 128.3, 130.2, 130.95, 131.8, 132.4, 136.15, 142.9, 146.8, 147.9. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{15}\text{ClN}_3\text{O}_5$ 376.0694; found 376.0678.

General Procedure for preparation of nitrones 10-13

Methanesulfonic acid (50 mg, 0.52 mmol) was added to a solution of oxaziridine **6-9** 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. The solution was diluted with dichloromethane (25 ml) and washed with a solution of sodium bicarbonate. The organic phase was dried on sodium sulfate, filtered, and concentrated.

3,3-Dimethyl-1-phenyl-3,4-dihydroisoquinoline 2-oxide (nitrone 10). Reaction of oxaziridine **6** (50 mg, 0.19 mmol) according to the general procedure afforded **10** (62%), isolated as a yellow solid, mp 86-87 °C; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.56 (s, 6H, 2- CH_3), 3.22 (s, 2H, CH_2), 6.86 (d, J 7.2 Hz, 1H), 7.22 (m, 2H), 7.31 (m, 1H), 7.50 (m, 5H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 24.7, 41.8, 67.2, 126.7, 127.0, 127.65, 128.36, 128.9, 129.05, 130.08, 131.14, 131.9, 143.0. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{18}\text{NO}$ 252.1382; found 252.1373

1-(4-Chlorophenyl)-3,3-dimethyl-3,4-dihydroisoquinoline 2-oxide (nitrone 11). Reaction of oxaziridine **7** (50 mg, 0.17 mmol) according to the general procedure afforded **11** (76%), isolated as a white solid, mp 125-127 °C; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.52 (s, 6H, 2- CH_3), 3.18 (s, 2H, CH_2), 6.83 (d, J 7.8 Hz, 1H), 7.18 (m, 1H), 7.29 (m, 2H), 7.48 (m, 4H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 24.6, 41.6, 67.2, 126.1, 127.1, 127.8, 128.5, 128.7, 130.1, 130.4, 131.0, 131.7, 134.8, 140.2. HRMS (ESI) $[\text{M} + \text{Na}]^+$ calc. For $\text{C}_{17}\text{H}_{16}\text{ClNO Na}$ 308.0812; found 308.0796.

3,3-Dimethyl-1-(4-nitrophenyl)-3,4-dihydroisoquinoline 2-oxide (nitrone 12). Reaction of oxaziridine **8** (50 mg, 0.16 mmol) according to the general procedure afforded **12** (80%), isolated as a white solid, mp 156-158 °C; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.55 (s, 6H, 2- CH_3), 3.22 (s, 2H, CH_2), 6.76 (d, J 7.8 Hz, 1H), 7.21 (m, 1H), 7.31 (m, 2H), 7.76 (d, J 8.2 Hz, 2H), 8.35 (d, J 8.2 Hz, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 24.6, 41.6, 67.8, 123.45, 125.7, 127.3, 128.0, 129.2, 130.2, 131.0, 131.6, 138.8, 139.6, 147.7. HRMS (ESI) $[\text{M} + \text{H}]^+$ calc. For $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_3$ 297.1233; found 297.1224.

1-(4-Chloro-3-nitrophenyl)-3,3-dimethyl-7-nitro-3,4-dihydroisoquinoline 2-oxide (nitrone 13). Reaction of oxaziridine **9** (50 mg, 0.13 mmol) according to the general procedure afforded **13** (59%), isolated as a yellow solid, mp 201-203 °C; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.53 (s, 6H, 2- CH_3), 3.32 (s, 2H, CH_2), 7.50 (d, J 8.2 Hz, 1H), 7.66 (d, J 2.2 Hz, 1H), 7.69-7.72 (m, 2H), 8.16 (dd, J 8.2, 2.2 Hz, 1H), 8.21 (d, J 2.2 Hz, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 24.6, 41.3, 68.3, 119.6, 123.4, 127.9, 128.2, 129.2, 130.7, 132.2, 134.95, 136.4, 137.5, 147.5, 147.9. HRMS (ESI) $[\text{M} + \text{Na}]^+$ calc. For $\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{O}_5 \text{ Na}$ 398.0514; found 398.0509.

Oxygen transfer to sulfides with oxaziridine 9

A solution of the oxaziridine **9** (0.50 mmol) in methylene chloride (2 ml) was added to a solution of sulfide (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 (dichloromethane) 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 sulfoxides were purified by chromatography on silica gel using dichloromethane / methanol 95:5 as eluent. The sulfoxides obtained were compared and identified with commercial samples. The various results obtained are presented in Table 3.

Characterisation data for sulfoxides

Methyl phenyl sulfoxide (entry 1)³⁶: ^1H NMR (400 MHz, CDCl_3) (ppm): 7.65–7.63 (m, 2H), 7.55–7.47 (m, 3H), 2.72 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) (ppm): 145.8, 131.2, 129.5, 123.6, 44.1.

p-Tolylmethyl sulfoxide (entry 2)³⁶: ^1H NMR (400 MHz, CDCl_3) (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) (ppm): 142.5, 141.6, 130.2, 130.1, 123.6, 44.1, 21.5.

4-Methoxyphenyl methyl sulfoxide (entry 3)³⁶: ^1H NMR (400 MHz, CDCl_3) (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) (ppm): 162.0, 136.6, 125.5, 114.9, 55.6, 44.0.

p-Chlorophenyl methyl sulfoxide (entry 4)³⁶: ^1H NMR (400 MHz, CDCl_3) (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) (ppm): 144.3, 137.3, 129.8, 125.1, 125.0, 44.1.

p-Nitrophenyl methyl sulfoxide (entry 5)³⁷: ^1H NMR (300 MHz, CDCl_3 , 278K, TMS) (ppm): 2.56 (s, 3H, Me), 7.84 (d, 2H) 8.34 (d, 2H). ^{13}C NMR (75 MHz, CDCl_3 , 278K, TMS) (ppm): 47.7, 124.5, 149.3, 153.1.

Diphenyl sulfoxide (entry 6)³⁶: ^1H NMR (400 MHz, CDCl_3) (ppm): 7.65–7.63 (m, 4H), 7.47–7.43 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) (ppm): 145.7, 131.2, 129.4, 124.9.

Dibenzyl sulfoxide (entry 7)³⁸: ^1H NMR (300 MHz, CDCl_3) (ppm): 3.89 (d, 4H), 7.21–7.40 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3) (ppm): 130.1, 129.0, 128.0, 57.1.

Benzyl phenyl sulfoxide (entry 8)³⁹: ^1H NMR (400 MHz, CDCl_3) (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) (ppm): 131.2, 130.4, 129.1, 128.9, 128.5, 128.3, 124.5.

Benzyl cyclohexyl sulfoxide (entry 9)⁴⁰: ^1H 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, 129.9, 128.5, 127.9, 57.0, 54.5, 27.0, 25.0, 24.9, 24.0.

Dimethyl sulfoxide (entry 10)⁴¹: ^1H NMR (300 MHz, CDCl_3) (ppm): 2.62 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3) (ppm): 40.8.

Acknowledgements

This research was supported by the Ministry of High Education and Scientific Research, Tunisia.

Supplementary Material

The Supplementary Material, copies of ^1H NMR and ^{13}C NMR spectra for compounds **2-6**, **6a**, **7**, **7a**, **8**, **8a**, **9**, and **9a**, associated with this article, can all be found in the online version of the text.

References

1. Emmons, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 6208–6209.
<https://doi/abs/10.1021/ja01578a043>
2. Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
[https://doi.org/10.1016/S0040-4020\(01\)89102-X](https://doi.org/10.1016/S0040-4020(01)89102-X)
3. Mlochowski, J.; Kubicz, E.; Kloc, K.; Mordarski, M.; Peczynska, W.; Syper, L. *Liebigs Ann. Chem.* **1988**, *5*, 455–464.
<https://doi.org/10.1002/jlac.198819880515>
4. Said, S. B.; Mlochowski, J.; Skarzewski, J. *Liebigs Ann. Chem.* **1990**, *5*, 461–464.
<https://doi.org/10.1002/jlac.199019900187>
5. Ningsanont, N.; Black, D. St.C.; Chanphen, R.; Thebtaranonth, Y. *J. Med. Chem.* **2003**, *46*, 2397–2403.
<https://doi/10.1021/jm020452h>
6. Peng, L.; Chen, C.; Gonzalez, C. R.; Balogh-Nair, V. *Int. J. Mol. Sci.* **2002**, *3*, 1145–1161.
<https://dx.doi.org/10.3390/i3111145>
7. Marchant-Brynaert, J.; Bounkhala Krouz, Z.; Vanlierde, H.; Ghosez, L. *Heterocycles* **1990**, *30*, 971–982.
8. <https://doi.org/10.3987/COM-89-S96>
Kacem, Y.; Kraiem, J.; Kerkeni, E.; Bouraoui, A.; Ben Hassine, B. *Eur. J. Pharm. Sci.* **2002**, *16*, 221–228.
[https://doi.org/10.1016/S0928-0987\(02\)00046-5](https://doi.org/10.1016/S0928-0987(02)00046-5)
9. Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703–5742.
[https://doi.org/10.1016/S0040-4020\(01\)89102-X](https://doi.org/10.1016/S0040-4020(01)89102-X)
10. Aydi, A.; Ben Gara, R.; Chaaben, H.; Ben Saad, L.; Fki, A. ELFeki; Belghith, H.; Belghith K.; Kammoun, M. *Biomed. Pharmacotherapy* **2016**, *82*, 660–668.
<https://doi.org/10.1016/j.biopha.2016.06.003>
11. Toda, F.; Tauaka, K. *Chem. Lett.* **1987**, *16*, 2283–2284.
<https://doi.org/10.1246/cl.1987.2283>
12. Andrae, S.; Schmitz, E. *Synthesis* **1991**, *5*, 327–341.
<https://doi.org/10.1055/s-1991-26459>
13. Zong, K.; Shin, S. I.; Ryu, E. K. *Tetrahedron Lett.* **1998**, *39*, 6227–6228.
[https://doi.org/10.1016/S0040-4039\(98\)01281-7](https://doi.org/10.1016/S0040-4039(98)01281-7)
14. Lin, Y.; Miller, M. J. *J. Org. Chem.* **2001**, *66*, 8282–8285.
<https://doi/abs/10.1021/jo010965g>
15. Damavandi, J. A.; Karami, B.; Zolfigol, M. A. *Synlett* **2002**, *6*, 933–934.
<https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2002-31903>
16. Mohajer, D.; Iranpoor, N.; Rezaeifard, A. *Tetrahedron Lett.* **2004**, *45*, 631–634.
<https://doi.org/10.1016/j.tetlet.2003.10.107>
17. Page, P. C. B.; Heer, J. P.; Bethell, D.; Lund, A.; Collington, E. W.; Andrews, D. M. A. *J. Org. Chem.* **1997**, *62*, 6093–6094.
<https://doi/abs/10.1021/jo9707545>
18. Kraim, J.; Ben Othman, R.; Ben Hassine, B. C. R. *Compt. Rend. Chem.* **2004**, *7*, 1119–1126.
<https://doi.org/10.1016/j.crci.2003.12.002>
19. Widmer, J.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 657–664.
<https://doi.org/10.1002/hlca.19740570318>

20. DesMarteau, D. D.; Petrov, V. A.; Montanari, V.; Pregnotato, M.; Resnati, G. *J. Org. Chem.* **1994**, *59*, 2762.
<https://doi/abs/10.1021/jo00089a020>
21. Vidal, J.; Damestoy, S.; Guy, L.; Hammachi, J.-C.; Aubry, A.; Collet, A. *Eur. J. Chem.* **1997**, *3*, 1691.
<https://doi.org/10.1002/chem.19970031019>
22. Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713.
<https://doi/abs/10.1021/ol0474507>
23. Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919
<https://doi/10.1021/cr00013a008>
24. Armstrong, A.; Edmonds, I. D.; Swarbrick, M. E.; Treweeke, N. R. *Tetrahedron* **2005**, *61*, 8423.
<https://doi.org/10.1016/j.tet.2005.06.085>
25. Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499.
<https://doi/abs/10.1021/cr000019k>
26. Page, P. C. B.; Vahedi, H.; Bethell, D.; Barkley, J. V. *Synth. Commun.* **2003**, *33*, 1943–1949.
<https://doi.org/10.1081/SCC-120020208>
27. Page, P. C. B.; McKenzie, M. J.; Allina, S. M.; Buckle, D. R. *Tetrahedron* **2000**, *56*, 9683–9695.
[https://doi.org/10.1016/S0040-4020\(00\)00923-6](https://doi.org/10.1016/S0040-4020(00)00923-6)
28. Bethell, D.; Page, P. C. B.; Vahedi, H. *J. Org. Chem.* **2000**, *65*, 6756–6760.
<https://doi/abs/10.1021/jo0003100>
29. Del Rio, R. E.; Wang, B.; Achab, S.; Bohe, L. *Org. Lett.* **2007**, *9*, 2265–2268.
<https://doi/abs/10.1021/ol0702573>
30. Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 2817–2818.
[https://doi.org/10.1016/0040-4039\(88\)85218-3](https://doi.org/10.1016/0040-4039(88)85218-3)
31. Kammoun, M.; Ben Salem, R.; Damak, M. *Synth. Comm.* **2012**, *42*, 2181–2190.
<https://doi.org/10.1080/00397911.2011.555050>
32. Kammoun, M.; Ben Saleh, H.; Damak, M. *Synth. Comm.* **2011**, *41*, 1520–1528.
<https://doi.org/10.1080/00397911.2010.487175>
33. Aydi, R.; Kammoun, M. *Synth. Comm.* **2016**, *46*, 134–144.
<https://doi.org/10.1080/00397911.2015.1122808>
34. McCoubey, A.; Mathieson, D. W. *J. Chem. Soc.* **1951**, *51*, 2851–2853.
<https://doi.org/10.1039/JR9510002851>
35. Bohe, L.; Kammoun, M. *Tetrahedron Lett.* **2004**, *45*, 747–751.
<https://doi.org/10.1016/j.tetlet.2003.11.040>
36. Yu, B.; Liu, A. H.; He L. N.; Li, B.; Diao, Z. F.; Li, Y. N. *J. Green Chem.* **2012**, *14*, 957–962.
<https://doi.org/10.1039/C2GC00027J>
37. Yang, C.; Jin, Q.; Zhang, H.; Liao, J.; Zhu, J.; Yu, B.; Deng, J. *Green Chem.* **2009**, *11*, 1401–1405.
<https://doi.org/10.1039/B912521N>
38. Mercier, E. A.; Smith, C. D.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2012**, *77*, 3508.
<https://doi/abs/10.1021/jo300313v>
39. Choi, S.; Yang, J. D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K. H.; Byeon, S. H.; Baik, W.; Koo, S. *J. Org. Chem.* **2001**, *66*, 8192–8198.
<https://doi/abs/10.1021/jo016013s>
40. Boudou, C.; Berges, M.; Sagnes, C.; Sopkova-de Oliveira Santos, J.; Perrio, S.; Metzner, P. *J. Org. Chem.* **2007**, *72*, 5403.
<https://doi/abs/10.1021/jo070700n>

41. Paquette, L. A.; Carr, R. V. C. *Org. Synth. Coll.* **1990**, 7, 453.
42. Ben Saleh, H.; Kammoun, M.; Hamdi, B.; Damak, M. *Synth. Comm.* **2012**, 42, 3296–3303.
<https://doi.org/10.1080/00397911.2011.580882>