Pergamon

Tetrahedron, Vol. 53, No. 31, pp. 10911-10920, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00696-0

Iron Dichloride Induced Isomerization or Reductive Cleavage of Isoxazoles: A Facile Synthesis of 2-Carboxy-azirines

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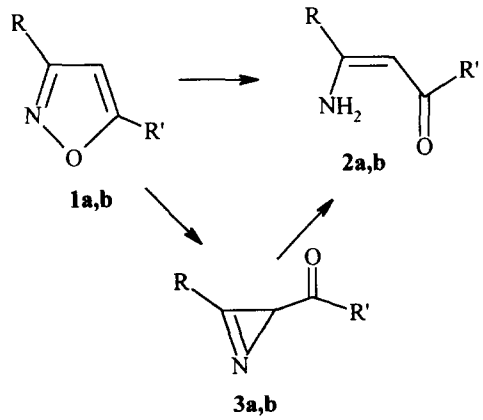
Abstract: 5-Alkoxy-isoxazoles and N,N-disubstituted-5-isoxazolamines were found to isomerize to azirine derivatives by the use of iron dichloride as catalyst. On the contrary 5-alkyl- and 5-aryl-isoxazoles in the presence of the same salt, undergo reductive cleavage to enaminoketones. A common reaction intermediate is proposed. © 1997 Elsevier Science Ltd.

INTRODUCTION

Isoxazoles are generally considered as useful synthons in organic synthesis. The isoxazole ring in fact can be easily cleaved to give β-diketones or other synthetic intermediates, but at the same time it is quite stable to many reagents so that is possible to manipulate the substituents on the ring in many ways before the cleavage reaction.[1] The reductive cleavage reaction of the isoxazoles **1a,b** leads to the formation of β-aminoenones **2a** or β-aminoesters **2b**. Isoxazoles can also isomerize to azirines **3a,b** which can be used as precursors of other heterocyclic rings[2] (Scheme 1).



a) R' = Alkyl or Aryl
b) R' = OAlkyl

Scheme 1

The most used method for the reductive cleavage of isoxazoles **1** to amino derivatives **2** is hydrogenation with Raney nickel, palladium on charcoal or platinum as catalysts.[1] In the last years many authors have proposed alternative methods to the use of hydrogen and in particular they found that reductive cleavage of isoxazoles **1a** can be performed *via* electron transfer by samarium diiodide[3], or iron(II) in the presence of dihydrolipoamide and water[4].

Some years ago, we found that it is possible to obtain 2H-azirine **3b** by treatment of 5-alkoxyisoxazoles **1b** with hydrogen by stopping the reaction after a few minutes, before reduction to enaminoesters **2b** takes place.[5] Azirines in the same reaction conditions easily undergo reduction to enaminoesters, so that they can be considered as intermediates in the **1→2** transformation. The use of an heterogeneous catalyst suggested that both steps may occur *via* a one-electron transfer, so we started to investigate the possibility to obtain azirines by promoting isomerization of **1** by a metal salt, which could act as one-electron donor. In this paper we wish to report the behavior of isoxazoles in the presence of various metal cations.

RESULTS and DISCUSSION

5-Methoxy-3-phenyl-isoxazole **1c** (Scheme 2) was allowed to react in acetonitrile with $FeCl_2{\cdot}4H_2O$, $NiCl_2{\cdot}6H_2O$, $NiCl_2$, $Fe(acac)_2$ or CuCl, and in all cases the corresponding azirine **3c** was obtained but the reagent of choice proved to be iron (II) chloride, as can be seen in Table 1.

Table 1. Reaction of **1c** with various promoters in acetonitrile at room temperature

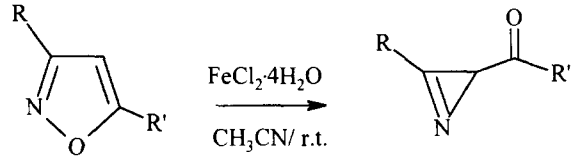
Promoter	Isox/Prom	Reaction time	Azirine (Y%)[a]
$FeCl_2{\cdot}4H_2O$	1:5	30 m	>95
$FeCl_2{\cdot}4H_2O$	1:0.05	2 h	>95
$NiCl_2{\cdot}6H_2O$	1:5	120 h	traces
$NiCl_2$	1:5	1 h	>95
$Fe(acac)_2$	1:5	19 h	>95
CuCl	1:5	120 h	12

a)Yields are calculated *via* HPLC using an internal standard.

The iron salt, in fact, even when used in catalytic amount (Table 1, entry 2), allows the complete isomerization of **1c** into **3c** in 2h at room temperature. $NiCl_2$ or $Fe(acac)_2$ also promote the isomerization reaction, although less efficiently: $Fe(acac)_2$ have to be used in a 5 molar excess to give complete conversion of the isoxazole **1c** into the azirine **3c** while $NiCl_2$ requires anhydrous conditions to promote isomerization. Copper

(I) chloride does not give satisfactory results as, even after many days, it promotes only a partial rearrangement of isoxazole **1c** to azirine.

Iron (II) promoted rearrangement of isoxazole derivatives to azirines was extended to other 5-heterosubstituted isoxazoles (Scheme 2) and in all these cases azirines were obtained quantitatively. isomerization reactions of isoxazoles **1d-g** are summarized in Table 2.



1c-g **3c-g**

c) R = Ph, R' = OMe
d) R = *p*-NO_2-C_6H_4, R' = OMe
e) R = *p*-MeO-C_6H_4, R' = OMe
f) R= Ph, R'= NMePh
g) R= Ph, R'= NMe_2

Scheme 2

Table 2. Reaction of **1d,e** ($5x10^{-3}$ M) and **1f,g** ($4x10^{-2}$ M) with hydrate $FeCl_2$ in acetonitrile at room temperature

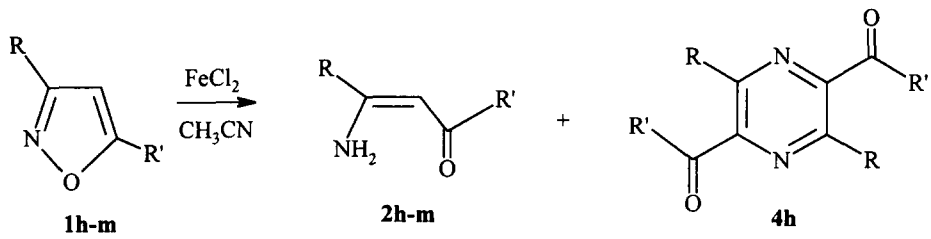
Isoxazole	Isox/$FeCl_2$	React.time	Azirine (Y%)[a]
1d	1 : 0.05	8 h	**3d** (>95)
1e	1 : 0.05	80 min	**3e** (>95)
1f	1 : 0.1	16 h	**3f** (>95)
1g	1 : 0.1	40 h	**3g** (>95)

a) Yields are calculated *via* HPLC using an internal standard.

As can been seen in Table 2, entry 1-2, electron-donating substituents at the 3-position on the aromatic ring make isomerization occur even faster, while substitution with an electron-withdrawing group in the same position results in a slower reaction, showing the same trend observed in the thermal rearrangement of isoxazole to azirine[6]. Azirines **3c-f** are all known compounds and they were identified by comparison of their physical data with those reported in literature; azirine **3g** was reported but not fully characterized.

Substitution at the 5-position with an aryl or an alkyl instead of an heteroatom directly attached to the ring (OMe, NR_2) is critical for the isomerization reaction. 3,5-Diphenylisoxazole (**1h**), in fact, does not react with iron (II) chloride at room temperature even after many days.

More harsh conditions, i.e. molar excess of promoter in refluxing solvent, allow 5-aryl or alkyl isoxazoles to react with the metal salt, but reduction takes place instead of isomerization. Reaction of diphenylisoxazole **1h** with iron chloride gave enaminoketone **2h** together with small amounts of pyrazine **4h** (Scheme 3). The corresponding benzoyl azirine **3**, was not detected even in small amount through HPLC analysis (an authentic sample was prepared by irradiation of **1h**[7]).



1h-m **2h-m** **4h**

h) R = R' = Ph
i) R = R' = Me
l) R =Me, R' = Ph
m) R= Ph, R'= Me

Scheme 3

It was reported that reduction of isoxazoles to enaminoketones by metal (0) complexes such as $Mo(CO)_6$ can be inhibited by excluding water from reaction medium[8], so we used anhydrous solvent and anhydrous iron chloride to see if in these conditions azirine could be found. Analysis of the crude gave the same products as in Scheme 3 and again no benzoyl azirine **3h**, was detected. Reduction of isoxazoles **1h-m** gave, in every case enaminoketones **2** as the only products (Table 3). Pyrazine derivatives were reported in some metal promoted reactions[9] of azirines or in thermal reaction of aminoisoxazoles[10].

Table 3. Reaction of 3,5-alkyl,aryl substituted isoxazoles with iron(II) salts in refluxing acetonitrile

Isoxazole	Promoter	Isox/$FeCl_2$	R. time	**2**(Y%)[a,b]	**4** (Y%)[a]
1h	$FeCl_2{\cdot}4H_2O$	1 : 3.5	22 h	**2h** (58)	**4h** (9)
1h	$FeCl_2$	1 : 5	40 h	**2h** (56)	**4h** (11)
1i	$FeCl_2$	1 : 3.5	10 h	**2i** (50)	
1l	$FeCl_2$	1 : 3.5	14 h	**2l** (70)	
1m	$FeCl_2$	1 : 3.5	14 h	**2m** (58)[c]	

a) Yields are given after purification by column chromatography; b) enaminoketones **2** were compared with authentic samples obtained from hydrogenation with Raney nickel of the corresponding isoxazoles; c) in this case 10% of starting material was also recovered

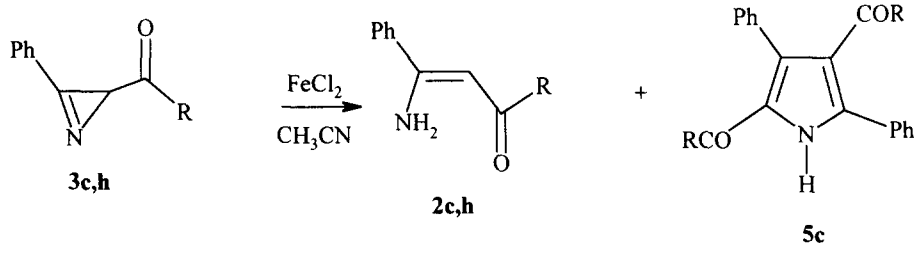
We also found that both 2-carbomethoxy-azirine **3c** and 2-benzoyl-azirine **3h** form enaminoenones in the presence of an excess of iron (II) (Table 4, Scheme 4).

Table 4. Reaction of azirines in acetonitrile in the presence of iron dichloride.

Azirine	Promoter	Az/Prom	React. time	Products (Yield)[a]
3c	$FeCl_2$	1 : 3	4 h	**2c**(10%) + **5c**(60%)
3h	$FeCl_2$	1 : 3	2.5 h	**2h**(80%)

a)Yields are given after purification by column chromatography.

In particular, reaction of **3c** with iron dichloride gave a pyrrole derivative **5c** together with enone **2c** (Scheme 4).



3c,h **2c,h** **5c**

c) R= OMe
h) R=Ph

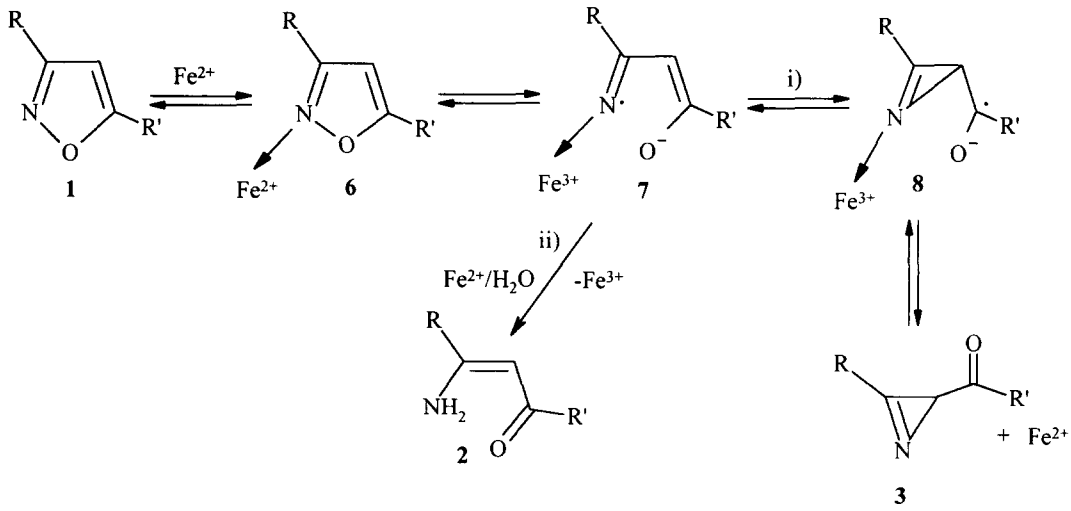
Scheme 4

Formation of pyrroles from azirines has been reported[11]. Starting from the same 2-carboxymethyl-2H-azirine **3c**, Komendatov et al. obtained by catalysis of copper stearate a pyrrole derivative.[12] Studies on the mechanism of this reaction are still under progress.

Catalytic isomerization of 5-alkoxy and 5-isoxazolamine by readily available iron dichloride represents therefore a simple and mild method for the obtainment of 2-carboxyazirine from alkoxyisoxazoles. Despite the high yield in fact, hydrogenation of the same isoxazoles requires laborious preparation of the catalyst, harsh conditions (50 atm) and a very careful control of reaction time[5]. Thermal rearrangement of isoxazoles, on the other hand, usually gives low yield and in some cases, as in the isomerization of **1c**, temperature has to be controlled carefully to avoid possible explosion[13]. The only attempt for promoting isomerization of isoxazoles[14] was done on 5-methoxy-3-phenyl-isoxazole in refluxing cyclohexane using copper stearate as promoter. The yield in this case is only 60% , no mechanism was proposed for this catalyzed reaction and the reaction was not extended to other isoxazoles.

In order to elucidate the mechanism of the iron (II) promoted isomerization of isoxazoles to azirines we decided to determine the order of the reaction. To a 2.9×10^{-3} M solution of isoxazole **1c** in acetonitrile, a 3% molar amount of iron (II) chloride was added under nitrogen at 25 °C; the final mixture was homogeneous. Reaction is a first order reaction with a kinetic constant of 5.8×10^{-4} s^{-1} with a correlation coefficient of 0.996.

The kinetic data suggested us to postulate a mechanism for which promoter concentration is constant during the course of the reaction so that reaction order depends exclusively from isoxazole concentration.



Scheme 5

The metal cation coordinates the nitrogen atom of the isoxazole ring, giving complex **6** and subsequently this complex undergo N-O bond cleavage by one-electron transfer from the metal to give the radical anion **7** which is in equilibrium with **8** (i). The intermediate **8** then gives one electron to Fe^{3+} to afford azirine **3**.
When R' is an alkyl or an aryl group, isoxazole **1** does not isomerize to azirine **3** but undergo reductive cleavage to enaminoketone **2**. For this reaction we envisage a mechanism (ii) that is similar to the one proposed for reduction of **1** with other metal salts[3,4] and that proceeds through the formation of the same intermediate **7** proposed for the isomerization.

As both azirine **3c** and **3h** can undergo reductive cleavage and as it was already found by Nitta[15] that in the presence of $Mo(CO)_6$ azirine **3h** is converted to isoxazole **1h,** we believe that at this point, it is possible to give a common mechanism for these two apparently different reactions: isomerization and reductive cleavage. In the presence of the metal, the species **1** and **3** are in equilibrium and this is shifted to the isoxazole or the azirine depending by the nature of the substituents on the ring. In particular this equilibrium is shifted towards azirine for R' = OMe or NR_2 and towards isoxazoles for R' = Ph, or Me. Under harsh conditions both **1** and **3** go to enamino derivative **2**.

EXPERIMENTAL

NMR spectra were recorded on a Bruker 250MHz with TMS as internal standard. MS spectra were performed on a Hitachi-Perkin Elmer RMU-6D (70 eV) or with a Finnigan TSQ 70. Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. Chromatographic separations were performed using Merck Kieselgel 60. HPLC analyses were performed on Varian 9010 equipped with a diode array detector.

Isoxazoles

5-Alkoxy-3-aryl-isoxazoles ***1c-e*** were prepared by reaction of the corresponding isoxazolones with diazomethane.[13,16] *N-Methyl-N,3-diphenyl-5-isoxazolamine* (**1f**) was prepared by cycloaddition of benzonitrile oxide to ethynyl-methyl-phenyl-amine.[17] *N,N-Dimethyl-3-phenyl-5-isoxazolamine (**1g**)* was prepared by cycloaddition of benzonitrile oxide to a ketene aminal[18]: to a stirred solution of benzohydroxymoyl chloride (0.312 g, 2 mmol) in diethyl ether, a solution of vinylidenebisdimethylamine[19] (1.14 g, 1 mmol) was slowly added at 0 °C. After one night, the mixture was washed with water and the organic layer was dried over sodium sulfate and evaporated. Column chromatography on silica gel (n-hexane/ethyl acetate 7/3 as eluent) afforded **1g** (0.21 g, 56%) as a white solid, m.p. (*n*-hexane) 76-77 °C. Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19 ; H 6.43, N, 14.88. Found: C, 70.22; H, 6.51; N, 14.91 IR (KBr): 1631 (vs); 1586 (m). Mass spectrum: m/z 188 (60);145 (13); 144 (100); 116 (29); 89 (11). ^{1}H NMR ($CDCl_3$): 7.75 (2H, m), 7.42 (3H, m), 5.20 (1H, s), 3.10 (6H, s).

*Isoxazoles **1h-m***, were prepared according to literature procedures.[20-23]

*General procedure for isomerization of **1c** to azirine **3c**:* 5-methoxy-3-phenyl-isoxazole (**1c**) (175 mg, 1 mmol) was dissolved in 100 mL of degassed acetonitrile. To this solution, the promoter was added under a stream of nitrogen, and the mixture stirred at room temperature either until complete conversion of **1c** or for a maximum of 5 days. Reaction was filtered on celite, and solvent was removed. Chromatography on silica gel gave *3-phenyl-2H-azirine-2-carboxylic acid methyl ester (**3c**)*[24]. Reaction conditions and results are shown in Table 1.

*Isomerization of **1d,e***: To a solution of 0.5 mmol of **1d,e** in 100 mL of degassed acetonitrile, a 5% molar amount of hydrate iron dichloride was added, and the mixture stirred for the time shown in table 2. Usual workup gave *3-(4-nitrophenyl)-2H-azirine-2-carboxylic acid methyl ester (**3d**)*[13] and *methyl 3-(4-methoxyphenyl)-2H-azirine-2-carboxylic acid methyl ester (**3e**)*[13] respectively. The results are given in Table 2.

*Isomerization of isoxazoles **1f,g***: To a solution of **1f,g** (4 mmol) in 100 mL of degassed acetonitrile 80 mg (0.4 mmol) of hydrate iron dichloride were added under a stream of nitrogen and the mixture stirred for the time indicated in Table 2. The crude was filtered on celite, the solvent removed and the mixture was chromatographed. Isoxazole **1f** gave *3-phenyl-2H-azirine-2-carboxylic acid methyl-phenyl-amide (**3f**)*[17]. Isoxazole **1g** gave *3-phenyl-2H-azirine-2-carboxylic acid dimethylamide (**3g**)*[25] as a viscous oil. Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.26; H, 6.51; N, 14.92. ^{1}H NMR ($CDCl_3$): 7.89 (2H, m), 7.55 (3H, m), 3.37 (3H, s), 3.10 (1H, s), 3.00 (3H, s). Yields are given in Table 3.

*Phenyl-(3-phenyl-2H-azirin-2-yl)-methanone (**3h**)* was prepared by photoirradiation of **1h** in benzene according to literature procedure.[7]

*General procedure for reduction of isoxazole **1h**:* To a degassed solution of isoxazole **1h** (220 mg, 1 mmol) in 16 mL of anhydrous acetonitrile, 5 mmol of anhydrous iron dichloride or 3.5 mmol of hydrate iron dichloride were added, and the mixture was refluxed for the time indicated in Table 3. The solvent was removed, the crude dissolved in dichloromethane, treated with a 1 M solution of HCl and washed with water. Column chromatography gave *3-amino-1,3-diphenyl-2-propen-1-one (**2h**)*[26] and *2,6-dibenzoyl-3,5-diphenylpyrazine (**4h**)* m.p. 157-159 °C. ^{1}H NMR ($CDCl_3$): 8.16 (2H, m), 7.70-7.20 (18H, m), ^{13}C NMR ($CDCl_3$): 196.1, 191.2 (C=O), Mass Spectrum: m/z 441 (M+1, 19), 440 (M^+, 58), 129 (12), 105 (100); IR (nujol) 1680 (C=O). Anal. Calcd. for $C_{30}H_{20}N_2O_2$: C, 81.80 ; H, 4.58 ; N, 6.36 . Found: C, 81.90; H, 4.61; N, 6.35. Yields are given in Table 3.

General procedure for reduction of isoxazoles ***2i-2m****:* To a degassed solution of isoxazoles **2i-m** (1 mmol) in 16 mL of anhydrous acetonitrile, 444 mg (3.5 mmol) of anhydrous iron dichloride were added and the mixture was refluxed for the time indicated in Table 3. The solvent was removed, the crude was dissolved in dichloromethane, treated with a 1 M solution of HCl, washed with water and the residue chromatographed on silica gel. Isoxazole **1i** gave *4-amino-3-penten-2-one* ***(2i)***[26]. Isoxazole **1l** gave *4-amino-1-phenyl-2-buten-1-one* ***(2l)***[27]. Isoxazole **1m** gave *4-amino-4-phenyl-3-buten-2-one* ***(2m)***[4]. Yields are given in Table 3.

Reduction of azirine ***3c****:* To a degassed solution of azirine **3c** (1 mmol) in 16 mL of acetonitrile, 380 mg (3 mmol) of anhydrous iron dichloride were added and the mixture was refluxed for 4h. The solvent was removed, the mixture was dissolved in dichloromethane, treated with a 1 M solution of HCl and washed with water. Chromatography on silica gel gave *3-amino-3-phenyl-2-propenoic acid methyl ester* ***(2c)***[28] and *3,5-diphenyl-1H-pyrrole-2,4-dicarboxylic acid methyl ester* ***(5c)***: m.p. 191-193 °C (lit.,[29] 192-193 °C) ^{1}H NMR ($CDCl_3$): (10H, m)3.67 (3H, s), 3.48 (3H, s). Yields are given in Table 4.

Reduction of azirine ***3h****:* To a degassed solution of azirine **3h** (1 mmol) in 16 mL of acetonitrile, 380 mg (3 mmol) of iron dichloride were added and the mixture was refluxed for 2.5 h The solvent was removed, the mixture was dissolved in dichloromethane, treated with a 1 M solution of HCl and washed with water. Chromatography on silica gel gave *3-amino-1,3-diphenyl-2-propen-1-one****(2h)***. Yields are given in Table 4.

ACKNOWLEDGMENTS

We gratefully acknowledge the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for support.

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(*Received in UK* 16 *May* 1997; *revised* 9 *June* 1997; *accepted* 12 *June* 1997)