# Photooxygenation of Non-Aromatic Heterocycles

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**Abstract:** Photooxygenation of non-aromatic heterocycles and cyclic compounds containing non-usual heteroatoms, namely silicon, germanium and tellurium has been reviewed. All three types of photooxygenation (Types I-III) can take place. Moreover the heteroatom can be frequently involved endorsing electron-transfer reactions which turn out to be the main pathways, even in singlet oxygen oxygenation. A vast collection of novel and unexpected products are often formed, sometimes in a stereocontrolled manner.

## 1. INTRODUCTION

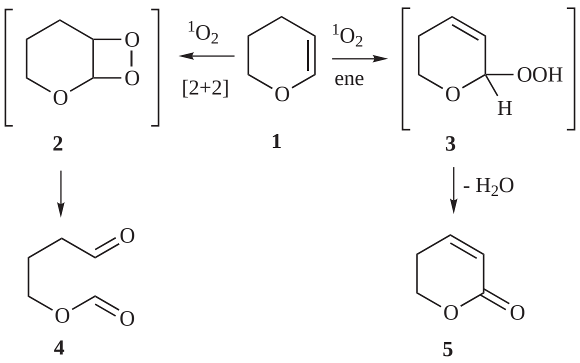
Since the first experiments by enthusiastic Ciamician [1] on the roof of his institute in Bononia (Bologna) University, a pletora of papers and books have been made regarding interaction of light with matter, and in this context photooxygenation, combination of light and oxygen generally in the presence of a suitable conjugated molecule (sensitized photooxygenation), has been widely used to introduce oxygenated functions in organic molecules.

Three common mechanisms are invoked for the sensitized photooxygenation which differ essentially by the different role of the sensitizer [2, 3]. So, the photoexcitated sensitizer can interact with the molecule by extracting hydrogen (Type I) or an electron (Type III), and the radical or the radical cation of the substrate so formed react with triplet oxygen or superoxide anion to give the oxygenated products. In Type II an energy transfer from the excited sensitizer to triplet ground state oxygen can occur generating singlet oxygen ($^1O_2$), a highly reactive species, whose behaviour towards organic molecules is continuously under investigation due to the chemical [4] and biochemical [5] implications. The electrophilicity of this species and its alkene-type character promote addition reactions to unsaturated systems ([4+2] cycloaddition [6], [2+2] cycloaddition [6], or ene-like reaction [7]). Singlet oxygen may also react at electron pair bearing heteroatom centers, e.g. sulfur, to give the corresponding oxide [4]. Sometime reactions with electron-rich substrates, such as amines [8], sulfides [9] and phenols [10], may proceed by electron transfer from the electron-rich substrate to singlet oxygen to give a cation radical-superoxide ion pair or charge-transfer complex. Coupling reaction of the ion pair could give the oxygenated product or a back-electron transfer could occur producing triplet oxygen and the starting compound. The latter route is particularly important for nitrogen-containing molecules, and some suitable derivatives, e.g. diazabicyclo[2.2.2]octane (DABCO), are specifically used as singlet–state oxygen inactivators [2, 4]. Typical sensitizers for singlet oxygen reactions are dyes as methylene blue (MB) or Rose Bengal (RB) or tetraphenylporphine (TPP) and tungsten-halogen lamps are used as light sources; aromatic ketones, as benzophenone, or cyanoaromatic compounds, as 9,10-dicyanoanthracene (DCA), are used in photooxygenation of Type I or III, respectively and mercury-lamps (preferably UV filtered) are used as light sources [2, 4c, 4d].

In 2005 we published a review on the photooxygenation of heterocyclic aromatic compounds with the aim to bring up-to-date on the latest twenty-year results [2]. In this review we focus our attention on the photooxygenation of non-aromatic heterocycles (unsaturated where bonds to the heteroatom are directly involved or saturated) [11] and have expanded the discussion to cyclic compounds containing non-usual heteroatoms, namely silicon, germanium and tellurium [12].

## 2. PHOTOOXYGENATION OF UNSATURATED HETEROCYCLES

The nucleophilicity of a double bond is enhanced by the presence of the heteroatom so that partially saturated derivatives as cyclic enol ethers or enamines react easily with singlet oxygen by [2+2] cycloaddition and afford the characteristic cleavage products from thermally unstable dioxetanes. The dioxetane-mode however competes with ene mode in the presence of adjacent allylic hydrogens. The nature of heteroatom, ring size, substitution as well as environmental factors influence the product distribution. So, in the photooxygenation of dihydropyran **1**, both dicarbonyl compound **4**, the product expected from cleavage of the dioxetane **2**, and dihydropyrone **5**, the dehydration product from the hy-



**4**/**5** ratio increases up to 58-fold from $C_6H_6$ to $CH_3CN$

**Scheme 1.**

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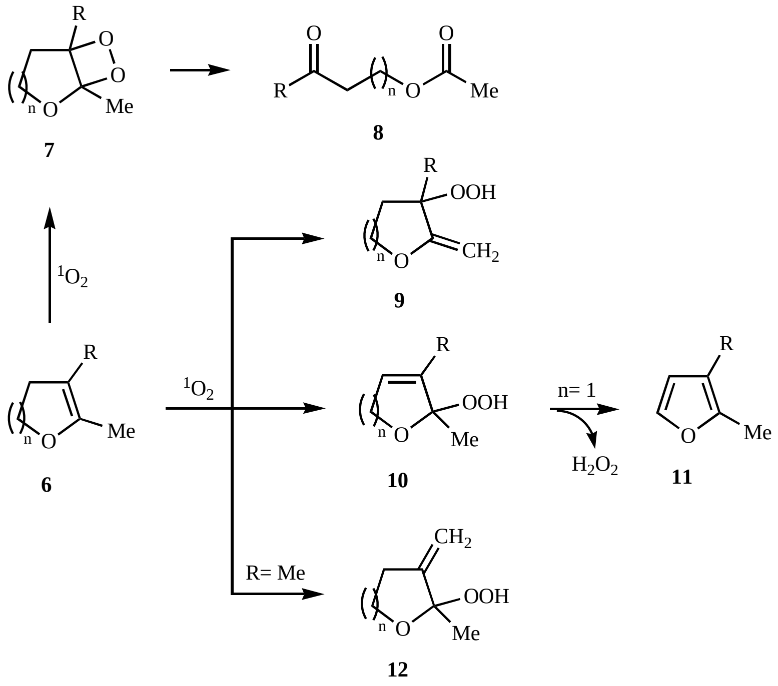
droperoxide **3**, are formed and the product ratio **4/5** varies over a 58-fold as the solvent changes from benzene to acetonitrile with polar solvent favouring the 1,2-addition (Scheme **1**) [13]. The solvent effect however seems to be associated with the unsymmetrical character of the enol ether substrate [13a].

Small rings and electron-donor substitution appear to favour the formation of dioxetanes at the expense of allylic hydroperoxides [14, 15]. Scheme **2** and Table **1** report the trend observed in oxygenated systems (dihydrofurans and dihydropyrans).

Significant is the strong substituent effect in the oxygenation of ethyl 3,4-dihydro-6-methyl-2*H*-pyran-5-carboxylate (Table **1**) and 5-acetyl analogue [15]. These compounds undergo the exclusive ene-reaction due to the presence of the electron-withdrawing ester and acetyl groups which further address the formation of the conjugated hydroperoxides as the preferred products [15]. It is interesting to note that hydroperoxides **10** (for n=1) undergo straightforward $H_2O_2$ elimination to give furans [14].

A different behaviour is observed in the singlet oxygenation of thio-analogues. Indeed, they essentially lead to dicarbonyl derivatives *via* dioxetanes. Less than 5% of allylic hydroperoxides is formed starting from five-membered derivatives as dihydrothiophene **13** while dioxetane mode is the unique route in six-membered derivatives as in 3,4-dihydro-2*H*-thiopyran **16** which gives exclusively compound **18** (Scheme **3**) [16]. The nature of heteroatom plays a role also in the thermal stability of dioxetane intermediate. S-substituted dioxetanes result more thermally unstable than O-analogues, and have been spectroscopically detected at very low temperatures (< -70 °C), if any [16].

The selective formation of dicarbonyl derivatives *via* dioxetanes is obviously observed in the presence of two het-

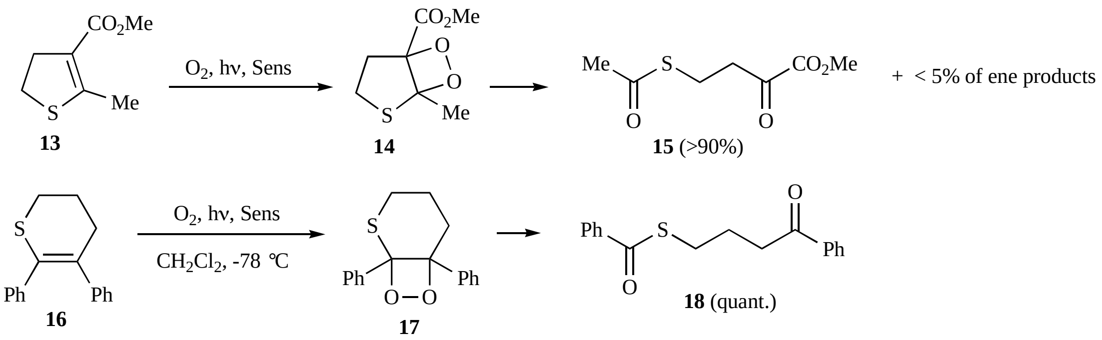


**Scheme 2.**

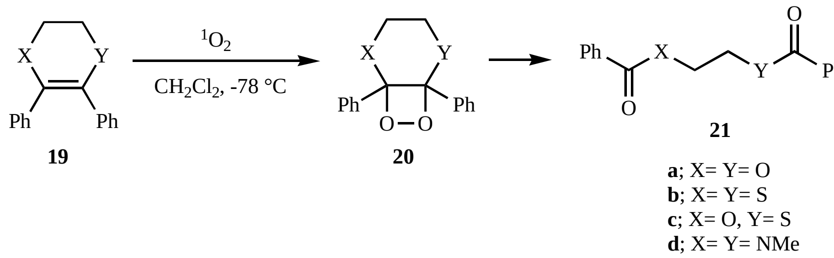
**Table 1.**

| entry | n | R | CCl₄ | | | | CH₃CN | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Products (%)[a] | | | | | | | |
| | | | 8 | 9 | 10 | 12 | 8 | 9 | 10 | 12 |
| **a**[14] | 1 | Me | 80 | - | 13 | 7 | 87 | - | 7 | 6 |
| **b**[14] | 1 | $CO_2Me$ | 3 | 14 | 83 | - | 44 | 6 | 50 | - |
| **c**[14] | 2 | Me | 28 | 52 | - | 20 | 35 | 55 | - | 10 |
| **d**[15] | 2 | $CO_2Et$ | - | 17 | 83 | - | - | 65 | 35 | - |

[a] By $^1H$ NMR.



**Scheme 3.**



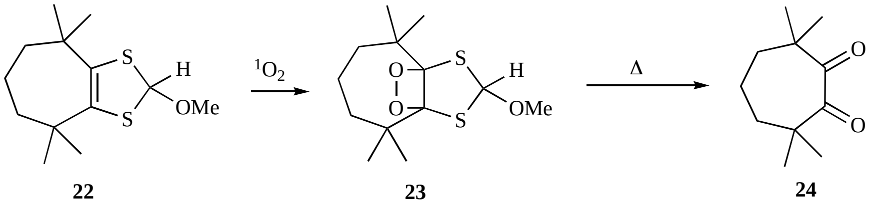
**a**; X= Y= O
**b**; X= Y= S
**c**; X= O, Y= S
**d**; X= Y= NMe

**Scheme 4.**

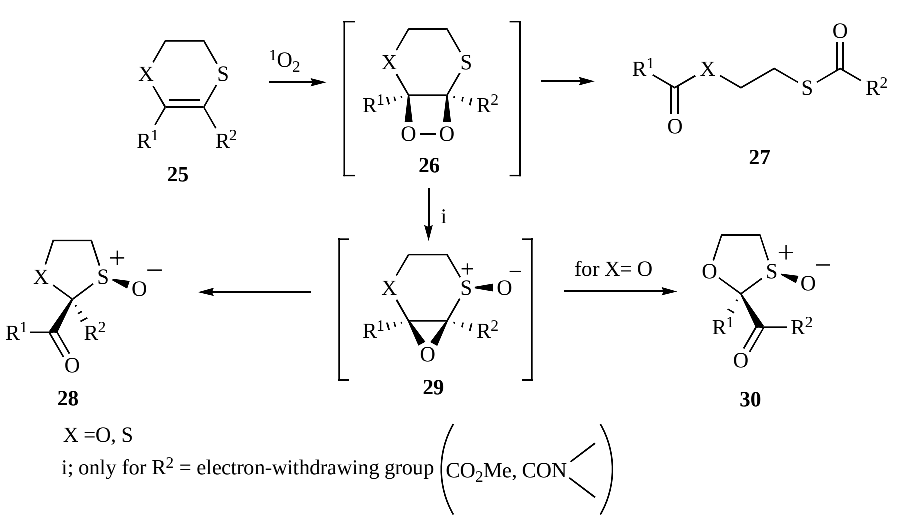
eroatoms on the double bond as in **19** (Scheme **4**) [17]. Once more the nature of the heteroatoms affects the thermal stability of the corresponding dioxetanes. A mechanism involving an intramolecular electron-transfer process has been proposed for the cleavage of unstable S- and N-substituted dioxetanes [17]. This mechanism requires that the stability of dioxetanes is related to the oxidation potential of the heteroatom substituents. So, dioxetanes bearing easily oxidized groups such as N- or S-substituents are dramatically less stable than a similar dioxetane with an O-group possessing a much higher oxidation potential [17].

As observed in above Schemes, fragmentation to dicarbonyl compounds *via* O-O and C-C bond breakage is the usual decomposition of dioxetanes. However peculiar rearrangements have also been observed. So, oxygenation of compound **22** sometime leads to diketone **24** derived from the decomposition of dioxetane **23** *via* C-S bond cleavages [18], as also observed in bis-, tris- and tetrakis-1,2-ethylthioethylenes (Scheme **5**) [19].

The presence of suitable substituents at appropriate positions may induce peculiar rearrangements. So, in the oxygenation of 5,6-dihydro-1,4-oxathiins **25** (X=O) [20] and 5,6-dihydro-1,4-dithiins **25** (X=S) [21] the formation of keto sulfoxides **28** and/or **30** has been observed in the presence of an electron withdrawing group at the double bond (Scheme **6**). It has been suggested that in the dioxetanes **26** the in-

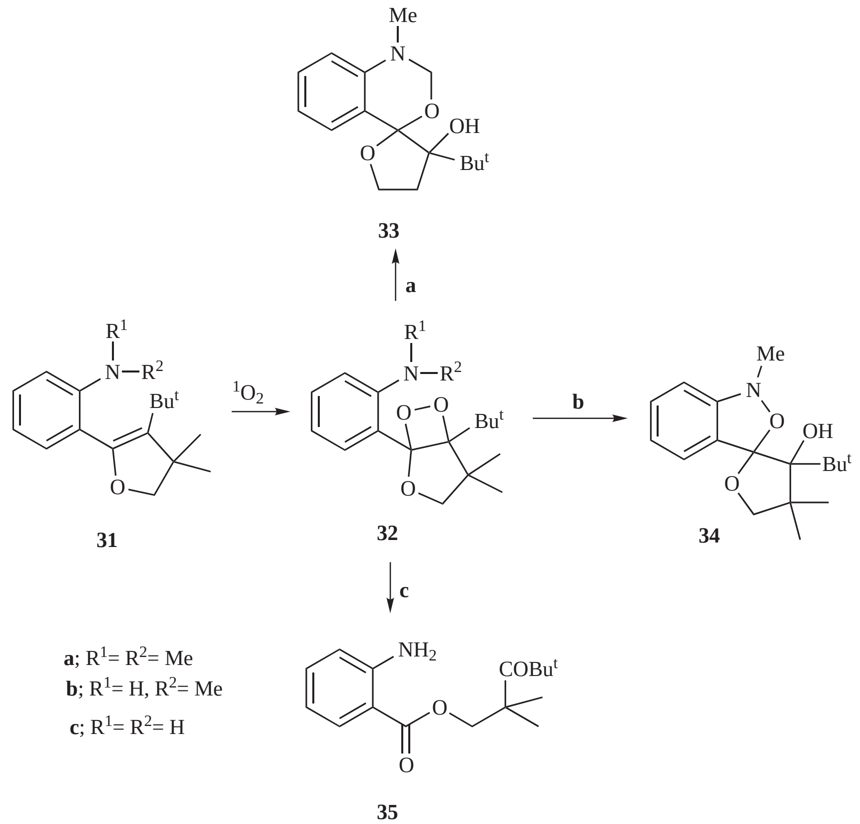


**Scheme 5.**

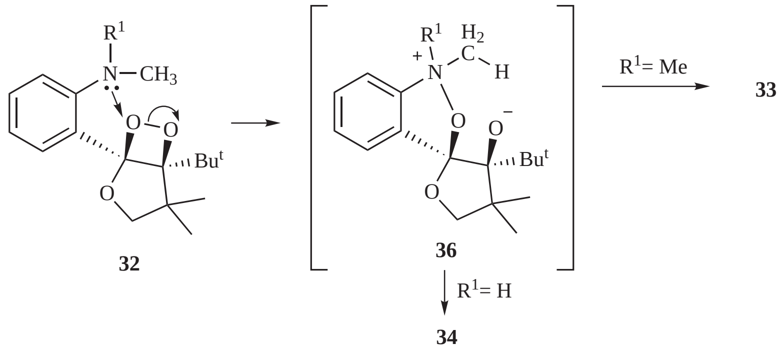


X =O, S
i; only for $R^2$ = electron-withdrawing group ($CO_2Me$, CON)

**Scheme 6.**



**Scheme 7.**



**Scheme 8.**

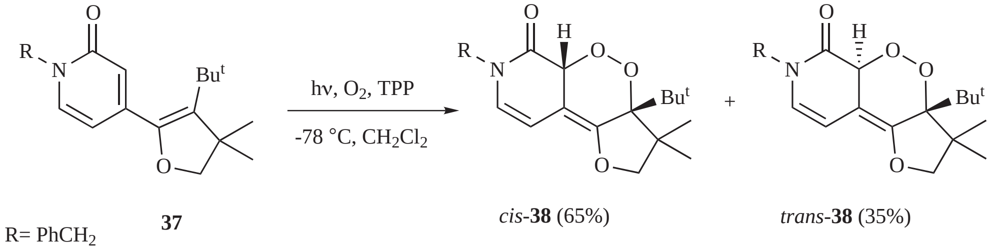
creased electron demand by the O-O bond favours the intramolecular nucleophilic attack of the ring sulfur leading to final products **28** and/or **30** *via* the labile undetected sulfoxide epoxides **29** The selective formation of compounds **28** for X=S is evidently due to the major migratory aptitude of sulphur than that of sulfoxide or oxygen moiety [21].

Heterocycles **33** and **34** have been obtained in high yields from the oxygenation of 2-(*o*-aminophenyl)-4,5-dihydrofurans **31a** and **31b** *via* unusual decomposition of dioxetanes **32** (Scheme **7**) [22].

These peculiar rearrangements would be induced by intramolecular nucleophilic attack of *o*-methylamino and *o*-dimethylamino groups at O-O bonds of the dioxetanes **32a,b** (Scheme **8**) [22]. In particular, the zwitterion **36a** should cause Stevens-like rearrangement by abstraction of a methyl proton by the close oxy anion leading to **33**. It is to be noted that the oxygenation of **31c** affords normal carbonyl product **35** (Scheme **7**) as do derivatives bearing a phenyl substituted with *N*-methylamino or *N*,*N*-dimethylamino groups at the *meta* or *para* position [22].

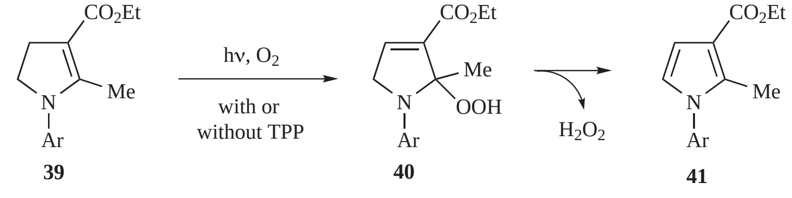
Interestingly, the oxygenation of similar enol ether **37** leads exclusively to the diasteromeric mixture of endoperoxides **38** (Scheme **9**) [23]. In this case [4+2]cycloaddition of singlet oxygen to diene system prevails on [2+2] addition to the double bond, albeit activated, and this trend is generally observed whenever a π-conjugated system is present in the substrate (see below).

Sometime dehydrogenation has been observed in the oxygenation of five-membered unsaturated heterocycles [14, 16, 24, 25]. So, pyrroles **41** are formed from dihydropyrroles **39** and, as above reported for compounds **10** (Scheme **2**) [14], it would be due to the decomposition of the intermediate hydroperoxides **40** (Scheme **10**) [24]. The substrates **39** (*N*-aryl cyclic enamines) have been found to be sensitizers of singlet oxygen [24].



**37**

**Scheme 9.**

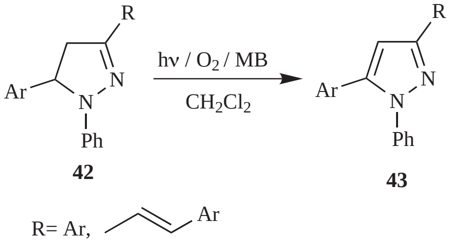


**39** **40** **41**

Ar= Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$

**Scheme 10.**

Dehydrogenation also occurs in the oxygenation of 1-phenyl-2-pyrazolines **42** (Scheme **11**) [25]. Some derivatives, e.g. 1-phenyl-3-[*p*-(dimethylamino)-phenyl]-2-pyrazoline and 3-[*p*-(diethylamino)-phenyl]-2-pyrazoline however are stable under the reaction conditions and capable of quenching $^1O_2$ efficiently. The authors suggest that the quenching mechanism would involve a charge-transfer process or weak molecular complexes, because these 2-pyrazoline derivatives have relatively high electron densities on their rings as supported by their low oxidation potentials [25].



**42** **43**

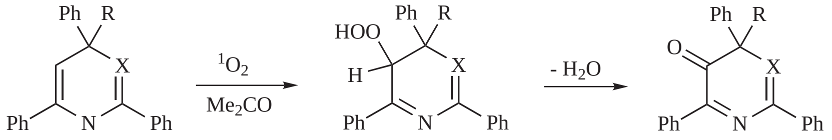
**Scheme 11.**

Pyridones **46** (X=CH) and pyrimidones **46** (X=N) are obtained in the RB-sensitized photooxygenation of 1,4-dihydropyridines **44** (X=CH) [26] and 1,4-dihydropyrimidines **44** (X=N) [27] *via* elimination of $H_2O$ from the related hydroperoxides **45** (Scheme **12**). The choice of acetone as oxygenating solvent is essential to obtain **46**.

Peculiar ene-type reactions have also been described which involve an allylic hydrogen linked to heteroatom or simply $O_2$ addition-double bond migration. For example, the photooxygenation of 2,5-dimethyl-4-hydroxy-3-(2*H*)-furanone **47**, a caramel-like, sweet, fruity flavour, leads in absolute ethanol to a variety of products (Scheme **13**) [28]. The key intermediate has been suggested to be the hydroperoxide **48** formed by the attack of singlet oxygen to the double bond at C-5 position. Ring opening to 5-hydroxy-2,3,4-hexanetrione intermediate **49**, hydrolysis, fragmentations, rearrangements and esterification would be the events leading to the observed products.

Products **53** and/or **54** (the latter together with **53** using methanol as solvent) have been isolated in the oxygenation of isoquinolinones **50** (Scheme **14**) [29]. The authors propose that, despite the presence of the highly activated enol-enamine C=C double bond, an ene-type electrophilic attack of singlet oxygen to C-6 of the substrates would occur giving the zwitterionic intermediates **51**. The latter would afford endoperoxides **52** by a transannular nucleophilic attack of the peroxidic anion to the *para*-carbonyl group. Homolytic cleavage of the O-O bond and heterolytic C-N bond scission result in the formation of **53** while products **54** derive from the nucleophilic trapping of the iminium cation in **51** or **52** by methanol (Scheme **14**) [29].

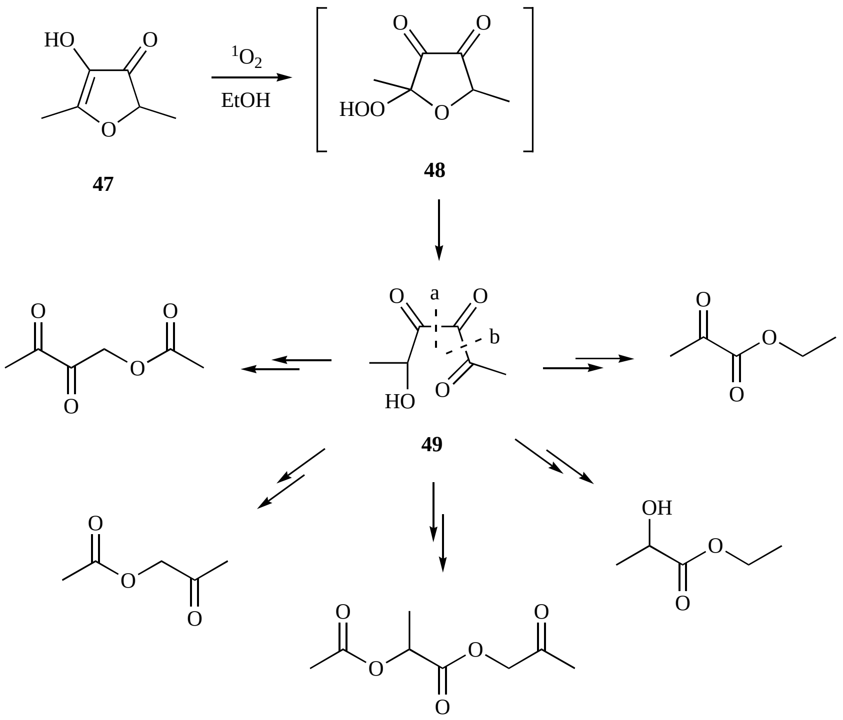
An interesting RB-sensitized photooxygenation reaction has been observed starting from 1,6-diazaphenalene **55** which leads in dilute solution to product **56** in 50 % yield (Scheme **15**) [30]. It is formed *via* uptake of oxygen at the **7**-position of **55** as an ene-like reaction, facilitated by electron release from the nitrogen at position-1, followed by dehydration. Although electron availability at C-3 might render this



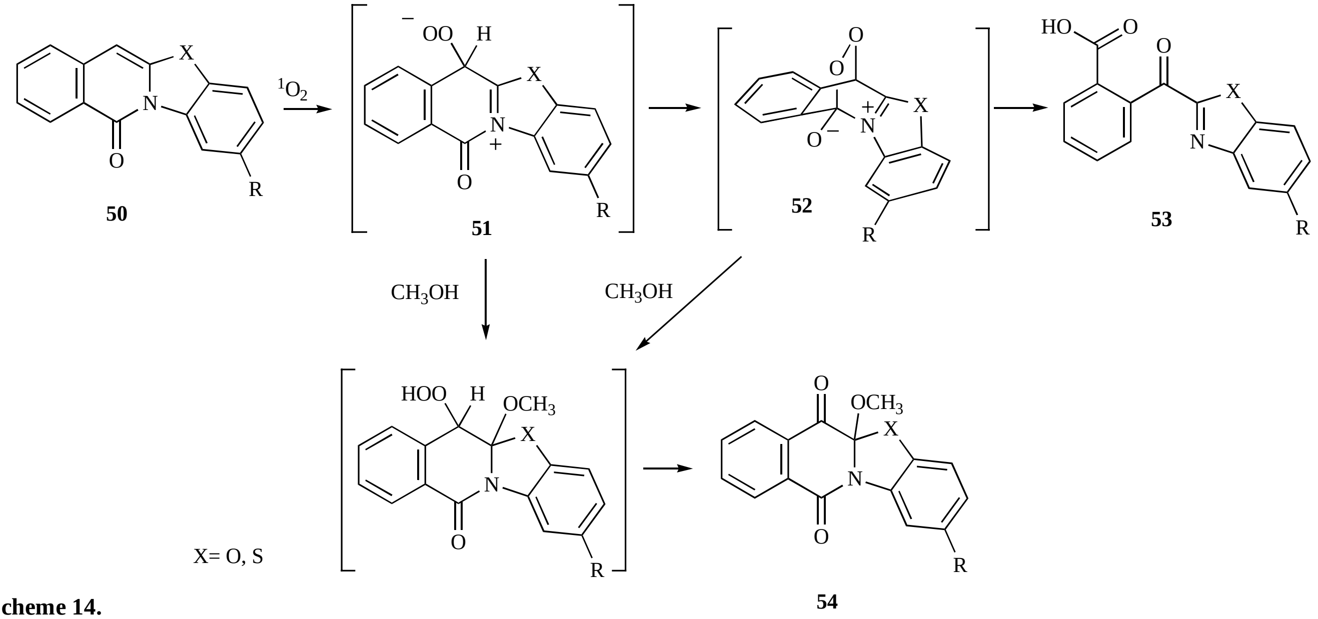
**44** **45** **46**

X = CH, N

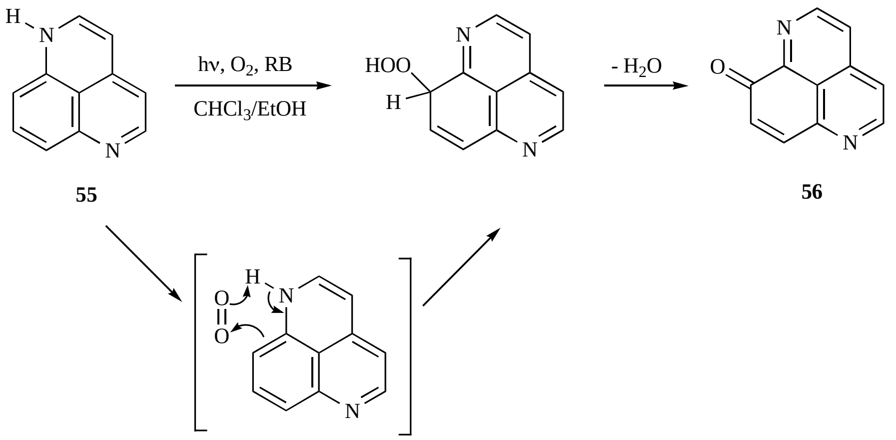
**Scheme 12.**



Scheme 13.



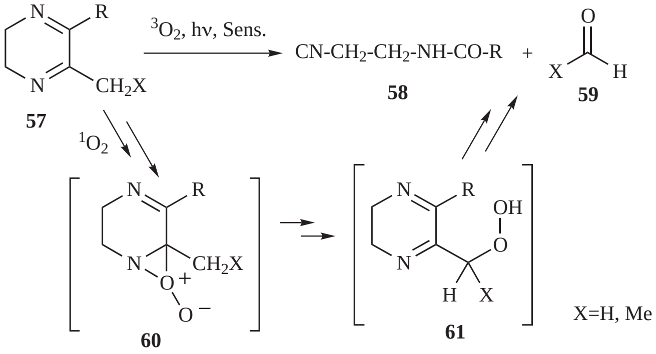
Scheme 14.



Scheme 15.

position a competitive site for attack by the electrophilic oxygen, the reaction at C-7 has the advantage of a favourable 6-membered transition state for C-O bond formation coincident with the breaking up of the N-H bond.

Reactivity of 2,3-dihydropyrazines towards singlet oxygen depends on the substitution. So alkyl-substituted 2,3-dihydropyrazines **57** afford 1-isocyano-2-(acylamino)ethanes **58** and aldehydes **59** (Scheme **16**) [31]. 5,6-Diphenyl derivative is inert [31b]. The unstable hydroperoxide **61** derived from a perepoxide intermediate **60** has been proposed as key intermediate in the formation of the observed products (Scheme **16**) [31, 32].



**Scheme 16.**

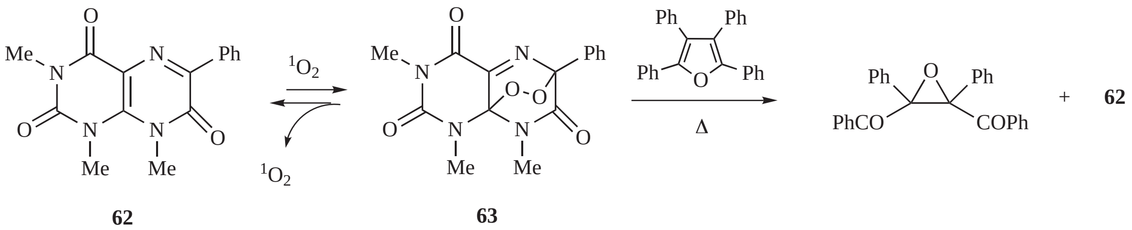
The presence of 1,4-dicarbosubstituted π-conjugated system in pyrazin-2-ones [33a] or condensed derivatives, as pteridin-2,4,7-trione **62** [33b], addresses the reaction to [4+2] cycloaddition and, hence, 1,4-endoperoxides are formed which lead to fragmentation products or undergo retro-cycloaddition, respectively. Liberation of singlet oxygen has been confirmed by trapping experiments using typical singlet oxygen acceptors [33b]. In particular, heating of an equimolecular solution of endoperoxide **63** and tetraphenylfuran in dichloromethane affords *cis*-dibenzoylstilbene oxide and the starting pteridone **62** in 82 % and quantitative yields, respectively (Scheme **17**) [33b].

Photooxygenation of tetramethyl-4*H*-pyrazole **64a** produces diketone **66** and $N_2$ presumably *via* the corresponding endoperoxide (Scheme **18**) [34]. The same intermediate has been proposed in the photosensitized oxygenation of the drug acetazolamide **64b** [35]. It however rearranges as reported for thiophene endoperoxides [36] and gives sulfine **67** (Scheme **18**) [35]. It is interesting to note that this product has also been obtained by unsensitized photooxygenation of acetazolamide and that the drug is able to oxidate 2,5-dimethylfuran (efficient acceptor for $^1O_2$) so showing that it posseses Type II photodynamic activity [35].

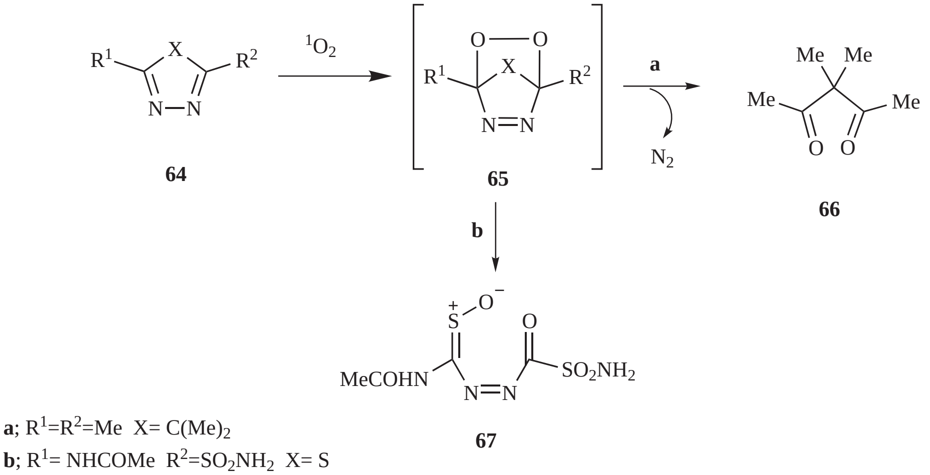
An endoperoxide intermediate **69**, formed by oxygen addition to the conjugated diene system, has also been invoked in the self-sensitized photooxidation of isoquinolin-3-one **68** (Scheme **19**). The opening of endoperoxide **69** by the solvent (methanol) would lead to compound **70** which by methanol elimination followed by irradiation under basic conditions affords norpontevedrine **71a**, key intermediate for pontevedrine **71b**, a 4,5-dioxoaporphine alkaloid. A “one pot” conversion of **68a** into **71a** is achieved by carrying out the irradiation in ethanolic alkali solution under oxygen atmosphere [37].

## 3. PHOTOOXYGENATION OF SATURATED HETEROCYCLES

Photooxygenation of acyclic sulfides as well as that of cyclic analogues has received much attention owing to the



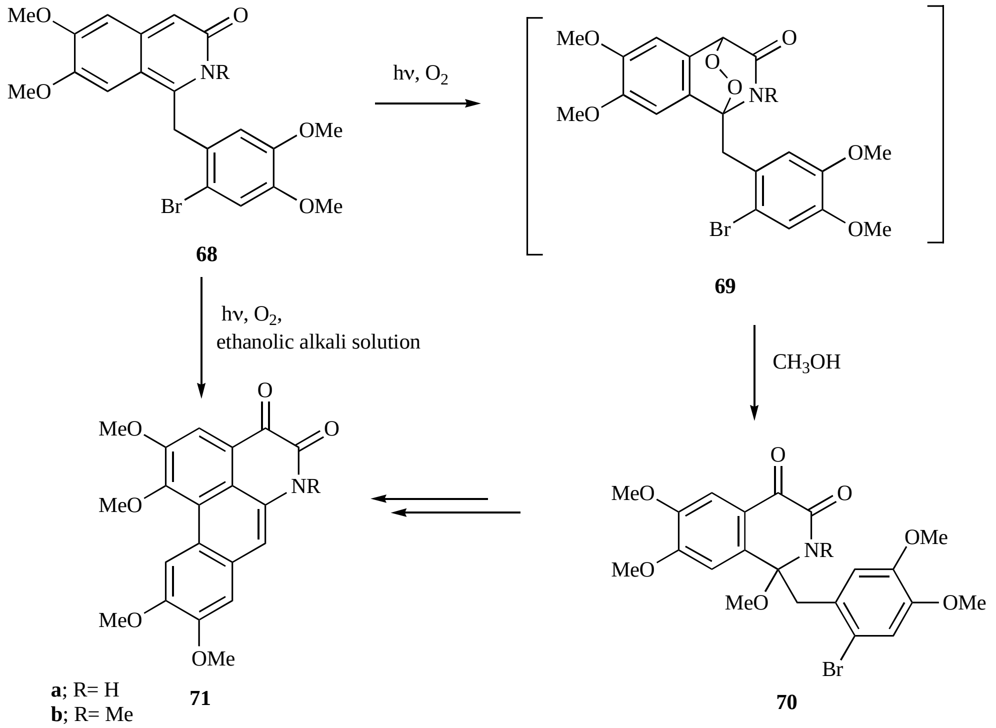
**Scheme 17.**



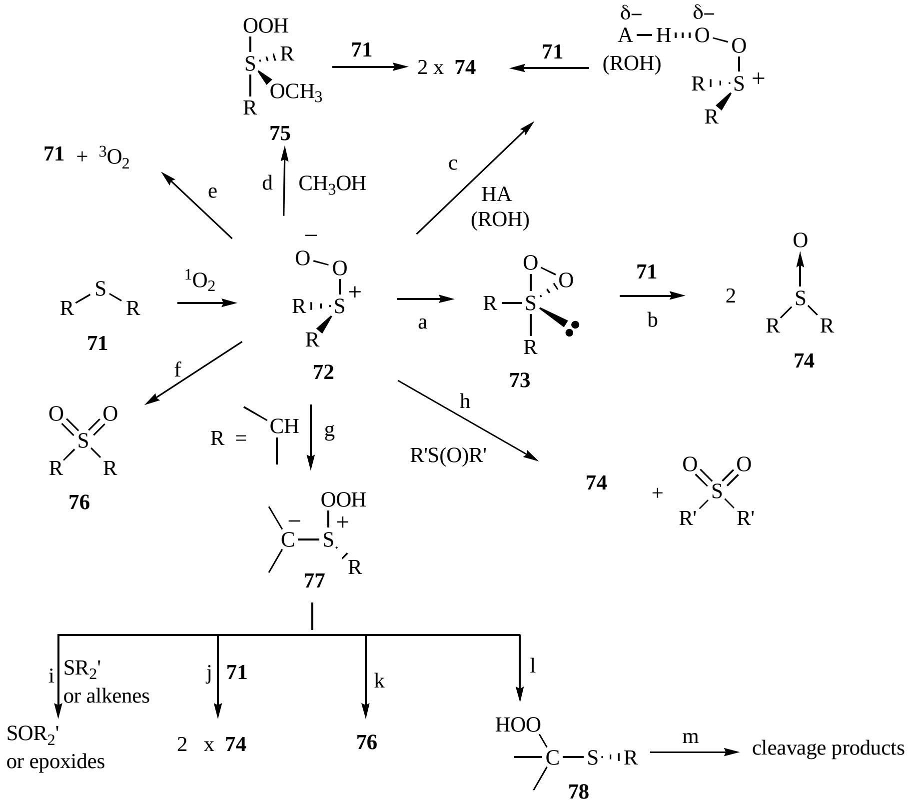
**a**; $R^1$=$R^2$=Me X= C(Me)$_2$

**b**; $R^1$= NHCOMe $R^2$=$SO_2NH_2$ X= S

**Scheme 18.**

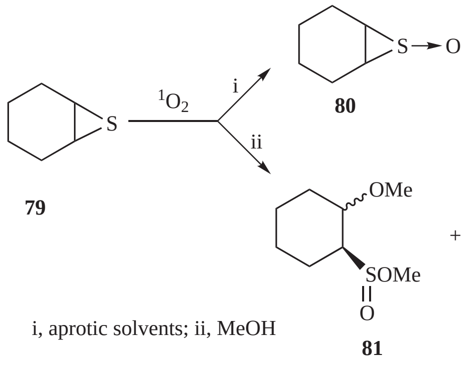


**Scheme 19.**

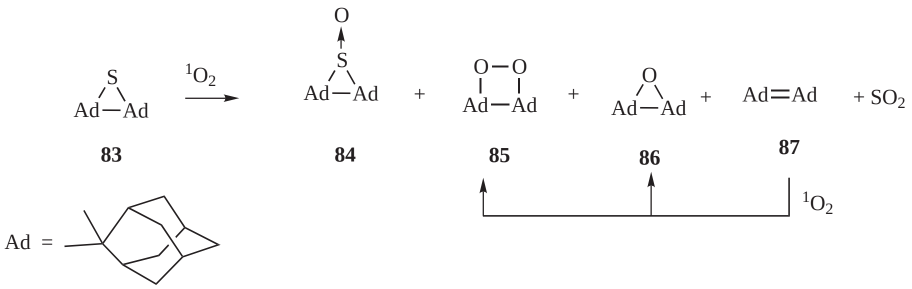


**Scheme 20.**

synthetic potential of the reaction [4a, 12, 38, 39] and further to the role of many natural sulfur-containing compounds in the activity of some enzymes and to the deactivation of the latter by active oxygen species [40]. Schenck first reported that dialkyl sulfides undergo photooxidation to give two moles of sulfoxides per mol of absorbed oxygen [41]. Since then great efforts have been devoted to the knowledge of this reaction, mainly to the identity and reactivity of initially formed peroxidic intermediates [4a, 12, 38, 42-44]. The widely accepted mechanism is that the reagents initially form a weakly bound persulfoxide **72** which collapses to thiadioxirane **73** (a) and this, in turn, reacts with sulphide substrate **71** to give two sulfoxides **74** (b) (Scheme **20**) [45]. The reaction is instead very complex as proven by ab initio calculations [43, 46], isotopic effects [47, 48], alcohol [49, 50] or protic medium effects [51]. Depending on sulphide structure,



**Scheme 21.**



**Scheme 22.**

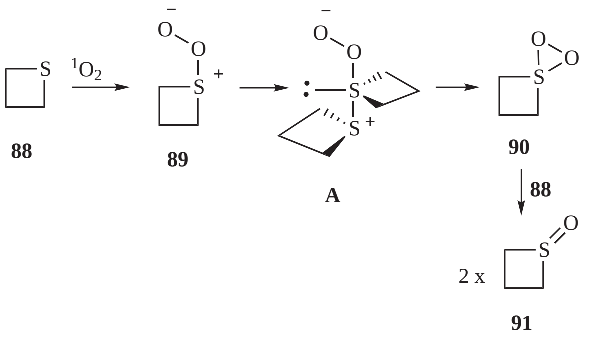
substituents and reaction conditions (solvent, concentration, temperature) the persulfoxide may undergo a myriad of inter- and intramolecular reactions (Scheme **20**).

In protic solvents stabilization occurs by hydrogen bonding (c) [45, 49-51] (or in MeOH by formation of a sulfurane intermediate **75** (d) [45]) and attack to a second molecule of sulphide is promoted leading to two sulfoxides. Under these conditions the reaction is very efficient. In aprotic medium more debated is the question of intermediates as well as less predictable the efficiency of the reaction. The persulfoxide **72** partitions between decomposition to sulfide and ground oxygen (e) (physical quenching) [45] and chemical processes. In particular, it may 1) convert into sulfoxide *via* thiadioxirane (a,b) [45]; 2) rearrange to sulfone **76** (f) [9d, 48, 52], sometime favoured by low temperature and low concentration [9d]; 3) be trapped by sulfoxides R'$_2$SO (h) [45, 50, 53]; 4) rearrange to a S-hydroperoxysulfonium ylide **77** (g). The successful formation of the S-hydroperoxysulfonium ylide **77** appears to be governed by a variety of factors including accessibility and acidity of the α-hydrogen [47]. In some cases the ylide may undergo a 1,2-OOH shift to a α-hydroperoxysulfide **78** (Pummerer rearrangement) (l) [54], and this one in some cases can lead to cleavage products (m) [46, 55]. The ylide **77** may be trapped by sulfides or alkenes (i, j) [56] or rearrange to sulfones (k) [57]. Recently a conformationally induced electrostatic stabilization (CIES) of the persulfoxide by a remote electron rich functional group has been proposed as yet another mechanism to increase the efficiency of the sulphide oxidation (see below) [58].

In cyclic sulfides formation of products depends significantly on the structure of the starting compounds and, in many cases, they display reactivity differences relatively to acyclic sulfides. Thus, in singlet oxygenation of thiiranes, the primary products are the thiirane oxides in non-nucleophilic solvents while in methanol sulfinic esters are found at low substrate concentration and thiirane oxides at high concentration [59]. This trend is observed also in the oxygenation of condensed thiiranes as **79** (Scheme **21**). Disulfides as **82** are sometime found particularly in the presence of an acid. Diphenyl-substituted thiirane is inert even after prolonged irradiation [59].

Strained thiiranes as biadamantylidene sulfide **83** give sulfoxides nearly quantitatively, even in methanol (Scheme **22**). In apolar solvent, in addition to the oxide **84**, desulfurization products, through SO$_2$ elimination, as dioxetane **85**, oxirane **86** and alkene **87** have also been evidenced, the first two deriving from singlet oxygenation of alkene **87** so formed [60].

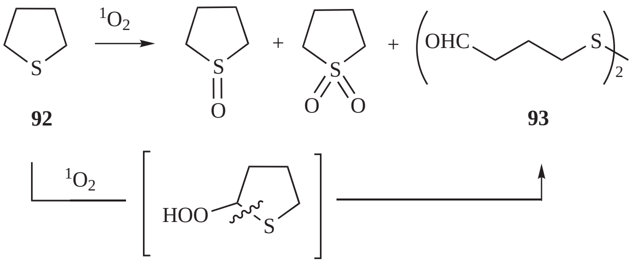
The four-membered ring sulphide, thietane **88**, gives the sulfoxide product **91**, even in aprotic medium [61]. A detailed kinetic study has indicated that it is due to a self-catalyzed mechanism, i.e. thietane itself apparently stabilizes the first formed intermediate (as in **A**), and thus S-oxidation competes significantly with the quenching [61]. The unique ability of **88** to catalyze its own oxidation is a result of a



**Scheme 23.**

small C-S-C angle which allows an unencumbered approach to the sulfonium sulphur [61].

Cleavage products or oxyfunctionalization α to sulfur have been observed in five-membered ring sulfides having α-hydrogens [54, 56, 62, 63]. Indeed, thiolane **92** gives in addition to sulfoxide and sulfone, the disulfide **93** corresponding to oxidation of the α-carbon (Pummerer rearrangement, path l in Scheme **20**) and ring opening of the hydroperoxide intermediate (Scheme **24**) [62].



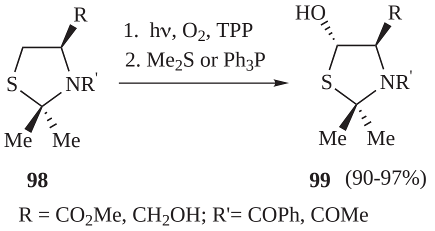
**Scheme 24.**

C-S Bond cleavage has also been observed for substituted or condensed thiolanes while the six- or seven-membered sulfides lead only to sulfoxides and sulfones [62]. C-S Bond cleavage has been explained on the basis of the acidity of α-proton which is significant in a five-membered ring as result from kinetic data on acidity of α-proton of cyclic sulfides [64].

In the singlet oxygenation of thiazolidine **94**, Ando *et al.* have found that the α-hydroperoxysulfide **95** is stable at 0°C and capable of oxidizing sulfides and phosphines (Scheme **25**) [54].

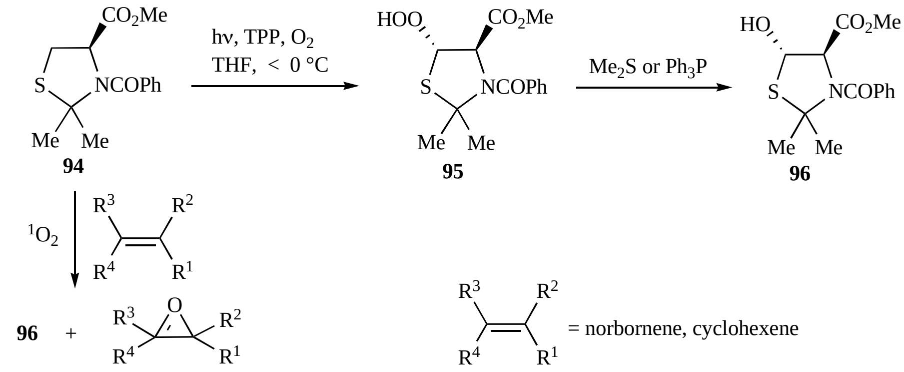
The alcohol **96** is stereospecifically formed with 4,5-*trans* configuration, and the optically active isomer gives the optically active alcohol as only one diastereomer [56, 63]. Significant is the cooxidation of alkenes to epoxides in the presence of alkenes inert toward $^1O_2$ (Scheme **25**) [56]. Control experiments have shown that hydroperoxide **95** is not responsible of this oxidation, so key intermediate would be the hydroperoxysulfoxide **97** which undergoes a 1,2-shift to hydroperoxide **95** (Pummerer rearrangement) or transfers oxygen to alkenes (Scheme **26**) [56].

The photooxygenation of thiazolidines **98** in the presence of *meso*-tetraphenylporphine followed by reduction of the intermediate hydroperoxides with triphenylphosphine ($Ph_3P$) or dimethyl sulphide ($Me_2S$) represents a mild procedure for a selective and stereospecific hydroxylation α to sulfur (Scheme **27**) [54].

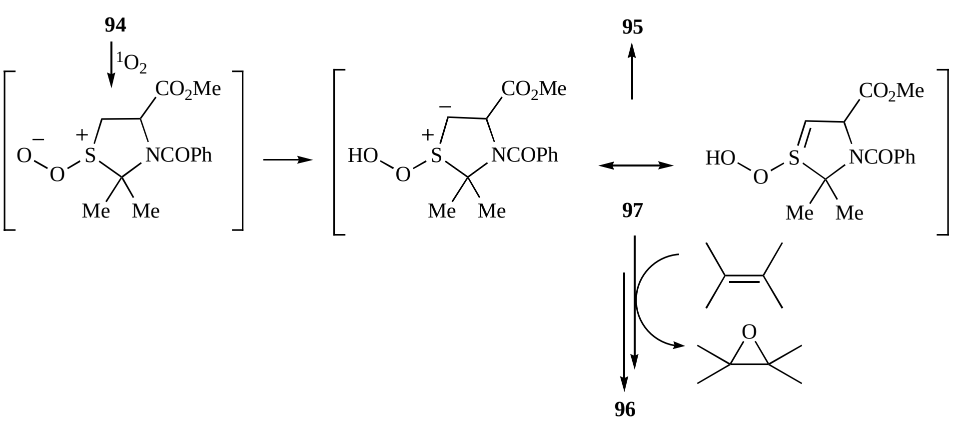


**Scheme 27.**

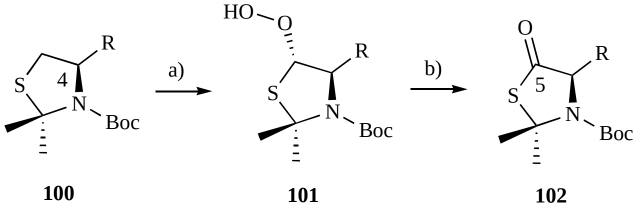
Interesting applications of this reaction to the synthesis of β,γ-unsaturated D-α-amino acids are depicted in Schemes **28** and **29** [65]. The *N*-acylthiazolidines **100**, derived from L-cystein, are oxidized to hydroperoxides **101** which are converted in 5-thiazolidinones **102**.



**Scheme 25.**



**Scheme 26.**



a)TPP/ $O_2$ / hν (125 W, halogen) / THF, -78°C
b) $Ac_2O$ / $Et_3N$ / THF, -78°C

Scheme 28.

Compounds **102** upon suitable simple reactions afford amino acids of high enantiomeric purity [65].

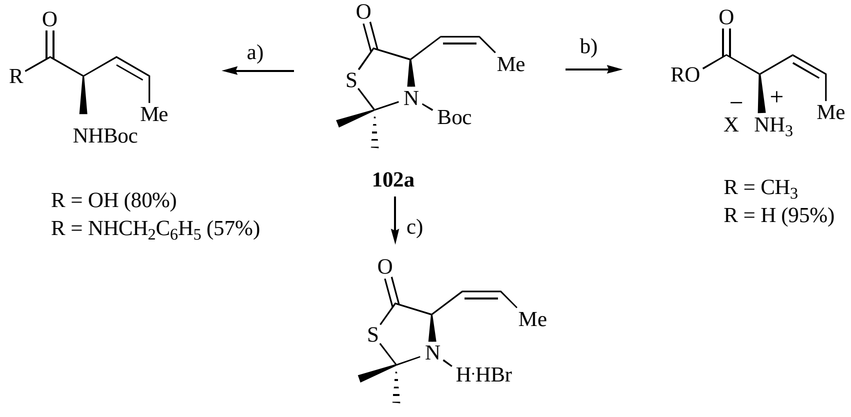
Some interesting applications starting from **102a** (R = CH=CHMe) are reported in Scheme **29**.

The presence of a good β-leaving group induces an oxidative elimination reaction leading to α,β-unsaturated sulfoxides. So, in the reaction of chlorothiane **103**, in addition of sulfoxides *cis*- and *trans*-**104,** compound **105** is found, derived from the corresponding hydroperoxysulfonium ylide as depicted in Scheme **30** [66].

Singlet oxygenation of 1,3-dithianes **106** leads to the corresponding 1-oxides **107** in good yields and good stereoselectivity, the latter being governed by steric factors (Scheme **31**) [67]. The methodology represents an important complement to conventional oxidizing methods. Indeed, *m*-chloroperbenzoic acid procedure gives unreacted starting reagent or, under exhaustive conditions (warming up and longer duration of reaction) leads to side products. Similar good yields have been obtained from the same dithiolanes by photosensitised electron transfer oxidation (oxygen saturated mixture of $CH_3CN/H_2O$; 1-cyanonaphtalene as sensitizer) [68]. However substitution patterns as well as the reaction conditions can affect the reaction course and carbonyl compounds and sulfones can be obtained starting from aryl-substituted 1,3-dithiolanes in addition to sulfoxides [68b].

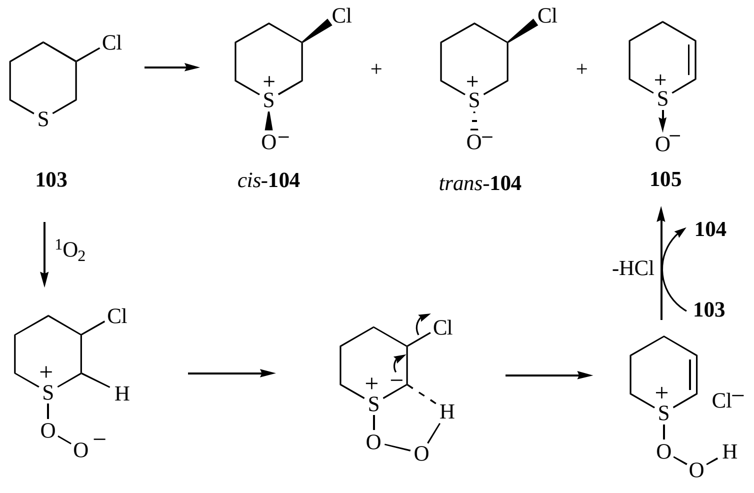
A triplet sensitizer as benzophenone induces photodethioketalization as reported in Scheme **32** for thioketal **108** [69]. The reaction has been successfully employed on thioketals of steroids and tetrahydrosantonine [69].

Highly stereoselective is the oxygenation of anancomeric (conformationally fixed) 1,3-dithianes **109** [47]. Compounds **109a**,**c**,**d** give exclusively (> 98%) the equatorial sulfoxides

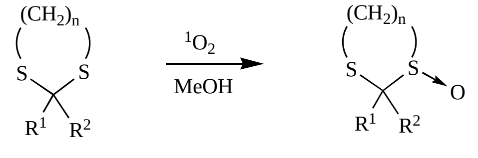


a) LiOH/ $H_2O$-THF
b) $CH_3OH$/ $(Me)_3SiBr$ or $(Me)_3SiCl$
c) $(Me)_3SiBr$/phenol/$CH_2Cl_2$

Scheme 29.



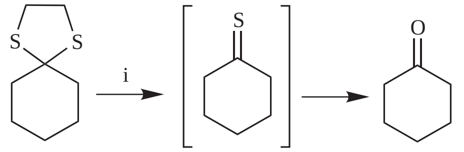
Scheme 30.



**106** **107**

| | |
|---|---|
| *n*=2 $R^1, R^2 = -(CH_2)_4-$ | (78%) |
| *n*= 2 $R^1, R^2 = -(CH_2)_5-$ | (68%) |
| *n*= 2 $R^1 = Ph, R^2 = H$ | (72%) |
| *n*= 2 $R^1 = Ph, R^2 = Me$ | (75%, stereoisomer ratio 7:1) |
| *n*= 2 $R^1 = Ph, R^2 = Et$ | (32%, stereoisomer ratio 4:1) |
| *n*= 3 $R^1 = Ph, R^2 = H$ | (72%) |

**Scheme 31.**



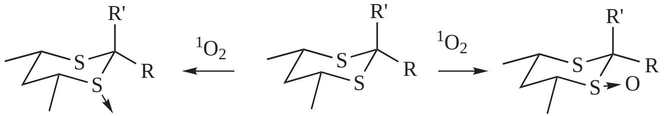
**108**

i; benzophenone, $O_2$, high pressure Hg-lamp (Pyrex filter)

**Scheme 32.**

**111a**,**c**,**d** (Scheme **33**). Axial oxidation suffers from destabilizing steric and electronic reactions between the oxidant and the axial hydrogen and with the axial lone pair on the remote sulphur. It has been observed in derivatives **109b**,**e** and has been explained through the addition of singlet oxygen to sulfur in energetically accessible twist-boat conformations.

More complex is the reaction of derivative **109c** which in addition to **111c** affords compounds **112-114** (Scheme **34**) [47].



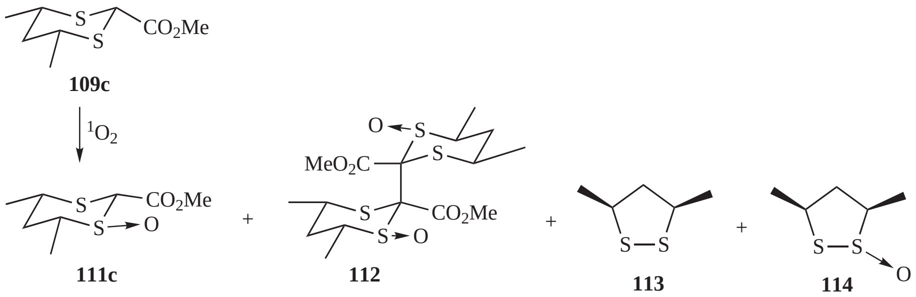
**110** **109** **111**

a; $R = CH_3$ , R' = H
b; R = H, $R' = CH_3$
c; $R = CO_2CH_3$, R' = H
d; R = Ph, R' = H
e; R = H, R' = Ph

**Scheme 33.**

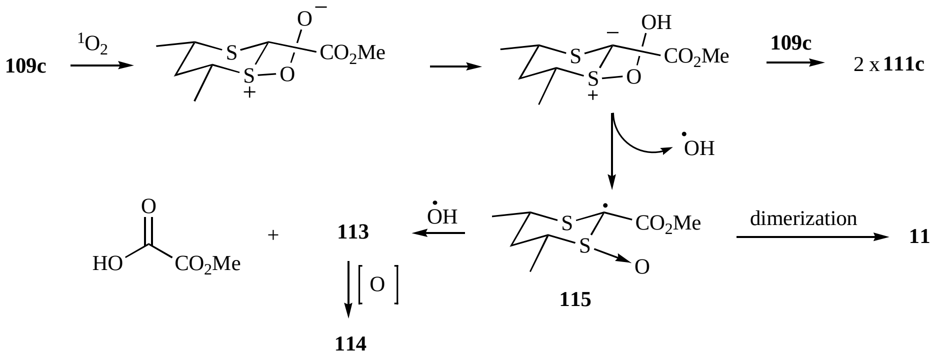
The key intermediate is assumed to be the captodatively stabilized radical **115** which should be formed by intramolecular electron transfer from the carbon-centered anion to the peroxy linkage in the hydroperoxysulfonium ylide (Scheme **35**).

It is interesting to note that S-oxidation is completely overcome in the presence of a double bond as in compound

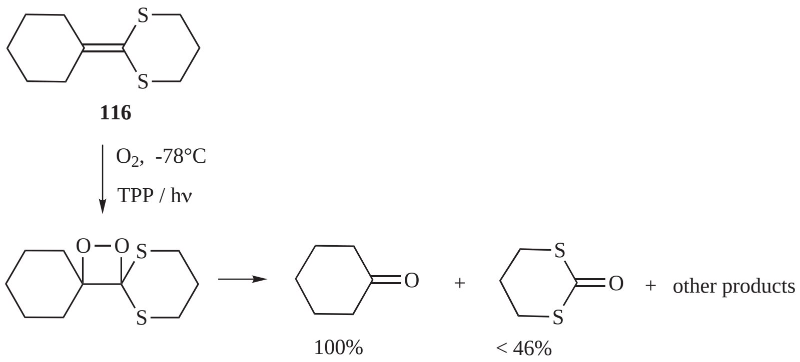


**109c** **111c** **112** **113** **114**

**Scheme 34.**



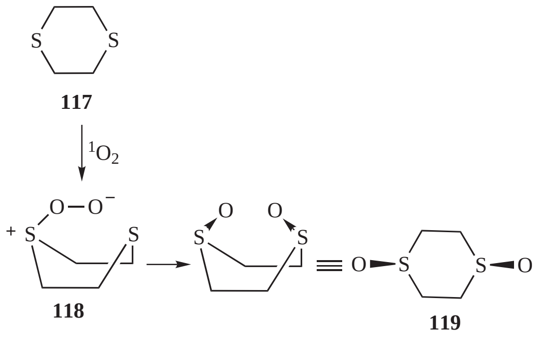
**Scheme 35.**



**Scheme 36.**

**116** which reacts with singlet oxygen by [2+2] cycloaddition leading to dioxetane cleavage products (Scheme **36**) [70].

A highly stereoselecive oxidation is observed in the reaction of 1,4-dithiane **117** which leads exclusively to *cis*-disulfoxide **119** when its concentration is $10^{-3}$ M or lower (Scheme **37**) [9d]. This is consistent with an intramolecular transfer of an oxygen atom in a persulfoxide intermediate at low concentration.

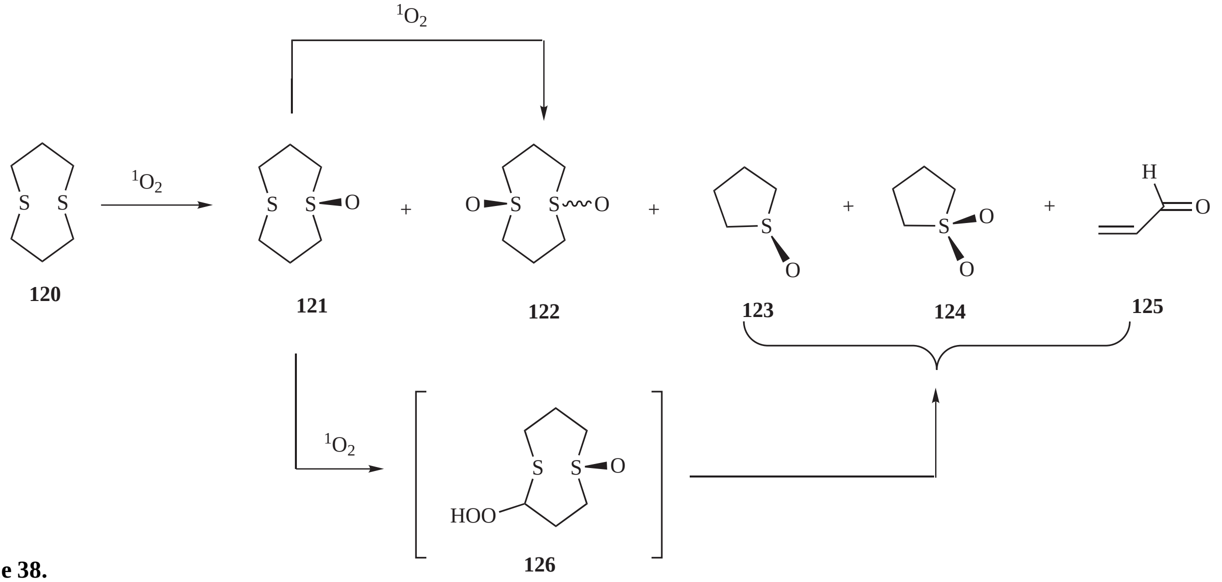


**Scheme 37.**

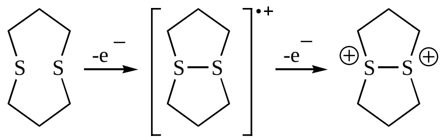
The sensitized photooxygenation of 1,5-dithiacyclooctane **120** is complex depending on the solvent and concentration [52, 58, 71]. Indeed it leads at high concentration to sulfoxide **121** as the primary product that further reacts to give a 86/14 mixture of the *cis* and *trans*-bissulfoxides **122** (Scheme **38**) [71]. At longer reaction times and lower concentrations of **120** the sulfoxide **121** also continues to react to produce cleavage products **123-125** presumably *via* an α hydroperoxysulphide intermediate **126** [71]. The mixture of products is formed and derives from two competing reactions, S-oxidation and C-S bond cleavage.

Recent kinetic studies by Clennan's group have shown that compound **120**, in comparison to either 1,4-dithiane or thiacyclohexane, exhibits an enhanced ability to chemically react than physically quench singlet oxygen [52,58b]. A conformationally induced electrostatic stabilization (CIES) has been suggested as yet another mechanism to increase the efficiency of these reactions. In particular, a transannular interaction occurs leading to formation of a S-S bond in both the radical cation and dication (Scheme **39**). The electronic interaction that lowers the energy of the transition state for its formation also increases the stability of the persulfoxide and suppresses physical quenching. Successively the conformationally induced electrostatic stabilization (CIES) sulphide photooxygenation mechanism has been computationally examined and extended to oxygen and NH groups. Investigation has confirmed the role of remote functional groups in stabilizing the related persulfoxide [58a].

A good chemoselectivity is observed in the singlet oxygenation of dithiocin **127** which leads essentially to sulfoxide



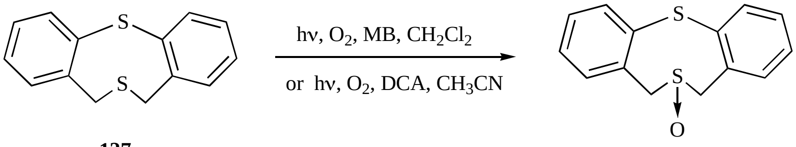
**Scheme 38.**



**120**

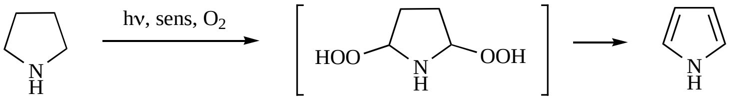
**Scheme 39.**

**128**, as expected due to the presence of activated α-hydrogens (Scheme **40**) [72]. The same result has been obtained in the DCA-sensitized oxygenation involving the reaction between the cation radical and superoxide anion [72].



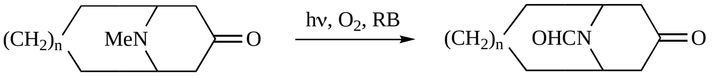
**127** **128**

**Scheme 40.**



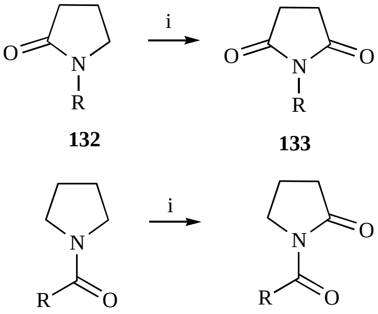
**129** **130**

**Scheme 41.**



**131**
**a**; n= 1
**b**; n= 0

**Scheme 42.**



**132** **133**

**134**

i; hν, Ph$_2$C=O, O$_2$, *t*-BuOH or C$_6$H$_6$

**Scheme 43.**

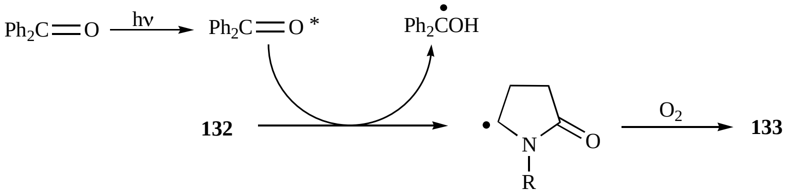
The reaction of nitrogen containing compounds with singlet oxygen often involves an electron transfer from the substrate to singlet oxygen with formation of substrate radical cation and superoxide anion. Physical quenching by a reverse ET is a significant reaction in the dye-sensitized photooxygenation of these compounds with the quenching efficiency decreasing in the order tertiary amines> secondary amines > primary amines, so tertiary amines are employed as typical singlet oxygen quenchers [2, 4c, 4d, 12, 73]. Chemical reactions occur, often *via* either by Type I or III mechanisms, and furnish carbonyl compounds and amines, resulting from *N*-dealkylation [74] or β-oxidation products [75] or dehydrogenation products [75, 76]. Starting from five-membered systems oxygenation can lead to the related aromatic compounds as does compound **129** which converts to pyrrole **130**, presumably *via* the intermediate hydroperoxide (Scheme **41**) [76b].

*N*-formyl derivatives resulting from α-oxidation have been found, e.g in the photooxygenation of some bicyclic amines as pseudopelletierine **131a** and tropinone **131b** or analogues (Scheme **42**) [74].

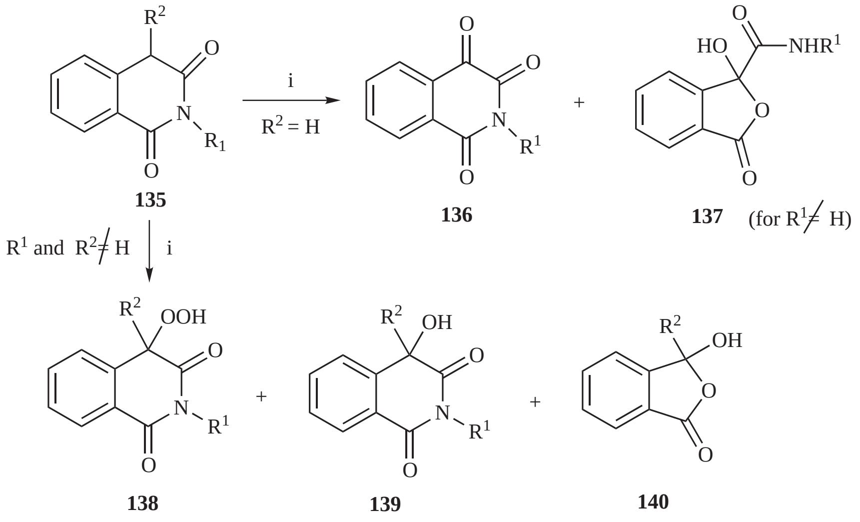
Oxygenation using 150 W medium-pressure Hg lamp (Pyrex filter), oxygen-saturated solution in *t*-BuOH, benzophenone as sensitizer allows lactams **132** to be transformed to the imides **133** (Scheme **43**) [77]. Similar trend has been observed also starting from amides **134** (Scheme **43**) [77a].

Oxidation is suggested to be initiated by abstraction of the hydrogen α to the amide nitrogen by the triplet benzophenone (Scheme **44**). Lactams which are substituted α to the nitrogen atom give α-hydroperoxy or hydroxyamides [77b].

Activation of a double bond by heteroatom is the key feature of the easy dye-sensitized photooxygenation of certain

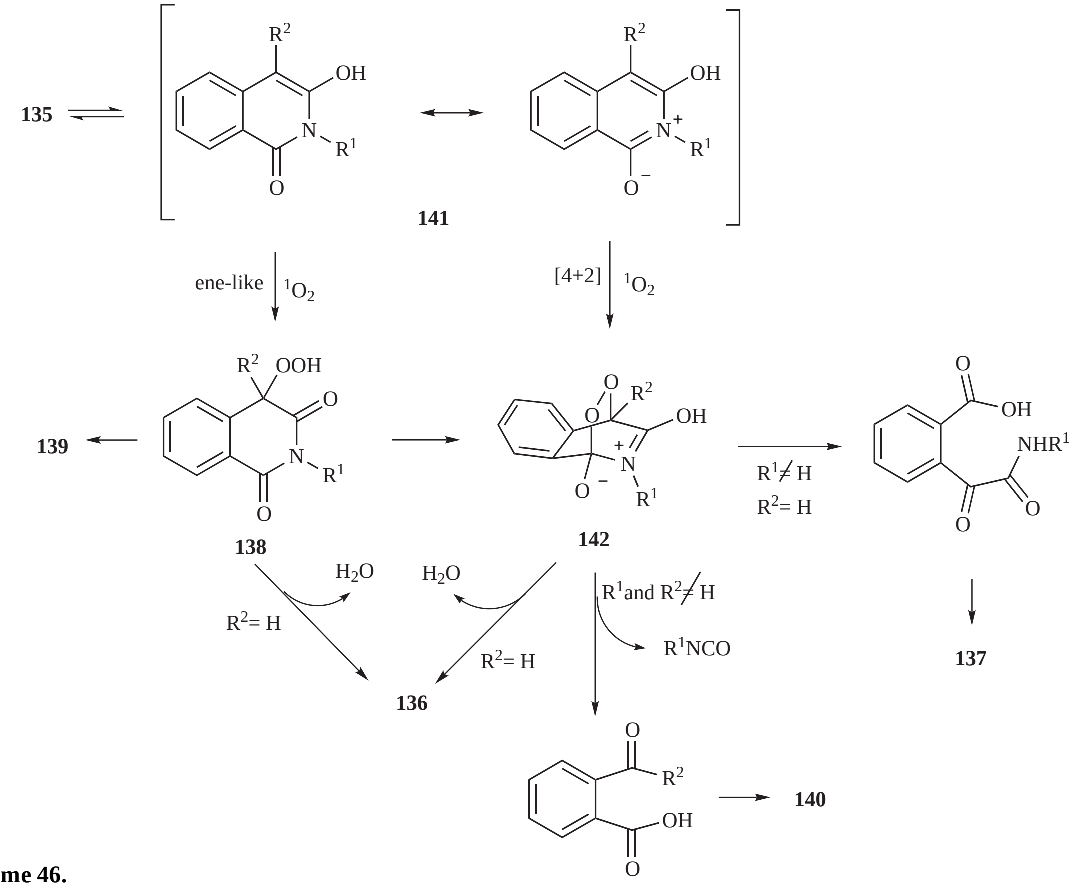


**Scheme 44.**



i; hν, $O_2$, RB /MeOH or TPP/benzene-pyridine

**Scheme 45.**

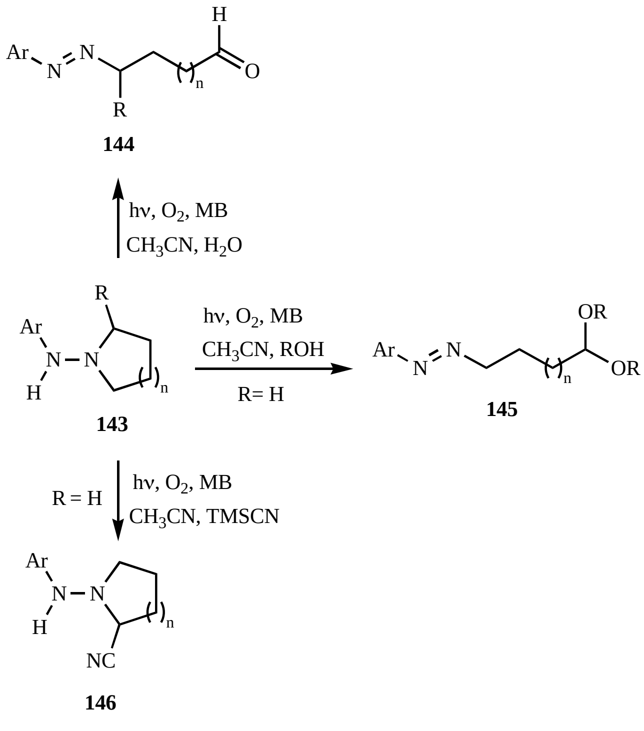


**Scheme 46.**

lactams *via* their enol forms and can be correlated to the oxygenation of enols. Indeed, it is known that singlet oxygen may react with enolic forms, e.g. of 1,3-diketones, and the reaction is favoured under suitable conditions (when the equilibrium is shifted toward the enol side or the electron density at the enolic C=C is increased) [78]. The oxygenation of 1,3-isoquinolinediones **135** represents an interesting example [79]. Indeed, while under typical singlet oxygen reaction conditions with TPP as sensitizer in benzene solution they are unreactive even on prolonged irradiation, photooxygenation occurs in methanol using RB as sensitizer or under basic conditions (benzene-pyridine) using TPP as sensitizer. Under these conditions the oxygenation leads to 1,3,4-isoquinolinetriones **136** and 3-hydroxybenzoisofuran-1-one-3-carbamides **137** for $R^2$=H [79a] and compounds **138**-**140** (for 4-alkylated derivatives) [79b] (Scheme **45**).

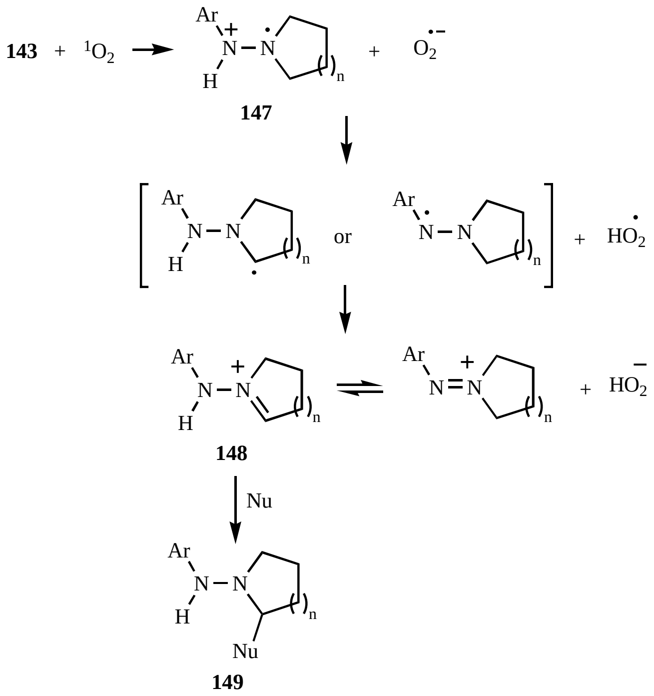
The authors explain the results *via* the intermediacy of hydroperoxides **138**, formed by singlet oxygen addition to the electron rich enol bond, and the intermediacy of the endoperoxides **142**, derived from **138** or directly by addition of singlet oxygen to the diene system of **141** (Scheme **46**) [79]. The role of pyridine or Rose Bengal, the latter *via* its anionic structure, is to act as hydrogen bond acceptors and, hence, to shift the keto-enol tautomerism equilibrium toward the enol side.

Interesting examples of photooxidation of nitrogen-containing compounds which does not lead to addition of oxygen but involves oxygen, have been recently reported for *N*-aminopiperidine and pyrrolidine derivatives [80, 81]. Indeed, the reaction of compounds **143** in the presence of MB and oxygen leads to acyclic aminoaldehydes **144** or aminodialkylacetals **145** using $CH_3CN/H_2O$ or $CH_3CN/ROH$ (9:1), respectively, as solvent [80]. Ring-opening of unsymmetrical derivatives occurs selectively at the bond between the nitrogen atom and the less substituted carbon. The reaction to compounds **144** proceeds smoothly with good to excellent yields (46-98%) and the resulting acyclic compounds conserve the high diastereomerical purity of the starting substrates (Scheme **47**). Oxidation of compounds **143** in the presence of trimethyl silyl cyanide (TMSCN) leads regio- and stereoselectively to $\alpha$-hydrazinonitriles **146** with good yields [81]. The $\alpha$-hydrazinonitrile obtained corresponds to the attack of the more substituted $\alpha$-C-H bond and in 4-methylpiperidine the substituent adopts *trans*-relationship with the CN group in the axial plane and the methyl group in the equatorial position.



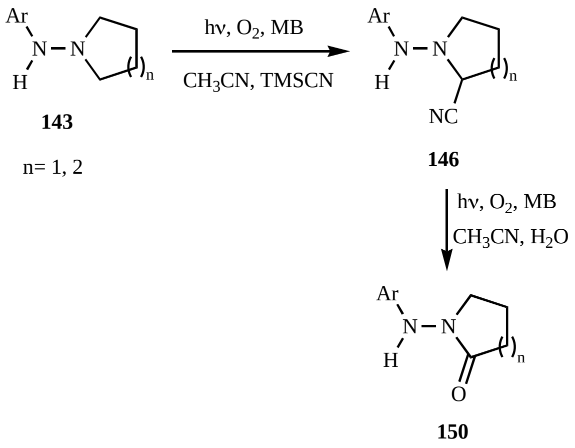
**Scheme 47.**

The key step is the formation of a hydrazinium alkylidene cation **148** which undergoes addition of a nucleophile giving **149** [81]. When $H_2O$ or ROH are used, ring-opening of the intermediate **149** leads to the final aldehyde **144** or acetal **145**, respectively. The radical cation **147** would be formed by electron transfer from the substrate to singlet oxygen (SET). The combination between hydrazinium alkylidene radical cation **147** and the superoxide anion $O_2^{\cdot -}$ could lead to oxidation products as reported in Scheme **48**.



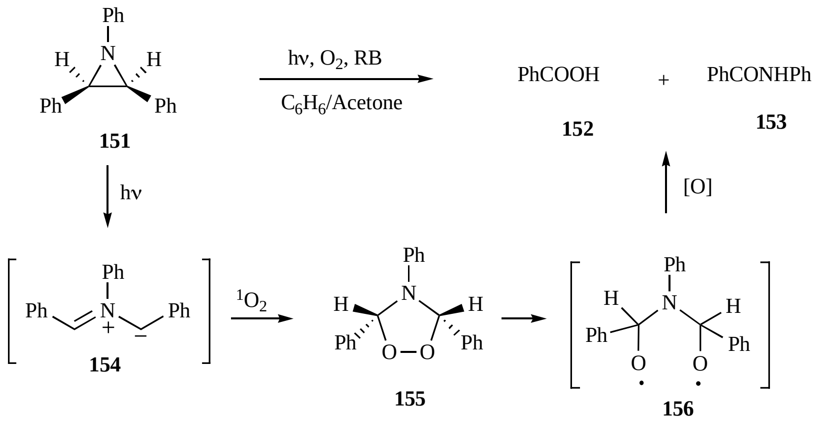
**Scheme 48.**

A useful application of the photooxidation by single electron transfer (SET) of *N*-arylaminopiperidines and *N*-arylaminopyrrolidines **143** is the "one-pot" synthesis of the corresponding lactams **150** (Scheme **49**) [82]. Indeed, irradiation by visible light in the presence of catalytic amount of methylene blue ($MB_{cat}$) and TMSCN gives cyanoproducts **146,** which are photooxidated in the presence of water to lactams **150**.



**Scheme 49.**

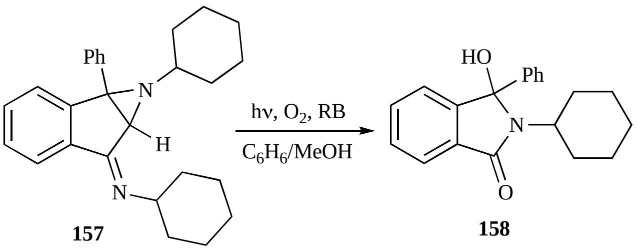
Rose Bengal-sensitized photooxygenation of strained cyclic amines as aziridines occurs but it leads to a variety of products depending on the nature of the substituents present in the ring [83]. It has been suggested that an azomethine ylide as **154** (Scheme **50**) is formed under photochemical conditions, and then it adds singlet oxygen to give the cyclic peroxide whose decomposition leads to the observed products. So, 1,2,3-triphenylaziridine **151** on photooxygenation gives benzoic acid **152** and benzanilide **153** by fragmenta-



**Scheme 50.**

tion of the 1,2,4-dioxazolidine intermediate **155** into the diradical intermediate **156** and subsequent oxidations [83a].

Starting from the bicyclic derivative **157**, 2-cyclohexyl-3-hydroxy-3-phenylphthalimidine **158** has been obtained in 51% yield through decomposition of the intermediate peroxide followed by hydrolysis and cyclization (Scheme **51**) [83b].

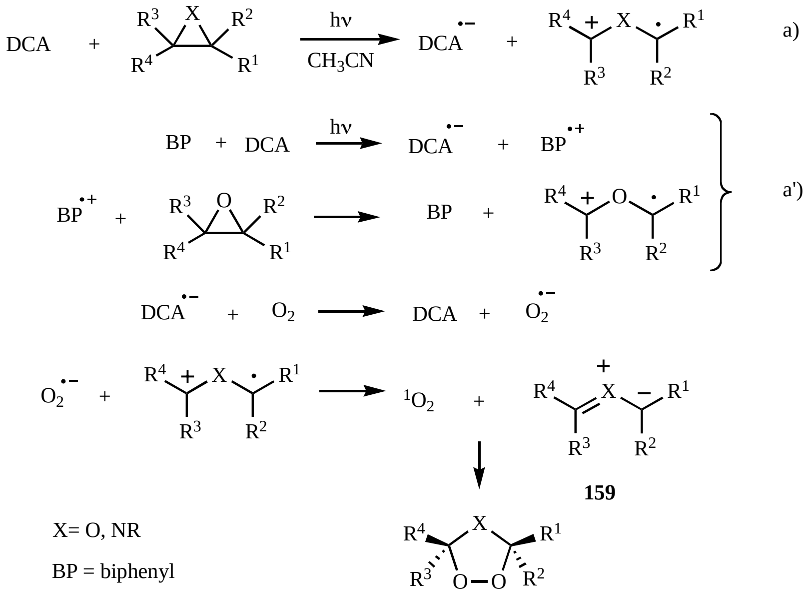


**Scheme 51.**

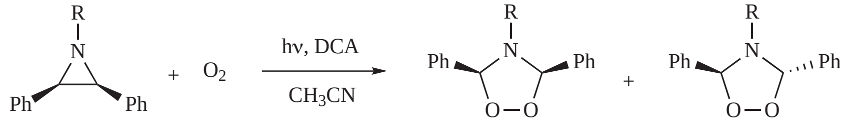
More controlled is the oxygenation of aziridines in the presence of cyano-substituted aromatic hydrocarbons such as 9,10-dicyanoanthracene (DCA) [84]. Under these typical electron-transfer conditions oxiranes, which are unreactive toward singlet oxygen, can be photooxygenated to form ozonides [85], and the efficiency of the reaction can be improved by using biphenyl (BP) [a'), Scheme **52**] [86]. The key step in these reactions involves electron transfer fluorescence quenching of the sensitizer by the substrate with formation of azomethine (X=N) or carbonyl ylides (X=O) **159** as intermediates (Scheme **52**). DCA-sensitized photooxygenations are, therefore, limited to easily oxidized substrates with oxidation potential of less than 2V vs. SCE in MeCN [87]. The efficiency of the reaction of less reactive oxiranes can be effected by using biphenyl (BP) which acts as a non-light-absorbing cosensitizer in conjuction with DCA; its action is explained considering that it is more easily oxidized than the substrate and therefore quenches singlet excited DCA more efficiently [86a].

Scheme **53** reports the results of oxygenation of compounds **160a-d**. 1,2,4-Dioxazolidines **161** are obtained in 39-83% yields [84a]. The *cis/trans* ratio of the peroxides appears to depend on the bulkiness of the substituent on the nitrogen atom which sterically destabilizes the azomethine ilide intermediate (**159** with $R^1$=$R^4$=Ph, X=N in Scheme **52**).

Investigation of the stereochemistry in the oxygenation of *cis*- and *trans*-**162** has shown that both isomers are converted to *cis*-ozonide **163** in 65% yield (Scheme **54**) [86a].



**Scheme 52.**

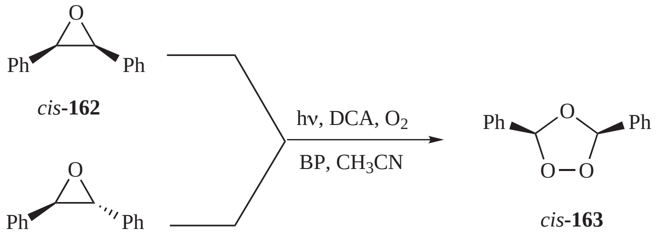


**160**

**161**

| | | |
|---|---|---|
| a; R= H | > 99 | < 1 |
| b; R= Me | 85 | 15 |
| c; R= $CH_2Ph$ | 40 | 60 |
| d; R= *t*-Bu | < 1 | > 99 |

**Scheme 53.**



*cis*-**162**

*trans*-**162**

*cis*-**163**

BP=biphenyl

**Scheme 54.**

The stereoselective formation of *cis*-**163** from both isomers has been explained assuming that equilibration occurs to afford the most stable *E*,*E*-conformer of carbonyl ylide **159** (X=O, Scheme **52**) which undergoes a concerted 1,3-addition of singlet oxygen generated by a second electron transfer [86a]. It is interesting to note that high stereoselectivity has been observed successively in other electron transfer reaction of oxiranes in the presence of TCNE although in this case neither an oxygen radical anion nor singlet oxygen is generated [88].

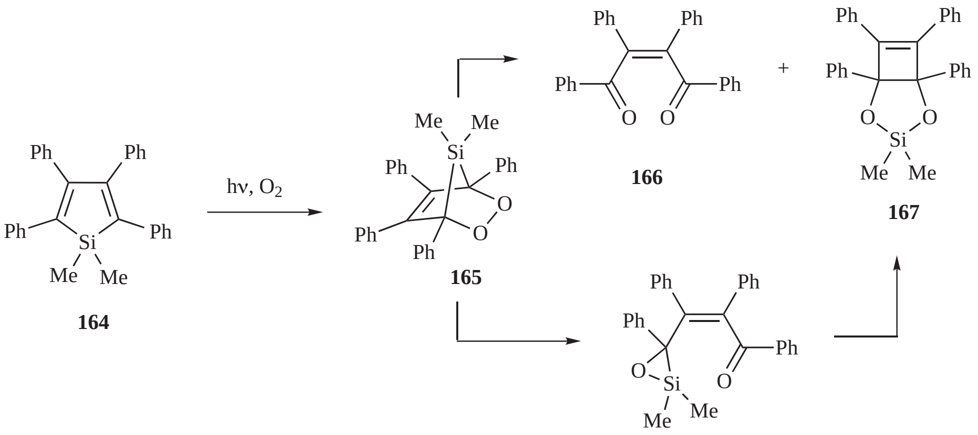
## 4. PHOTOOXYGENATION OF SILICON, GERMANIUM AND TELLURIUM-CONTAINING COMPOUNDS

Much attention has been drawn to the reaction of organosilicon compounds with molecular oxygen in the recent years due to the role of this species in the oxidation and degradation of polysilanes, which have potential technological usefulness [89]. Light-induced oxidations have also been studied mainly to gain mechanistic information. Less investigated has been the photochemistry of germanium-containing molecules or analogues [90]. A peculiarity of compounds that contain group 14 to group 14 or group 14 to carbon bonds is that they can act as excellent electron donors. These bonds indeed are subject to cleavage by various electrophiles, and due to their low ionization potential these compounds undergo efficient electron transfer reactions [90]. This trend is generally observed in the photooxygenation reactions, too.

The classical [4+2] addition of oxygen to the diene system appears to be involved in photooxygenation of silacyclopentadiene **164** which leads to dicarbonyl compound **166** presumably *via* the related endoperoxide **165** with extrusion of the metal (Scheme **55**) [91]. A peculiar bicyclic product **167** has also been obtained and has been suggested to form *via* **168** (Scheme **55**) [91a].

The presence of a Si-Si σ bond entails bond cleavage and oxygen addition, even in unsaturated molecules. Rearrangement or decomposition induced by silicon may lead to characteristic final products. So, dioxygen insertion has been observed in the photooxygenation of 1,2-disiletene **169** in acetonitrile/methylene chloride in the presence of DCA [92]. The reaction affords the corresponding 1,2,3,6-dioxadisilin **170** in moderate yield together with 1,2,5-oxadisilolene **171** (Scheme **56**).

Similar results are obtained in the presence of methylene blue (MB) or 2,4,6-triphenylpyrilium perchlorate while



**164**

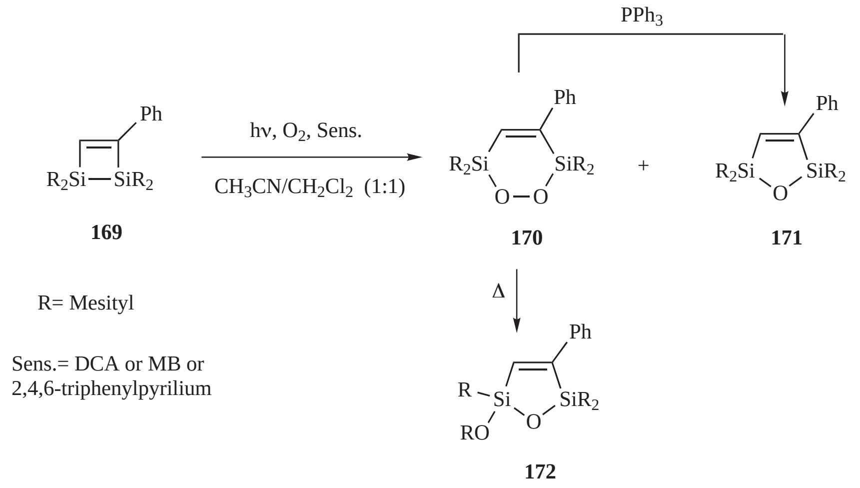
**165**

**166**

**167**

**168**

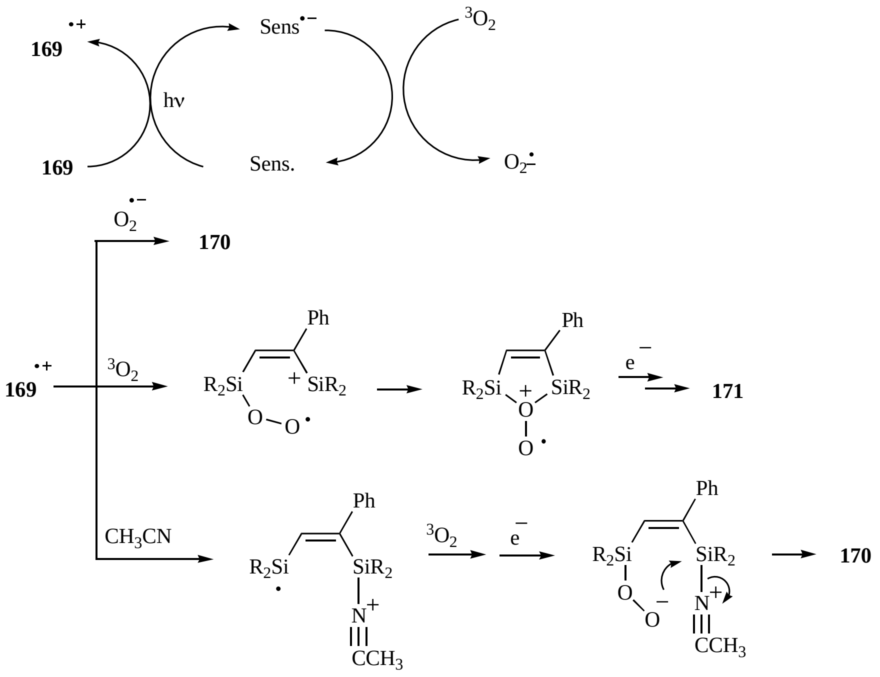
**Scheme 55.**



R= Mesityl

Sens.= DCA or MB or
2,4,6-triphenylpyrilium

**Scheme 56.**

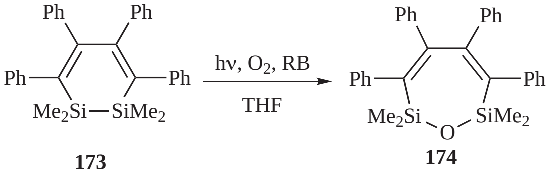


**Scheme 57.**

compound **169** appears stable under singlet oxygen oxygenation accounted conditions, i.e in the presence of a typical singlet oxygen sensitizer as TPP [92]. The reaction is therefore suggested to involve a photo-induced electron transfer from disilitene **169** to the excited singlet state of the sensitizer and attack of superoxide anion (or ground oxygen) to the silyl radical cation $\mathbf{169}^{+\cdot}$ as reported in Scheme **57** [92].

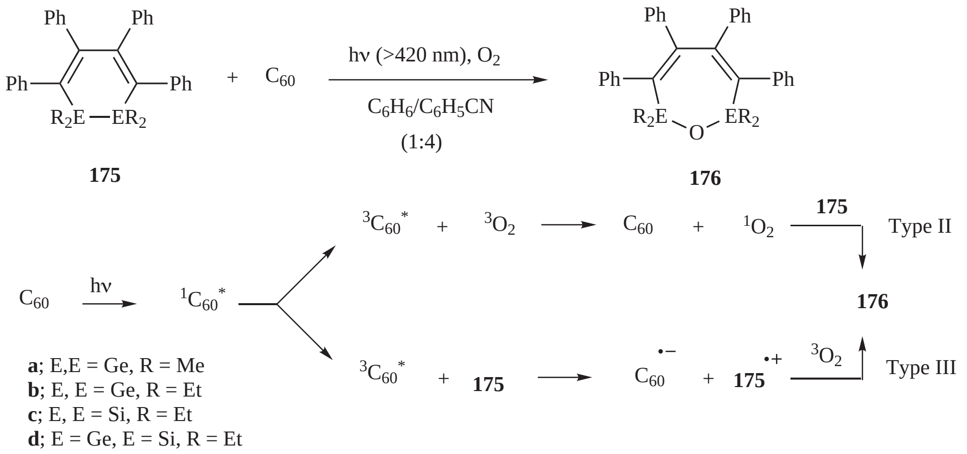
An increasing ratio of **170** to **171** is observed on increasing acetonitrile in the solvent composition, and this has been interpreted assuming that acetonitrile acts as the nucleophile to stabilize the cation radical $\mathbf{169}^{+\cdot}$ and assists the ring closure to **170** (Scheme **57**). Peroxide **170** reacts easily with triphenylphosphine ($PPh_3$) to give **171** while it decomposes gradually at room temperature to afford siloxane **172** *via* Criegee type rearrangement (Scheme **56**). A very similar behaviour has been observed in electron-transfer oxygenation of 1,2-digermetenes confirming the involvement of cation radical-initiated cycloaddition [93].

Oxygen insertion prevails also in the RB-sensitized photooxygenation of **173** despite the presence of a π-conjugated system usually highly reactive under these irradiation conditions (Scheme **58**) [94]. Only a cyclic disiloxane **174** has in fact been obtained.



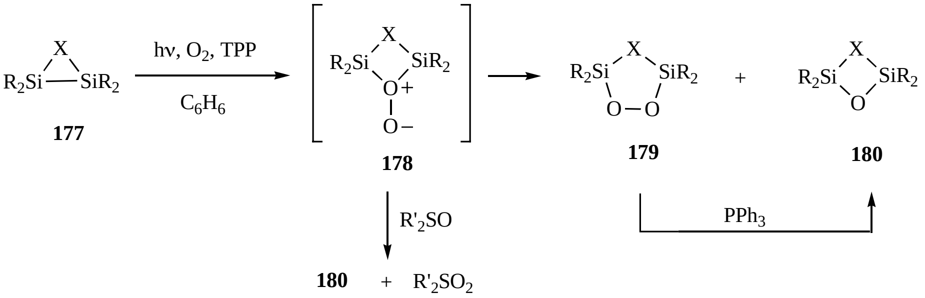
**Scheme 58.**

Similar trend has been observed in the irradiations of benzene-benzonitrile solutions of compounds **175** which in the presence of C60 lead to compounds **176** (Scheme **59**) [95]. Processes of both Type II and III have been proposed



**a**; E,E = Ge, R = Me
**b**; E, E = Ge, R = Et
**c**; E, E = Si, R = Et
**d**; E = Ge, E = Si, R = Et

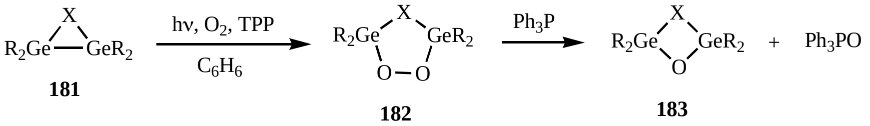
**Scheme 59.**



**a**;[96a] X = O, R= 2,6-diisopropylphenyl; 2,6-diethyl- or dimethylphenyl; mesityl

**b**;[96b] X = $CH_2$, R= mesityl

**Scheme 60.**



**a**; X= $CH_2$, R= 2,6- diethylphenyl
**b**; X= N-Ph, R= mesityl

**Scheme 61.**

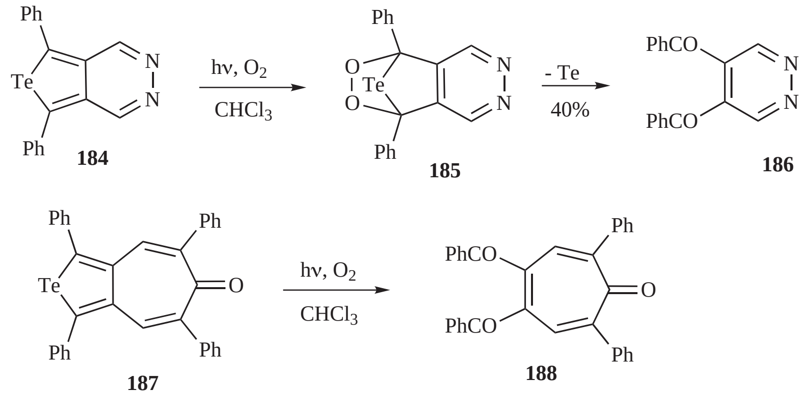
(Scheme **59**). In the first case, singlet oxygen is generated by an energy transfer reaction between the photoexcited $^3C_{60}$* and triplet oxygen, while in the second pathway the radical cation $\mathbf{175}^{+\cdot}$ reacts with triplet oxygen. Assumption has been confirmed by suitable experiments using a typical $^1O_2$ sensitizer as Rose Bengal, and an electron-transfer sensitizer as DCA [95].

Strained disiliranes as **177** give the corresponding 1,2-peroxides **179** by TPP-sensitized oxygenation [96]. It has been suggested that $^1O_2$ may approach perpendicularly to the Si-Si bond to afford peroxonium ion **178**. The nucleophilic oxygen-atom transfer capability of **178** has been evidenced towards sulfoxides (Scheme **60**). Compounds **180**, which are sometime found in little amounts, can be obtained by triphenylphosphine ($PPh_3$) treatment of **179**.

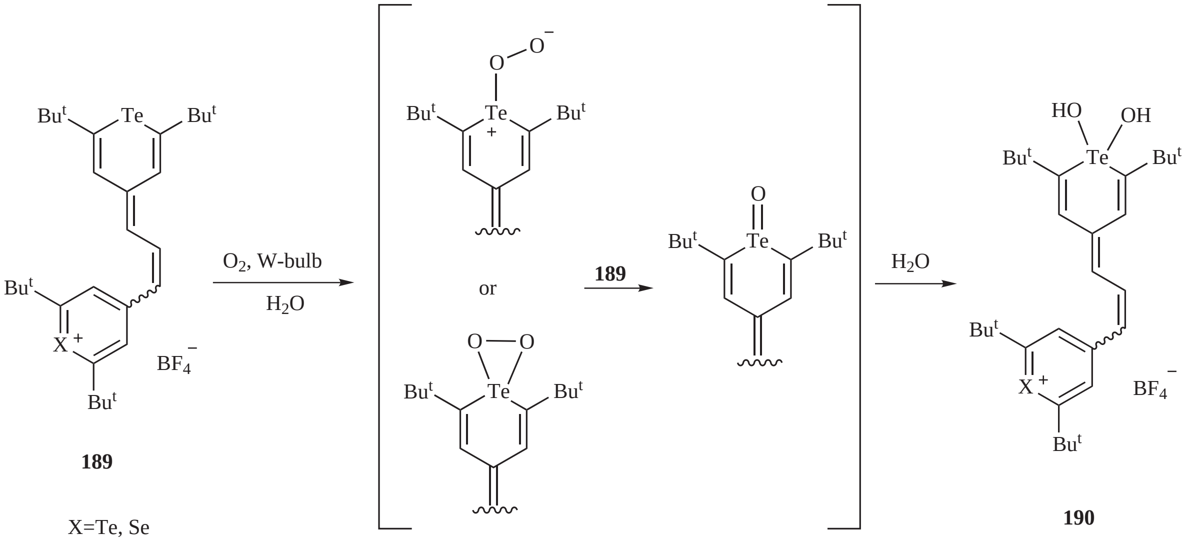
Singlet oxygenation of digermirane **181a** and azadigermiridine **181b** proceeds similarly and affords 1,2-peroxides **182a** and **182b** in good yields (Scheme **61**) [97]. The latter compounds are remarkably stable if compared with analogous silicon compounds (**182a** has been structurally characterized by X-ray analysis) according with a trend well documented. Both peroxides **182a**,**b** are quantitatively reduced to compounds **183** with triphenylphosphine ($PPh_3$) [97].

Heavier organochalcogen compounds as seleno- or tellurium-compounds have been little investigated if compared with sulphur-containing molecules. Oxidations with metal elimination have sometime been observed in the photooxidation of diverse acyclic and cyclic compounds [98]. In particular, tellurophenopyridazine **184** decomposes under the influence of light and oxygen into 4,5-dibenzoylpyridazine **186** presumably *via* the peroxide **185,** derived from Diels-Alder reaction of singlet oxygen with **184**, with extrusion of the metal (Scheme **62**) [99]. Analogously, 4,5-dibenzoyl-2,7-diphenyltropone **188** is formed in 43% yield by visible light photooxidative detelluration of compound **187** (Scheme **62**) [99].

Oxidation at the atom site has been observed in tellurapyrylium dyes such as **189** (Scheme **63**) [100]. These com-



**Scheme 62.**



**Scheme 63.**

pounds are able to produce singlet oxygen and react with it. The authors suggest intermediates similar to persulfoxide **72** or thiadioxirane **73** intermediates (Scheme **20**) to explain the oxidation. Dihydroxides **190** are hydrated forms of telluroxides.

It is interesting to note that the presence of tellurium in these dyes enhances significantly the quantum efficiency for the generation of and the rate of reaction with singlet oxygen [100].

## 5. CONCLUSION

It should be evident from the above survey and preceding review that the field of photooxygenation of heterocycles is a very active area of research and offers a lot of interesting applications. In addition to the initial synthetic interest, due to the widespread use and presence of heterocycles, the response of these systems to photooxygenation is of high importance in various fields of science (from environmental chemistry to biochemistry, from engineering to medicine). The use of photodynamic therapy (PDT) in diseases as psoriasi or some sorts of cancers is of current application [101]. On the other hand the importance of the photosensitization processes induced by drugs, usually heterocyclic compounds is easily understood taking into account the increasing number of reports dealing with this question [5a]. Moreover, light and oxygen play a significant role in the fate of organic molecules in the environment and their action can be influenced by highly conjugated molecules as dyes or polycyclic aromatic hydrocarbons (PAH), which either can accelerate the phototransformations or promote the formation of singlet oxygen [102].

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