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ARTICLE

Peracid Oxidation of Dihydroisoquinoline Iminium

Mouna Bouzid, Hassen Ben Salah and Majed Kammoun✉

ABSTRACT

The peracid oxidation of iminium 4 with *m*-chloroperbenzoic acid (*m*-CPBA) does not lead to the oxaziridinium salt but mainly yielded to a mixture of lactame **6** and nitro compound **7**, as two minor products, and enamine **5** as the major product.

KEYWORDS

Peracid oxidation, Iminium, Enamine.

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Author affiliations:

Laboratory of Medicinal and Environmental Chemistry, Sfax University, Higher Institute of Biotechnology, BP 1169, 3029 Sfax, Tunisia

✉To whom correspondence to be addressed:

E-mail: majed.kammoun@isbs.usf.tn

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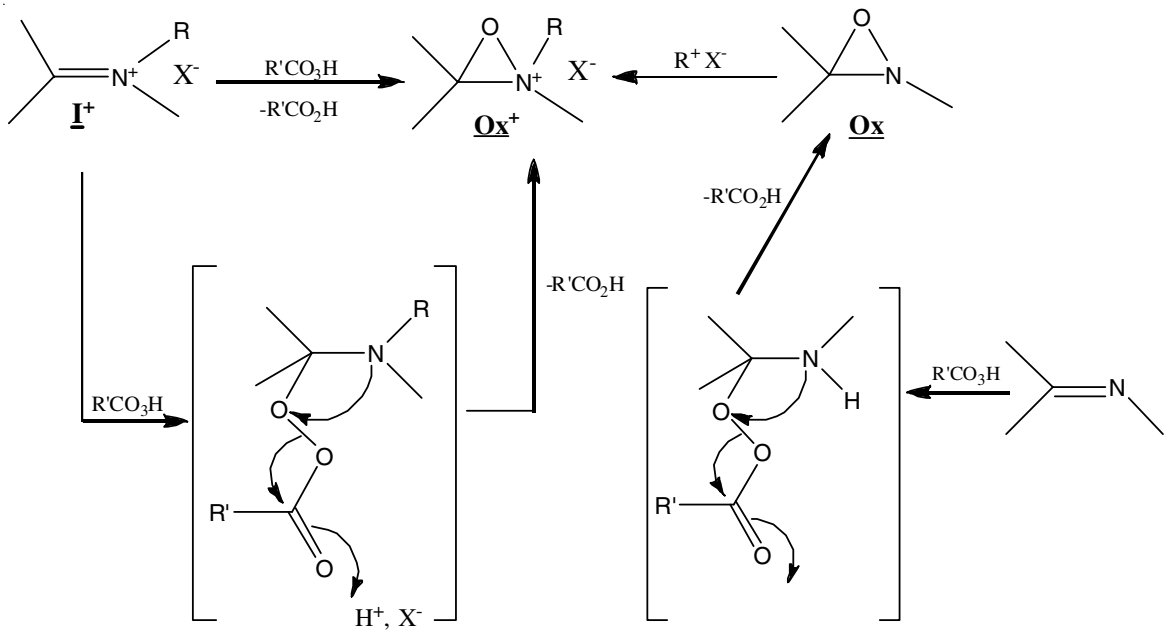
INTRODUCTION

The iminium function is an important functional group in organic synthesis [1]. As synthetic building blocks, iminium salts represent activated, masked carbonyl compounds. Due to its enhanced electrophilic character, the iminium function usually reacts easily with a wide range of nucleophiles. In fact, oxidation of the iminium with a peracid has been the subject of a limited number of studies. In this context, three types of reactions have been described such as [1] oxidative fragmentation of the double bond [2], the formation of an amide to an iminium substituted at carbon with hydrogen [3] and the formation of oxaziridinium salt [4,5].

This reaction involves the nucleophilic properties in a two-step mechanism: nucleophilic attack by the iminium peracid leading to a *gem*-amino perester followed by intramolecular nucleophilic substitution. This reaction resembles to the peracid oxidation of imines leading to oxaziridines [6-9] (**Scheme-I**).

Oxaziridinium salts have been known since 1976 [4,5] as oxygen atom transfer agents towards nucleophiles. Since 1987, several oxaziridinium salts have been described [10-12] and used for epoxidation in stoichiometric amounts [13-15] or in catalytic processes [16-19]. Dioxiranes [20], *N*-sulfonyloxaziridines [21] and *N*-phosphonyloxaziridines [22] are oxygen transfer reagents, which can perform epoxidation reactions. The oxaziridinium function [23] shows similar properties. Preliminary results have shown that oxygen transfer reactions to olefins take place using either an isolated oxaziridinium salt, or prepared *in situ* by peracidic oxidation of the corresponding iminium salt [10-12]. Using the latter strategy, a catalytic cycle has been developed [16-19].

As part of our continued interest in the synthesis of diverse models of oxaziridinium salt, in the present article, the results of peracid oxidation of iminium **4** with *m*-chloroperbenzoic acid are reported.



Scheme-I: Synthesis of oxaziridinium salt

EXPERIMENTAL

Solvents were purified by standard methods. Melting points were determined under microscope with a Leitz Wetzlair device and are uncorrected. Mass spectra (MS) were obtained by electronic impact (70 eV) (EI) on a spectrometer AEI MS-50. IR spectra were recorded in the range 4000-400 cm^{-1} using a Nicolet Impact 410 spectrometer by transmission through KBr pellets containing 1 % of crystals. HRMS spectra were acquired with an electrospray time of flight analyzer in MS/MS (EBE geometry Tof) mass spectrometer in positive ion mode. NMR spectra were recorded on an AC 300 or 400 Brüker spectrometer at 300 or 400 MHz for ^1H and 75 or 100 MHz for ^{13}C NMR. Chemical shifts (δ) are given in ppm 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 UV light.

Synthesis of imine (2) [8]**:** To a cooled (0 ºC) solution of sulfuric acid (95 %) was added dropwise 1.1 mL of CH_3CN in 20 mL of hexane under magnetic stirring. Then (1.57 g, 10.43 mmol) of tertiary alcohol (**1**) (commercial product) in 15 mL of hexane was added to the solution. At room temperature, the resulting mixture was stirred at 68 ºC for 2.5 h. Then, the solution is cooled again at room temperature and versed on ice-cold water under magnetic stirring. The solution is alkalined with ammonia. The organic layer is extracted with dichloromethane, washed with a solution saturated in sodium chloride, dried over sodium sulfate and filtered. The solvent is removed *in vacuo*. Yield 80 %, Yellow oil, IR (KBr, ν_{max}, cm^{-1}): 1574 (Ar), 1627 (C=N), 2966 (CH_3); ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 6H, 2-CH_3), 2.40 (s, 3H, CH_3), 2.70 (s, 2H, CH_2), 7.14 (m, 1H), 7.29 (m, 1H), 7.35 (m, 1H), 7.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.16, 27.91, 38.91, 53.76, 125.46, 126.86, 127.84, 128.34, 130.93, 136.37, 161.93 ppm; GC-MS (EI): *m/z* (%): 173(M+1)$^+$,158 (100), 145 (20),130(34), 115(60), 103(4), 91(20), 77(8), 63(10), 51(8).

Synthesis of imine (3): The cold imine (**2**) (500 mg, 2.80 mmol) is added dropwise to 2.5 mL of conc. sulfuric acid. A solution of 380 mg KNO_3 in 1.4 mL of sulfuric acid is added dropwise at 0 ºC. The reaction mixture was stirred at room temperature for 2 h and then at 60 ºC for 4 h. After maintaining to room temperature, the reaction medium is poured into ice-cold water and alkalined with liquid ammonia. The organic phase is extracted with dichloromethane, washed with a solution saturated in sodium chloride, dried on sodium sulfate and filtered. The solvent was removed *in vacuo*. Yield 92 %, brown solid, m.p. 68 ºC, IR (KBr, ν_{max}, cm^{-1}): 1335 (NO_2), 1517 (Ar), 1626 (C=N), 2974 (CH_3); ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 6H, 2-CH_3), 2.45 (s, 3H, CH_3), 2.79 (s, 2H, CH_2), 7.32 (d, *J* = 8.1 Hz,1H), 8.20 (dd, *J* = 8.1, 2.1 Hz, 1H), 8.31 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.86, 27.76, 38.91, 54.27, 120.58, 125.96, 128.84, 129.34, 143.86, 147.16, 160.87 ppm; GC-MS (EI): *m/z* 218 [M+1]$^+$, 203 (67), 190 (32), 176 (18),157 (52), 144 (8),130 (22), 115 (57), 102 (9), 89 (15), 76 (11), 63 (9); HRMS calculated for $C_{12}H_{14}N_2O_2$: 218.1052, found: 218.1073.

Synthesis of iminium (4): Iminium **4** was prepared by methylation of imine **3** (500 mg, 2.30 mmol) with Meerwein salt in dichloromethane (15 mL). The concentrate was chromatographed on silica gel, with CH_2Cl_2/MeOH as eluent. Then crystallization in a biphasic system acetone/ether (1:1) gave 400 mg of yellow crystals. Yield 54 %, m.p. 170 ºC; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.61 (s, 6H, 2-CH_3), 3.13 (s, 3H), 3.54 (s, 2H), 3.91 (s, N-Me),7.83 (d, *J* = 8,1 Hz ,1H), 8.62 (dd, *J* = 8.1, 2.1 Hz, 1H), 8.86 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.15, 24.07, 38.82, 39.94, 64.61, 125.82, 129.49, 130.85, 131.13, 143.97, 148.56, 177.33 ppm; MS (FAB): 233 ($M^{+\bullet}$-tetrafluoroborate), 217(233-16), 187(233-46). Analysis calcd. (found) % for $C_{13}H_{17}N_2O_2BF_4$: C, 48.78 (48.66); H, 5.35 (5.19); N, 8.75 (8.59).

Peracid oxidation of iminium 4: A solution of iminium **4** (500 mg, 1.56 mmol) in 20 mL of anhydrous acetone was

added quickly and under magnetic stirring (567 mg, 3.28 mmol) of *m*-chloroperbenzoic acid (*m*-CPBA) titrated to 95 % and (131 mg, 3.11 mmol) of Na_2CO_3. The reaction mixture is stirred until complete disappearance of active oxygen of the medium observed in paper impregnated with sodium iodide. The reaction mixture was filtered before evaporation of the solvent under vacuum. The crude product was taken up in dichloromethane washed three times with a concentrated solution of sodium bicarbonate, then with a saturated solution of sodium chloride. The organic phase dried over sodium sulfate was filtered and then the solvent is evaporated *in vacuo*. ^{1}H NMR analysis of the crude reaction in $CDCl_3$ showed the presence of 9 % of derivative **7**, 23 % of lactame **6** and 68 % of enamine **5**. A column chromatography on silica gel (CH_2Cl_2) then ethyl acetate afforded 35 mg of derivative **7**; 85 mg of lactame **6** and 207 mg of enamine **5** with the yields of 7 %, 17 % and 41 %, respectively.

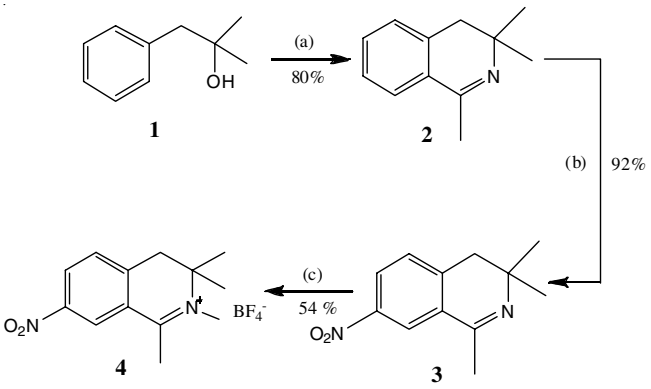
Spectral data for lactam 6: m.p. 74-76 ºC; IR (Nujol, ν_{max}, cm^{-1}): δ 1645 (O=C-N), 1527, 1345 (C-NO_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 6H), 3.09 (s, 2H), 3.18 (s, 3H, N-Me), 7.35 (d, *J* = 8 Hz, 1H), 8.25 (dd, *J* = 2, 8 Hz, 1H), 8.89 (d, *J* = 2 Hz ,1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.20, 27.39, 56.01, 123.61, 126.16, 128.68, 130.1, 143.12, 147.5, 200.35 ppm; MS (IE): 234 ($M^{+\bullet}$, base peak); 219 (234-16). Analysis calcd. (found) % for $C_{12}H_{14}N_2O_3$: C, 61.53 (61.47); H, 6.02 (5.89); N, 11.96 (11.88); O, 20.49 (20.38).

Spectral data for enamine 5: m.p. 78-80 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (s, 6H), 2.61 (s, 3H), 2.91 (s, 2H), 3.66 (d, *J* = 3 Hz, 1H), 3.78 (d, *J* = 3 Hz, 1H), 7.36 (d, *J* = 6 Hz, 1H), 8.06 (dd, *J* = 3.6 Hz, 1H), 8.16 (d, *J* = 3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.23, 31.40, 41.06, 56.98, 87.12, 118.55, 123.84, 128.38, 133.21, 139.84, 145.20 ppm; MS (IE): 232 ($M^{+\bullet}$- base peak); 217(232-15). Analysis calcd. (found) % for $C_{13}H_{16}N_2O_2$: C, 67.22 (67.17); H, 6.94 (6.79); N, 12.06 (11.99); O, 13.78 (13.58).

Spectral data for nitro derivative 7: m.p. 101-102 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.57 (s, 6H), 2.7 (s, 3H), 3.78 (s, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 8.25 (dd, *J* = 2.4, 8.4 Hz,1H), 8.55 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.85, 29.85, 41.35, 89.06, 124.17, 125.99, 133.54, 139.63, 142.29, 146.91, 200.07 ppm; MS (IC^+, isobutane): 267 $(M+H)^+$; 220 (267-47). Analysis calcd. (found) % for $C_{12}H_{14}N_2O_5$: C, 54.13 (54.02); H, 5.3 (5.21); N, 10.52 (10.36); O, 30.05 (30.18).

RESULTS AND DISCUSSION

The synthesis of representative iminium **4** has been synthesized starting from the commercially available *tertiary* alcohol **1**. Imine **2** was obtained by the cyclization of *tertiary* alcohol **1** by Ritter-type procedure. The nitration of imine **2** under the soft conditions [1,24] selectively led to the derived **3** with good yield. The methylation of imine **3** led to iminium **4** with a yield of 54 % (**Scheme-II**).

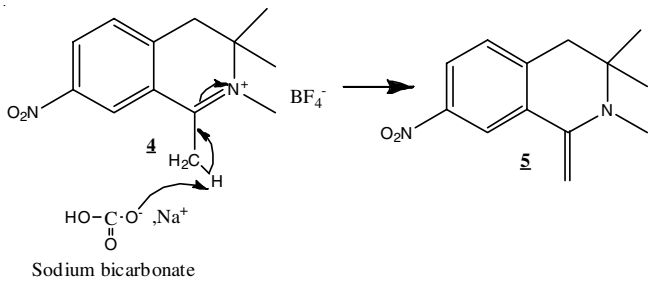


(a) H_2SO_4, CH_3CN, hexane; 68 °C, 2.5 h; (b) KNO_3-H_2SO_4; rt, 2 h; 60°C 4 h; (c) $Me_3O^+BF_4^-$, CH_2Cl_2, rt

Scheme-II: Synthesis of iminium **4**

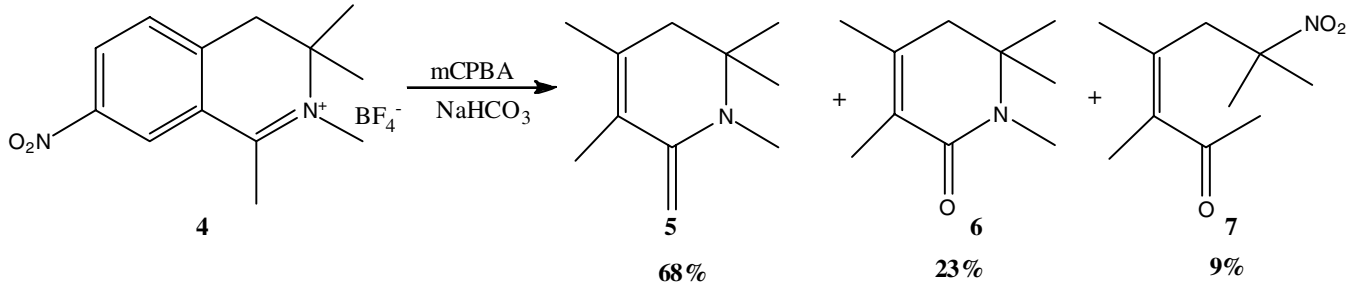
The iminium **4** was oxidized with two equivalents of *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of two equivalents of Na_2CO_3 in acetone. ^{1}H NMR analysis of the crude reaction product in deuterated chloroform showed the presence of 9 % of nitro compound **7**, 23% of lactame **6** and 68% of enamine **5** (after isolation assignments) according to **Scheme-III**.

Enamine **5** is formed by the reaction of base $NaHCO_3$ with iminium **4** (**Scheme-IV**). The enamine **5** oxidized to *m*-CPBA to form an intermediate **8**. A dual oxidation is carried out leading to the formation of lactam **6** while releasing formaldehyde with *m*-CPBA (**Scheme-V**).

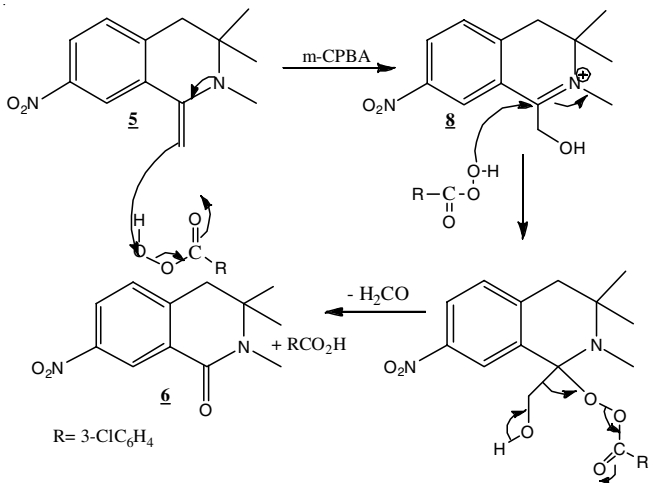


Scheme-IV: Formation of enamine **5**

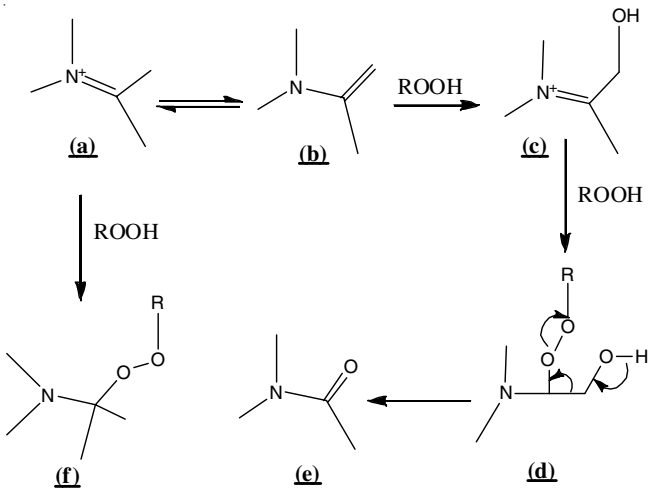
The known reactions of peroxide reagents [25], such as hydrogen peroxide and peracid with enamine and iminium,



Scheme-III: Peracid oxidation of iminium **4**



Scheme-V: Formation of lactam **6**



Scheme-VI: Reactions of peroxide reagents with enamine and iminium

reflect the dual character of electrophilic or nucleophilic reagents and can lead to a pseudo-base (f), iminium hydroxyl (c) or to amide with a loss of one carbon (e) (**Scheme-VI**).

However, the formation of minor compound **7** is mainly due to a peracid oxidation of iminium **4** (**Scheme-VII**). Compound **4** was first oxidized to obtain, *in situ*, oxaziridinium salt **9**, the latter by base catalysis present in the medium, led directly to the ring-opened compound **10** by rearrangement [26-29]. The hydrolysis of the compound **10** lead to a ketoamine **11** which, the oxidation with an equivalent of active oxygen, lead to the nitroso compound **12** which, in the presence of a new oxidation, lead to compound **7**.

Conclusion

The present study investigated the peracid oxidation of iminium **4** in order to prepare a new oxaziridinium salt. The oxaziridinium salt is not obtained instead three interesting products, namely enamine **5**, lactame **6** and nitro compound **7** were isolated. This work helps us to understand the behaviour of dihydroisoquinoline iminium, substituted in position **1**, with peracid oxidation.

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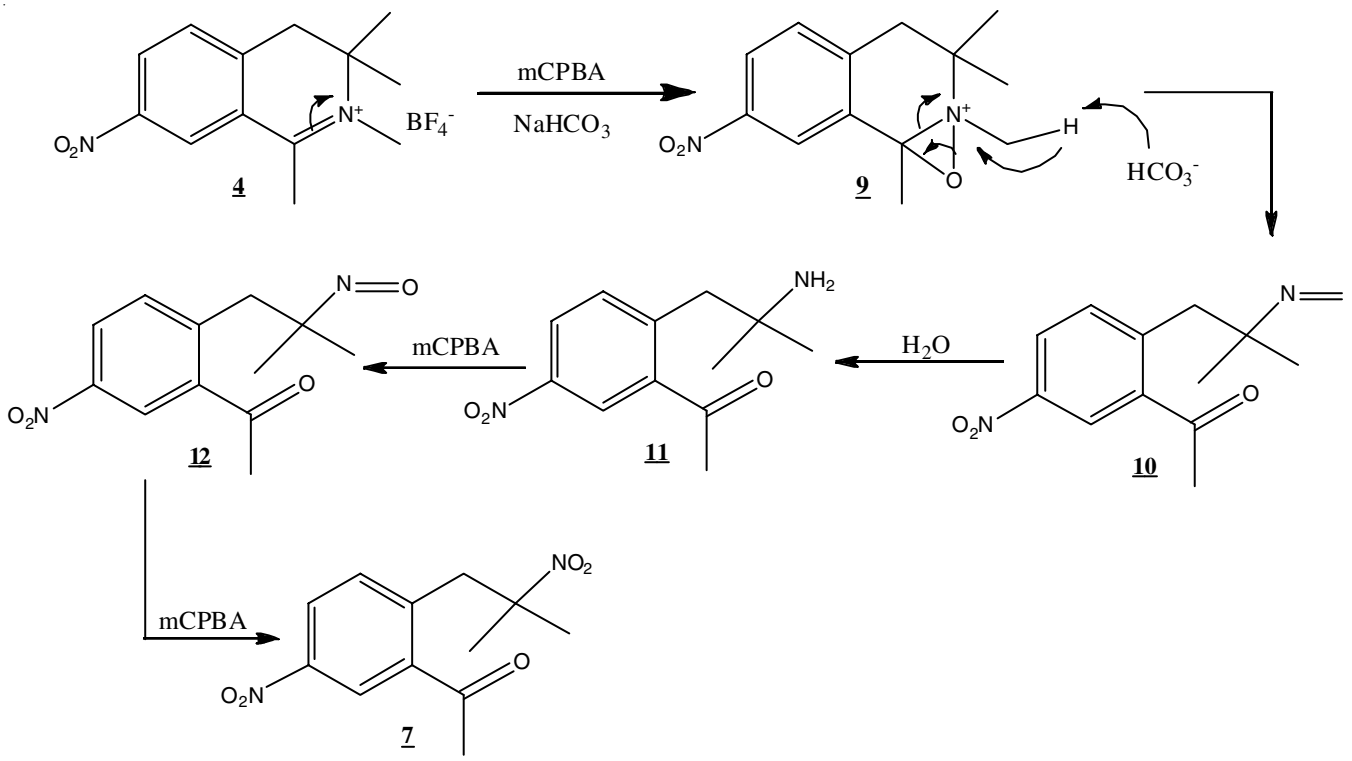

Scheme-VII: Mechanistic hypothesis of compound **7** formation

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