

# Cyclic and Acyclic Azaperoxides

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## ABSTRACT

The review integrates and systematically describes the data on the synthesis of three-, four-, five-, six-, and eight-membered cyclic and acyclic amino-peroxides.

**Keywords:** Aza-Peroxide Compounds; Dioxaziridines; Dioxazetidines; Dioxazetes; Dioxadiazetidines; 1,2,4-Dioxazolidine; Dioxatetrahydropyridazines; Endoperoxides; Ozonolysis; Tetraoxazaspiroalkanes; Tetraoxazaspiroalkanes; Acyclic Aminodiperoxides; Catalysis

## Introduction

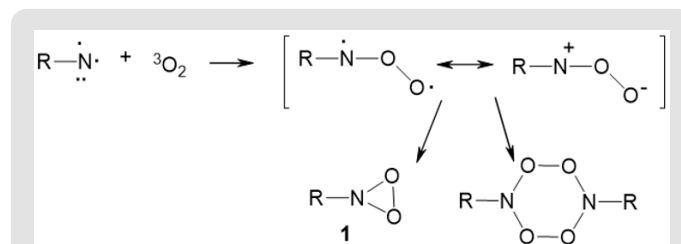
The enhanced interest in organic peroxide compounds is caused by their broad scope of applications, first of all, in chemical and pharmaceutical industry and in laboratory practice. A real breakthrough in the synthesis of peroxide compounds was made after the discovery of the antimalarial activity of peroxides, which is utilized in highly efficient medicinal drugs (artemisinin, artesunate, artemether, dihydroartemisinin). The advances in the peroxide chemistry and pharmacology stimulated the research related to the synthesis of heteroatom-containing peroxides. Out of heteroatom-containing peroxides, attention of researchers is focused on amino-peroxides. This enhanced interest in aza-peroxides is attributable to the fact that many natural compounds (verruculogen, dioxetanone) and antimalarial agents (RKA182 and OZ439) contain aza-peroxy moieties in the molecules. The extensive biological activity of nitrogen-containing peroxides promoted active research on the development of synthetic routes to new classes of acyclic and cyclic amino-peroxides.

It is noteworthy that a compound containing both a nitrogen atom and a peroxide group in the molecule was first mentioned in the world literature back 1900 [1]. Despite more than a 100-year history, amino-peroxides remain poorly studied because of complicated synthesis and small number of available preparation methods. In view of the high practical significance of fundamental and applied research dealing with the synthesis and use of amino-

peroxides and extensive interest of researchers in this promising and intriguing field of chemistry, in the present review, we attempted to give a critical account of the achievements of both foreign and Russian researchers engaged in the synthesis and studies of the properties of three-, four-, five-, six-, and eight-membered cyclic and acyclic amino-peroxides with the goal of integrating published results.

## Three-Membered Aza-Peroxides

The simplest cyclic peroxide derivatives are composed of a 3-membered ring consisting of one nitrogen and two oxygen atoms. These dioxaziridine rings can be formed both from nitro compounds [RN(O)O] and from nitroso O-oxides (RN(O)O) (Scheme 1). Dioxaziridines 1 (aza-dioxiranes) have not been isolated in a pure state, but have been identified as unstable intermediates in solutions in 2-methyltetrahydrofuran at 77 K [2] or acetonitrile at 298 K [3].



**Scheme 1:** Reaction of nitrene with O<sub>2</sub>.

Dioxaziridines are unstable at room temperature. Most often, they are detected by UV spectroscopy. The key methods used to generate dioxaziridines are photooxidation of aryl azides and

O-substituted diazeniumdiolates according to Scheme 1. The main representatives of dioxaziridines and methods for their generation are summarized in Table 1.

**Table 1:** Generation of dioxaziridines 1 (RNO<sub>2</sub> dioxiranes).

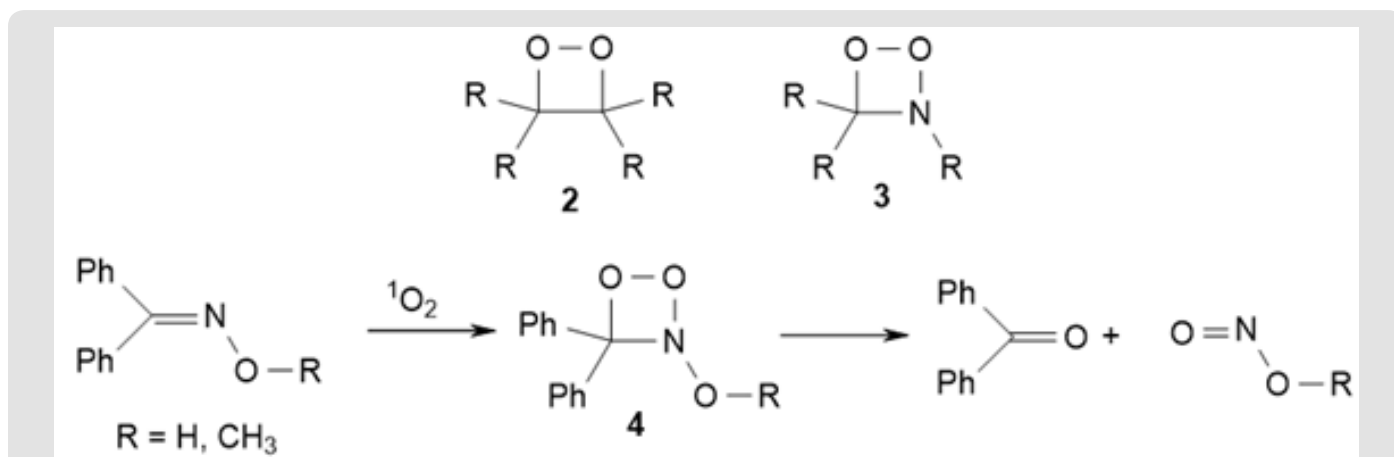
Year	Structure	Evidence for the formation	T (K)	Generation method	Refs
2004		Luminescence data	298	A	[4,5]
2002		Luminescence data	298	C	[6]
2001		Kinetic measurements	298	D	[7]
2001		Luminescence data	293	A	[8]
1996	 Ar = <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> , Ph, <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<sup>18</sup> O <sub>2</sub> marker	298	B	[2]
1991		<sup>18</sup> O <sub>2</sub> marker	298	B	[9]
1987		<sup>18</sup> O <sub>2</sub> marker	298	B	[10]

Note: A, Matrix isolation upon photooxidation of ArN<sub>3</sub>; B, photooxidation of ArN<sub>3</sub> at room temperature in solution; C, substrates adsorbed on natural rubber; D, photooxidation of diazeniumdiolate in solution at room temperature.

#### Four-Membered Aza-Peroxides

Four-membered aza-peroxides are represented by three types of compounds: dioxazetidines, dioxazetes, and dioxadiazetidines. 1,2-Dioxetanes 2 without nitrogen atom in the ring are among the most readily accessible four-membered peroxide heterocycles, which are synthesized by treatment of alkenes with singlet oxygen [11,12]. Adamantyl- and alkoxy-substituted 1,2-dioxetanes are

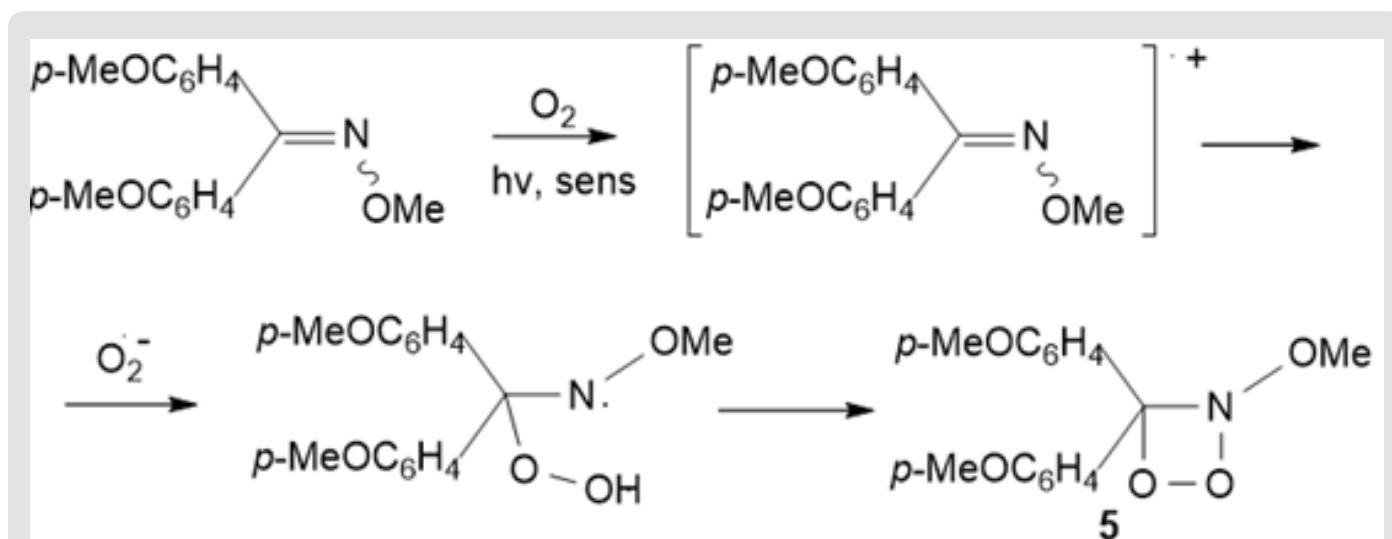
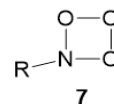
most stable, whereas other derivatives easily decompose to carbonyl compounds [13]. A similar decomposition pathway should be expected for 1,2,3-dioxazetidines 3, which are generated upon the reaction of singlet oxygen with imines [14,15]. This reaction was first studied in relation to treatment of benzophenone oxime with singlet oxygen to give the oximate anion and O-methyl ether 4 (Scheme 2) [16].



**Scheme 2:** Photooxidation of O-methyl ethers.

However, C=N containing compounds are not always able to be converted by this photooxidation mechanism. The photooxidation of acyclic ketoximes, aromatic aldoximes and ketoximes, and  $\alpha$ -oximino ketones yields the corresponding aldehydes resulting from the competing oxidation of the C=C bond [17]. Amidoximes behave in a similar way, but in this case, the anionic species react with oxygen to give nitriles and amides (via intermediate acyclic peroxide derivatives) rather than 1,2,3-dioxazetidines [18]. Another reaction pathway to the intermediate formation of 1,2,3-dioxazetidine

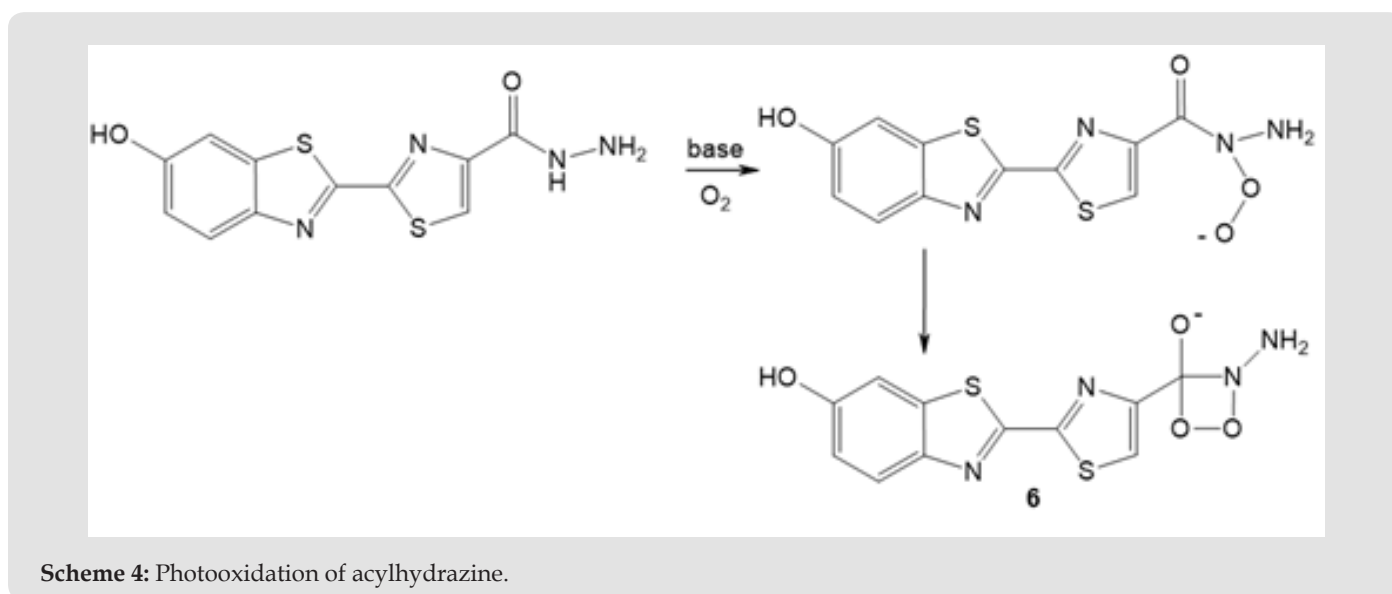
5 involves, instead of singlet oxygen, UV-induced photooxidation of N-methoxy-4-methoxyphenyl-4'-methylphenylmethanimine in the presence of 9,10-dicyanoanthracene as a photosensitizer (Scheme 3) [19,20]. The 1,2,3-dioxazetidine 5 thus formed decomposes to give diaryl ketone and methyl nitrite with photoisomerization of the C=N double bond [19].



**Scheme 3:** UV photooxidation of N-methoxy-4-methoxyphenyl-4'-methylphenylmethanimine with the photosensitizer 9,10-dicyanoanthracene.

1,2,3-Dioxazetidine 6 is formed as an intermediate upon luminescence of acyl hydrazide based on 5-methyldehydrogluciferin in the presence of a strong base (Scheme 4) [21]. Nitroso compounds such as N,N-dimethyl-4-nitrosoaniline possess bleaching properties

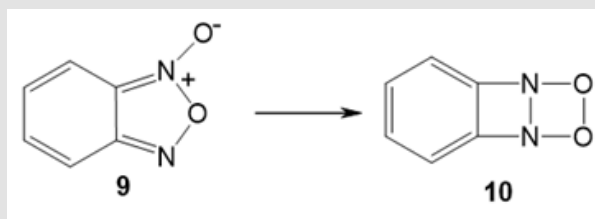
owing to the reaction of singlet oxygen with imidazole or histidine [22], which involves the step of endoperoxide formation [23,24]. The authors assume the intermediate formation of trioxazetidine 7 upon the [2 + 2]-cycloaddition of nitroso groups.



**Scheme 4:** Photooxidation of acylhydrazine.

1,2,3,4-Dioxadiazetidines **8** are dimers of nitroso compounds. They are also products of [2 + 2]-cycloaddition of azo compounds and oxygen. Nevertheless, they have not yet been

characterized. An example of intermediate formation of energetic 1,2,3,4-dioxadiazetidene **10** upon isomerization of benzofurazan 1-oxide (benzofuroxan) **9** has been reported [25] (Scheme 5).

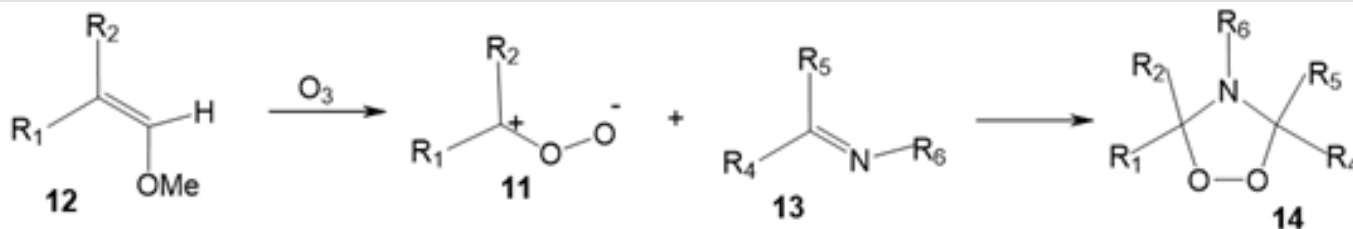


Scheme 5: Isomerization of benzofurazan 1-oxide.

### Five-Membered Aza-Peroxides

**Ozonolytic Methods for the Synthesis of Five-Membered Aza-Peroxides:** The most efficient method for the preparation of cyclic aza-peroxides is the ozone oxidation of the olefinic bond

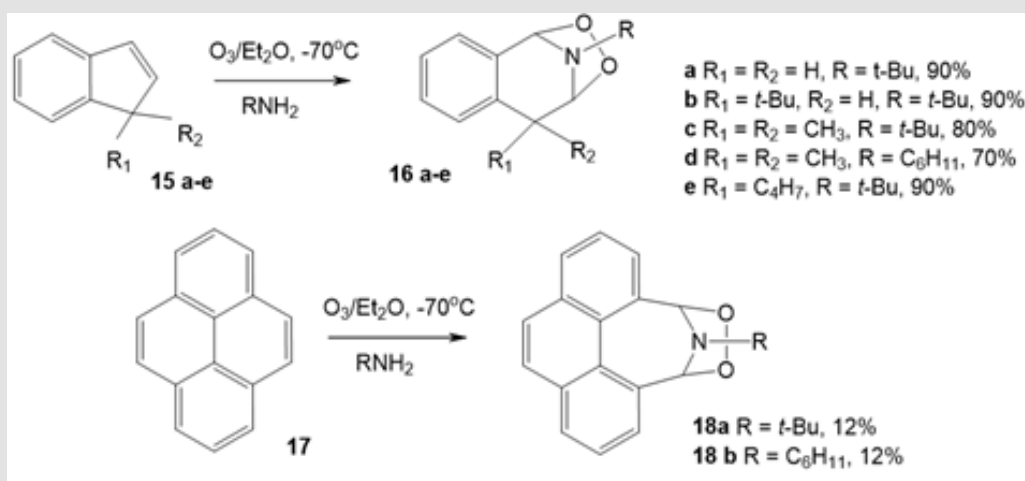
in the presence of nitrogen-containing compounds. For instance, ozone treatment of vinyl ethers **12** in the presence of imines [26] leads to the [3+2]-cycloaddition of carbonyl oxides **11** generated upon ozonation to appropriate imines **13** to give 1,2,4-dioxazolidine five-membered ring **14** (Scheme 6).



Scheme 6: Synthesis of 1,2,4-dioxazolidines by the ozonolysis of vinyl ethers in the presence of imines.

It is noteworthy that the reactivity of intermediate carbonyl oxide **11** in this reaction depends on the steric factors involved in its approach to the imine, which are normally determined by the carbonyl oxide structure. The reaction is stereoselective in most cases: out of the 26 compounds obtained by this method, only seven products were formed as isomer mixtures [26]. The ozone oxidation of indene **15a-e** and pyrene **17** derivatives in the presence of primary amines afforded bicyclic 1,2,4-dioxazolidines [27]. Treatment of a mixture of substituted indenenes **15a-e** and primary

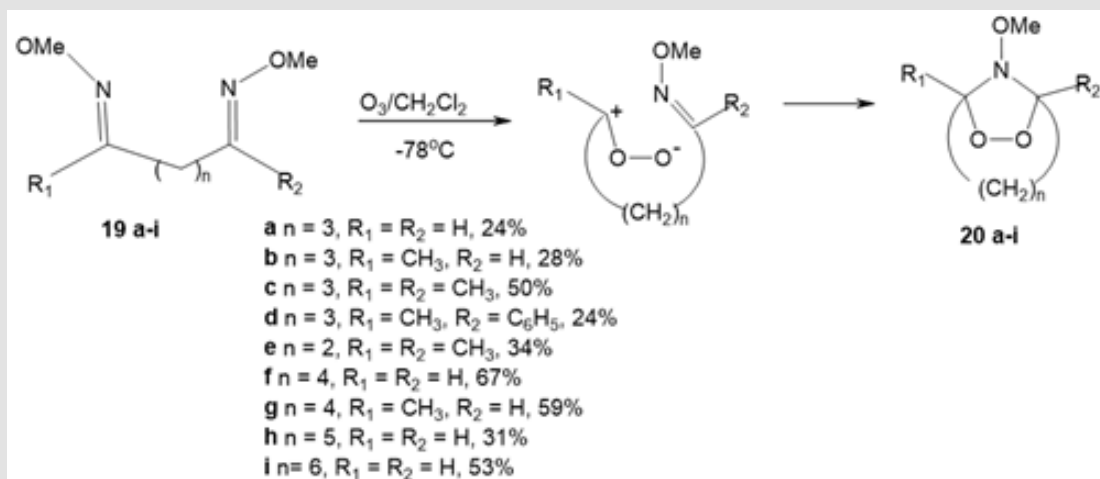
amines with ozone at  $-70^{\circ}\text{C}$  gave 1,2,4-dioxazolidine derivatives **16a-e** in high yields. Ozonolysis of pyrene **17** under similar conditions resulted in the synthesis of cyclic amino-peroxides **18a,b**, but the conversion was low (Scheme 7). Various primary amines such as cyclohexylamine, benzylamine, aniline, and tert-butylamine can serve as the nitrogen cross-components. Unlike primary amines, secondary amines cannot be used in this reaction, as they are readily oxidized themselves.



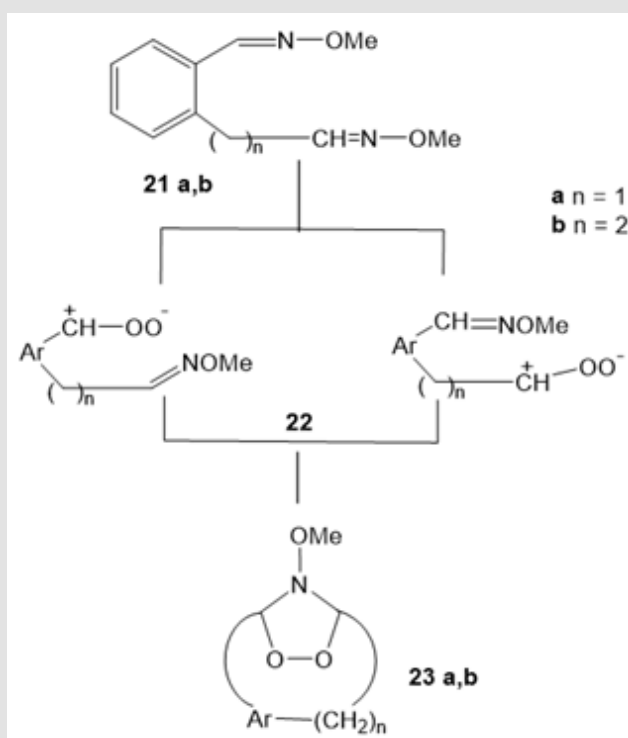
Scheme 7: Synthesis of 1,2,4-dioxazolidines derivatives by the ozonolysis of indenenes in the presence primary amines.

An efficient method for the formation of N-methoxy-substituted 1,2,4-dioxazolidine moiety is ozonolysis of dimethyldioximes of 1,4- and 1,5-diarbonyl compounds [28]. This one-step method is characterized by good conversion and stereoselectivity. While developing studies on ozonolysis of vinyl ethers in the presence of imines, K. Griesbaum and co-workers investigated ozonolysis in the absence of carbonyl oxide acceptors. The reaction of dimethyldioximes 19a-e with ozone in an inert solvent afforded N-me-

thoxy-1,2,4-dioxazolidine derivatives 20a-e (Scheme 8). Relying on these data, Kang-Ryul Lee and co-workers [29] accomplished ozonation of acyclic O-methylated dioximes 19f-i with  $n = 4-6$  and aromatic O-methylated dioximes 21a and 21b (Scheme 9). Ozonolysis of 19f-i in dichloromethane at  $-78^{\circ}\text{C}$  furnished the corresponding bicyclic 1,2,4-dioxazolidines 20f-i in 67, 59, 31, and 53% yields, respectively.



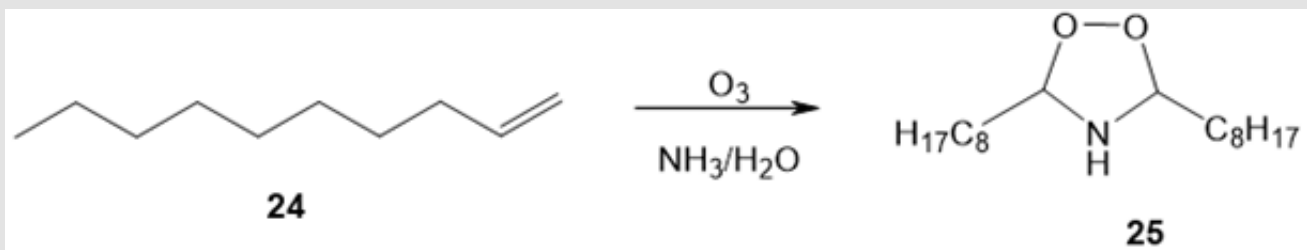
Scheme 8: Ozonolyses of the O-methylated dioximes.



Scheme 9: Synthesis of O-methylated-1,2,4-dioxazolidines by ozonolyses of O-methylated dioximes.

The ozonolysis [29] of aromatic O-methylated dioximes 21a and 21b in dichloromethane at  $-78^{\circ}\text{C}$  gave rise to aromatic 1,2,4-dioxazolidines 23a and 23b via intermediates 22 in 65 and 35% yields. Yet another example of ozonolytic preparation of 1,2,4-dioxazolidines

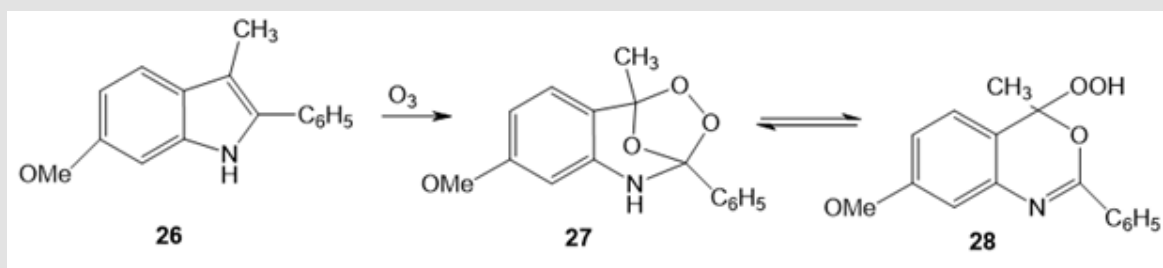
is ozonation of 1-decene 24 in a homogeneous system containing ammonia and water (Scheme 10) [30]. The amino-peroxide 25 thus formed was unstable and decomposed in air.



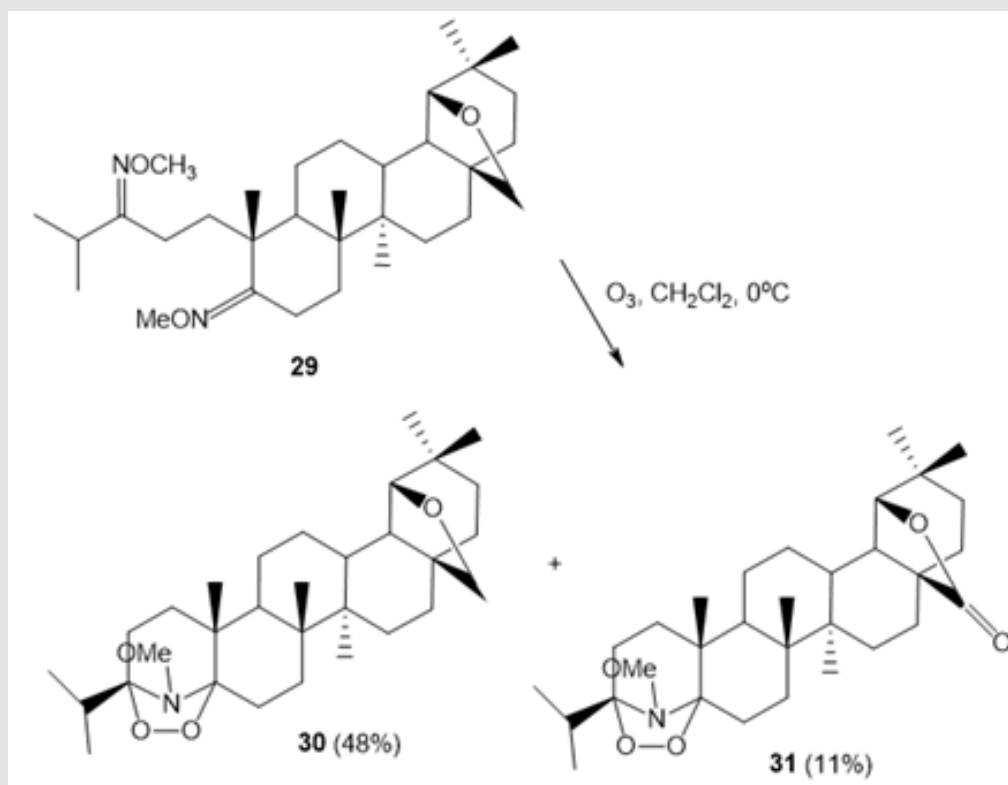
**Scheme 10:** Synthesis of 1,2,4-dioxazolidines.

The ozonation of 3-methyl-6-methoxy-2-phenylindole (2-phenylskatole) 26 leads to 2-phenylbenzoxazine hydroperoxide 27 and hydroperoxide 28 (Scheme 11) [31]. The first synthesis of triterpenoid amino-peroxide with 1,2,4-dioxazolidine moiety by ozonation of 3,5-seco-18 $\alpha$ -oleane 3,5-bismethyl dioxime 29

in  $CH_2Cl_2$  at  $0^\circ C$  has been discussed in the literature [32]. The reaction is stereoselective and gives only one (3*S*,5*S*)-diastereomer of 19 $\beta$ ,28-epoxy-A-neo-3,5-seco-3*S*,5*S*-dioxo-3,5-N-methoxyazo-18 $\alpha$ -oleane 30 (48%). 19 $\beta$ ,28-Epoxy-28-oxo-A-neo-3,5-seco-3*S*,5*S*-dioxo-3,5-N-methoxyazo-18 $\alpha$ -oleane 31 is formed as a side product in 11% yield (Scheme 12).



**Scheme 11:** The ozonation of 3-methyl-6-methoxy-2-phenylindole.

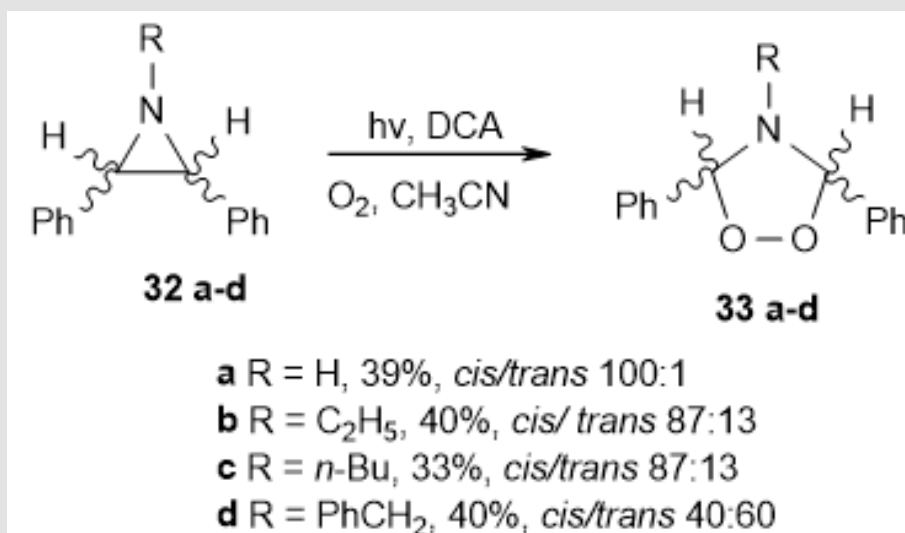


**Scheme 12:** Synthesis of triterpenoid-based 1,2,4-dioxazolidines by ozonolysis of allobetulin derivatives.

## Photochemical Methods for the Synthesis of Five-Membered Aza-Peroxides

1,2,4-Dioxazolidines can be prepared by photochemical oxidation with singlet oxygen. Using this approach, 1,2,4-dioxazolidines 33a-d were synthesized for the first time

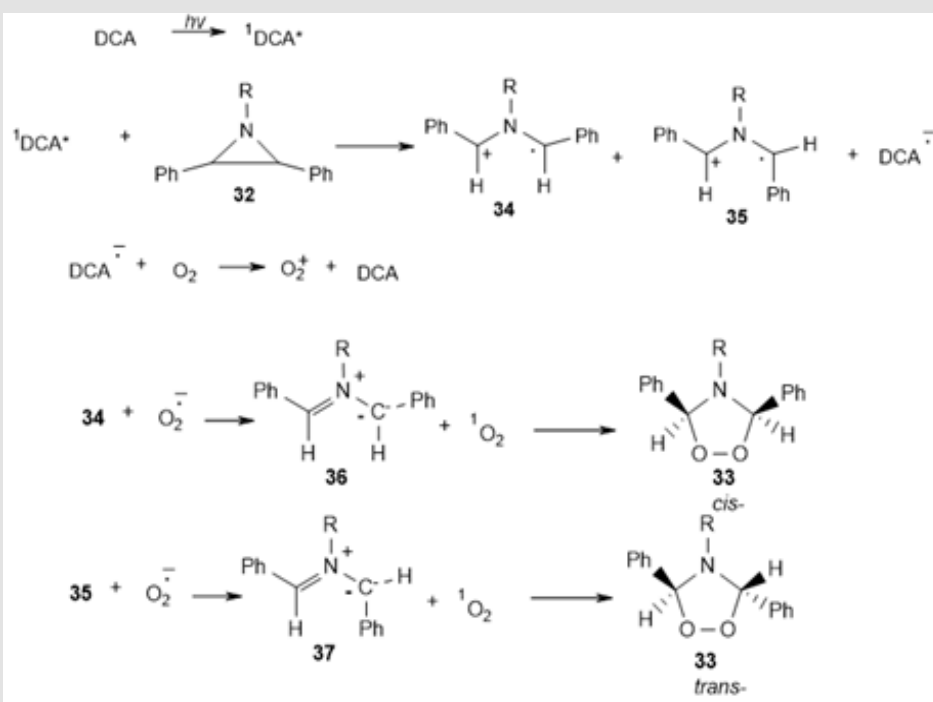
by photooxidation of aziridines 32a-d in dry acetonitrile in the presence of 9,10-dicyanoanthracene (Scheme 13) [33-35]. The reaction is stereoselective if no steric restrictions are present at the nitrogen atom. The stereochemistry of the reaction products does not depend on cis-/trans- positions of substituents at the neighboring carbon atoms in the starting compounds.



**Scheme 13:** Formation 1,2,4-dioxazolidines by electron-transfer photooxygenation of aziridines.

The presumptive scheme of photochemical transformation of aziridines 32 into 1,2,4-dioxazolidines 33 includes aziridine ring opening under the action of singlet 9,10-dicyanoanthracene to give radical cations 34 and 35 in which the *cis*-configuration is the most stable. Then electron transfer takes place, resulting in azomethines 36 and 37, which undergo 1,3-dipolar cycloaddition with singlet

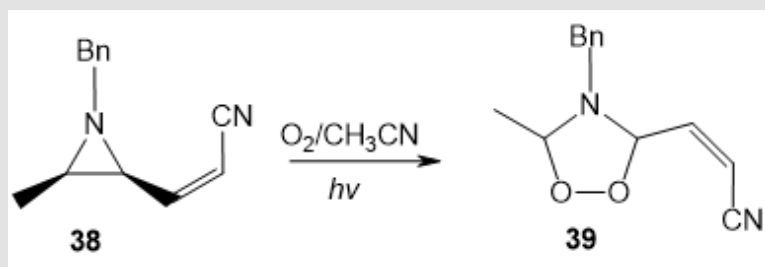
oxygen to give 1,2,4-dioxazolidine compounds 33a-d (Scheme 14). If bulky substituents are present, *cis*-configuration of the intermediate radical cation 34 becomes unfavorable, which results in the formation of a mixture of *cis*- and *trans*- amino-peroxides. Therefore, the reaction is stereoselective only in the former case [33-35].



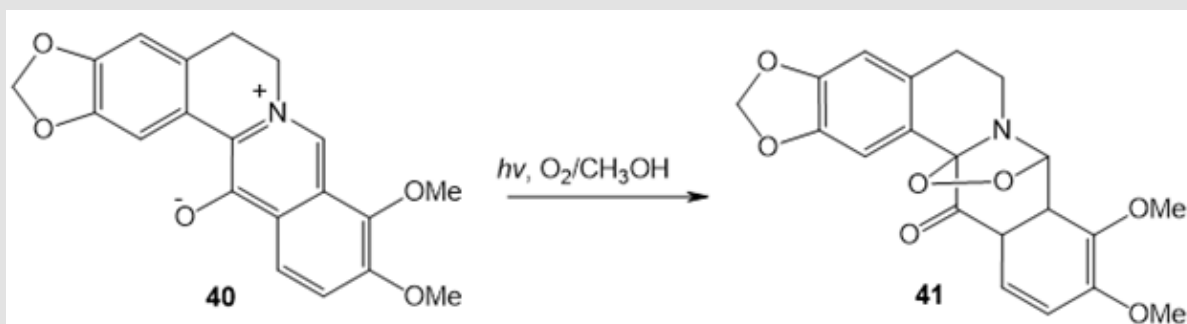
**Scheme 14:** Proposed mechanism involving addition of singlet oxygen to intermediate azomethine ylides.

An example of photochemical synthesis of (Z)-(4-benzyl-5-methyl-1,2,4-dioxazolidin-3-yl) acrylonitrile 39 in 24% yield by irradiation of cis-methylaziridine in acetonitrile has been reported (Scheme 15) [36]. The visible light irradiation of the alkaloid derivative 13-oxidoberberine 40 in the presence of Bengal Rose dye afforded amino-peroxide 41 in 42% yield [37]

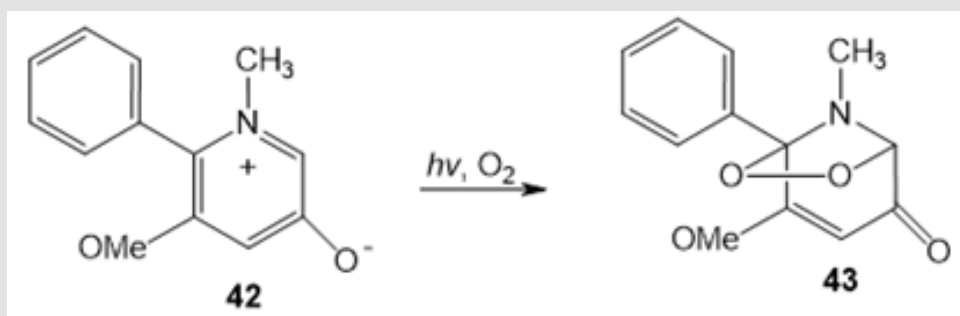
(Scheme 16). Y. Tamura and co-workers used photooxidation of 5-methoxy-1-methyl-6-phenylpyridin-3-olate 42 to perform a similar transformation giving 1,3-dipolar cycloadduct 43 (Scheme 17) [38]. 4-Hydroxy-1,2,4-dioxazolidine 45 was formed only as an intermediate in the photooxidation of N-methylnitron 44 (Scheme 18) [21].



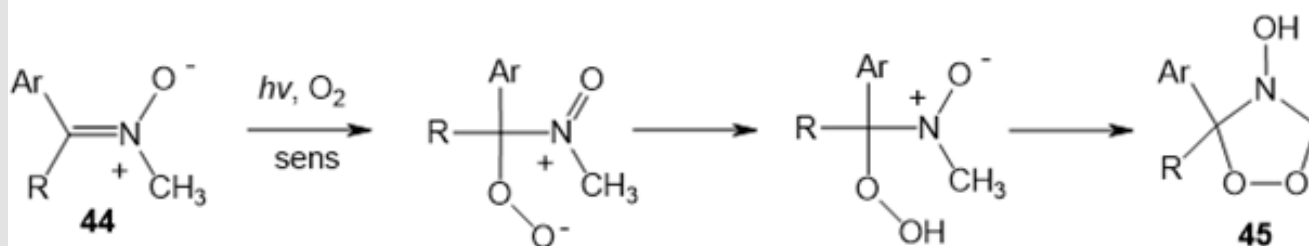
Scheme 15: Reactions of aziridines with molecular oxygen.



Scheme 16: Photo-oxygenation of phenolic betaines.



Scheme 17: Photooxygenation of 5-methoxy-1-methyl-6-phenylpyridinium-3-olate.



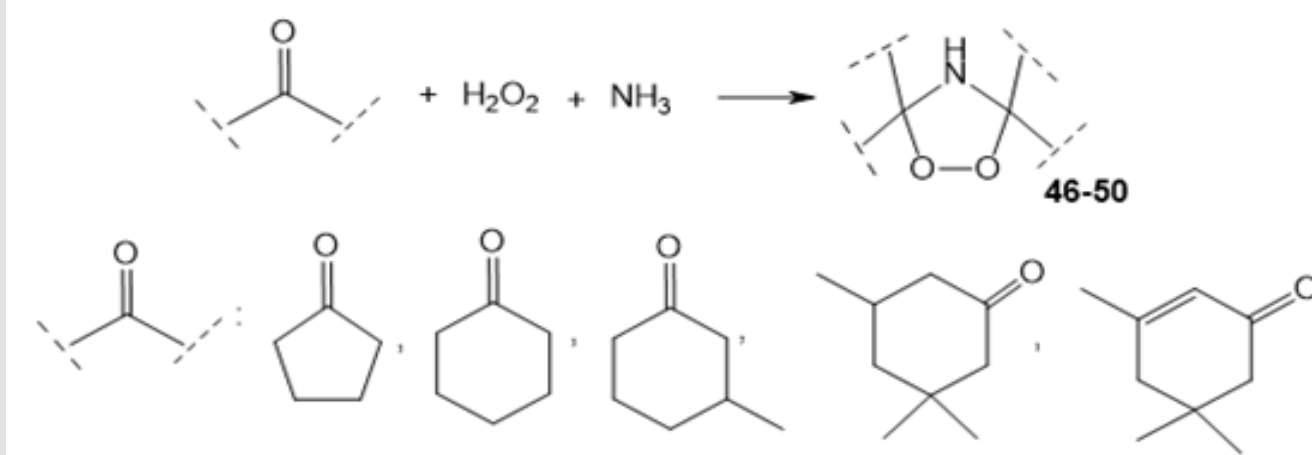
Scheme 18: Photooxygenation of nitron.



### Miscellaneous Methods for the Preparation of Five-Membered Aza-Peroxides

The ozonation and photooxidation of appropriate unsaturated compounds are the major methods for the preparation of the

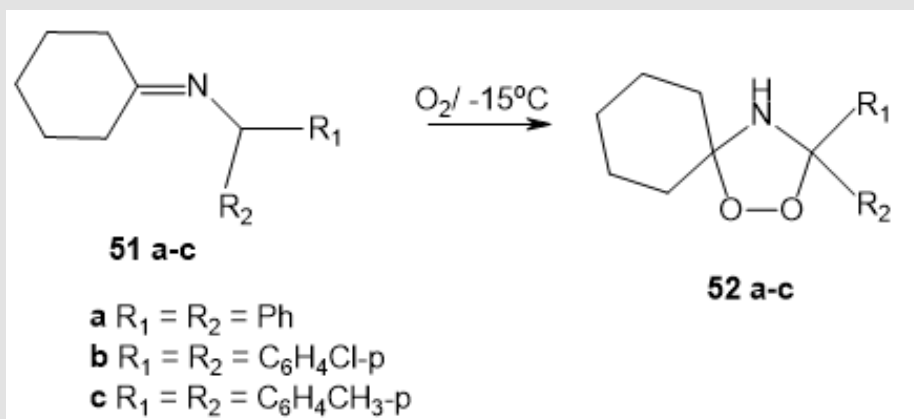
1,2,4-dioxazolidine moiety. However, an amino-peroxide moiety can also be generated using some other approaches. A simple method for the synthesis of 1,2,4-dioxazolidines 46-50 in moderate yields is the Mannich reaction of alicyclic ketone with hydrogen peroxide and ammonia (Scheme 19) [39].



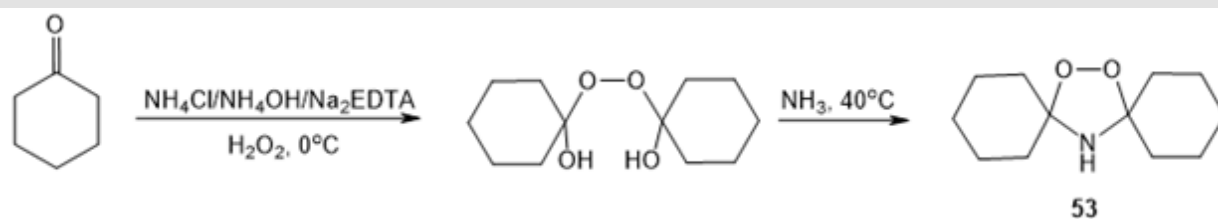
**Scheme 19:** Aminoperoxides from carbonyl compounds.

A synthetic route to 1,2,4-dioxazolidines 52a-c (formed in 60-80% yield) via oxidation of imines 51a-c in a petroleum ether-benzene solution with air oxygen at  $-15$  to  $-20^\circ C$  was discussed (Scheme 20) [40]. 1,1'-Peroxycyclohexylamine 53, which is a key intermediate in the production of Nylon-6 polymer [41], was also prepared by treatment of cyclohexanone with  $H_2O_2$  in the presence of  $NH_4Cl/NH_4OH$  and  $Na_2EDTA$  followed by treatment

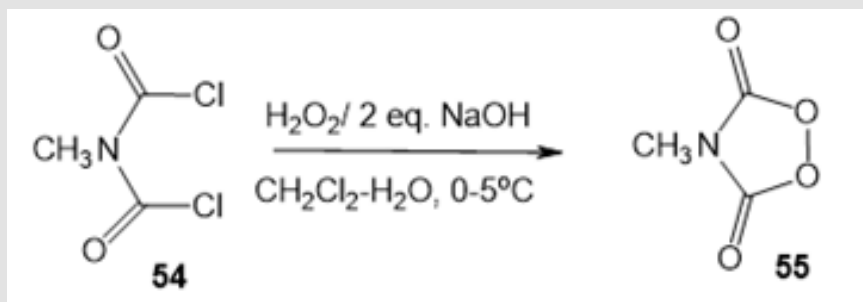
with  $NH_3$  (Scheme 21) [42]. Mention should be made of the only method for the synthesis of 1,2,4-dioxazolidine-3,5-dione 55, a promising compound for industrial application as an initiator of free radical polymerization [43]. The reaction comprised treatment of N-methyliminodicarbonyl dichloride 54 with  $H_2O_2$  under alkaline conditions (Scheme 22).



**Scheme 20:** Synthesis of 1,2,4-dioxazolidines.



**Scheme 21:** Preparation of 1,1'-peroxycyclohexylamine.

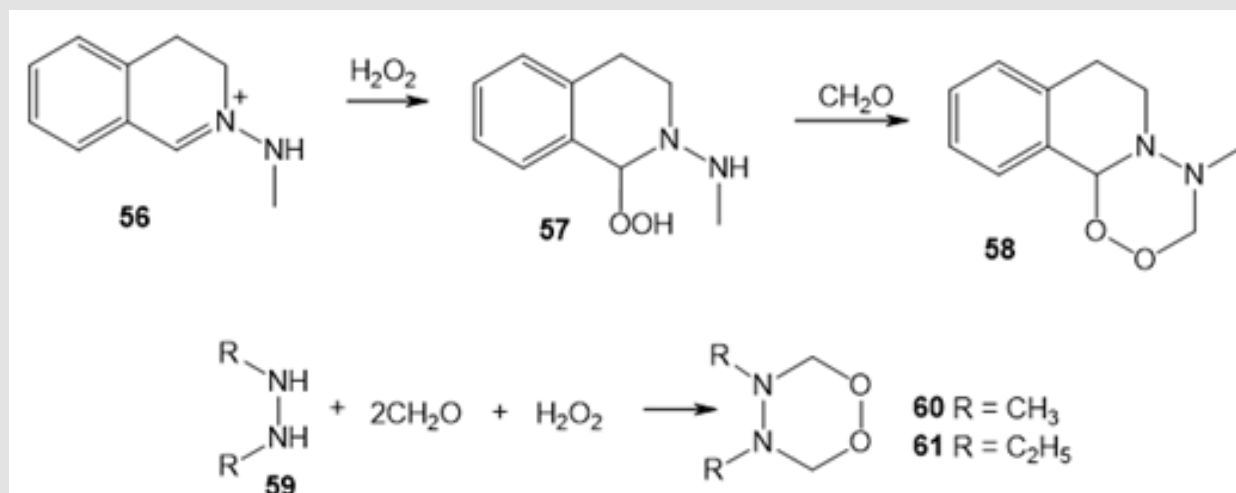


Scheme 22: Cyclic imidodiacyl peroxide.

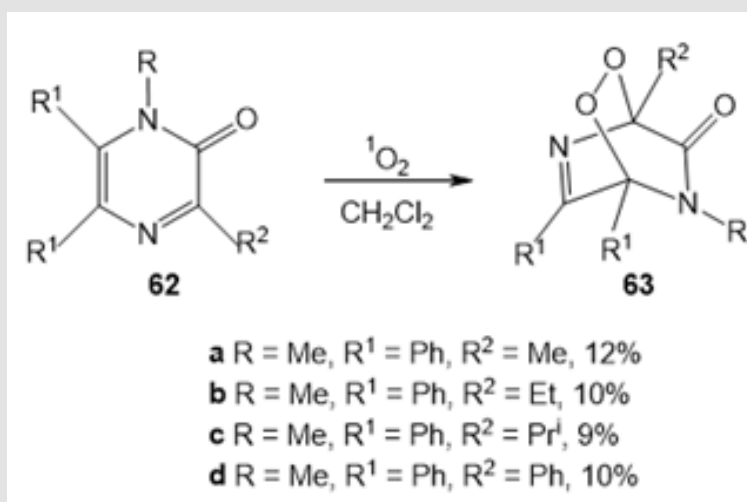
### Six-Membered Amino-Peroxides

A synthetic route to 1,2-dioxatetrahydropyridazines 58, 60, and 61 [44] consisting in the reaction of compound 56 or 1,2-dialkylhydrazines 59 a,b with  $\text{CH}_2\text{O}$  and  $\text{H}_2\text{O}_2$  was proposed (Scheme 23). The authors suggested the intermediate formation of

hydroperoxide 57. The six-membered amino-peroxides reported in the literature are mainly endoperoxides prepared by photooxidation of nitrogen-containing ketones. Indeed, photooxidation of pyrazin-2-ones 62 with singlet oxygen in the presence of Methylene Blue dye gave rise to epidioxypyrazin-2-ones 63 with a six-membered amino-peroxide ring in the molecule (Scheme 24) [45].



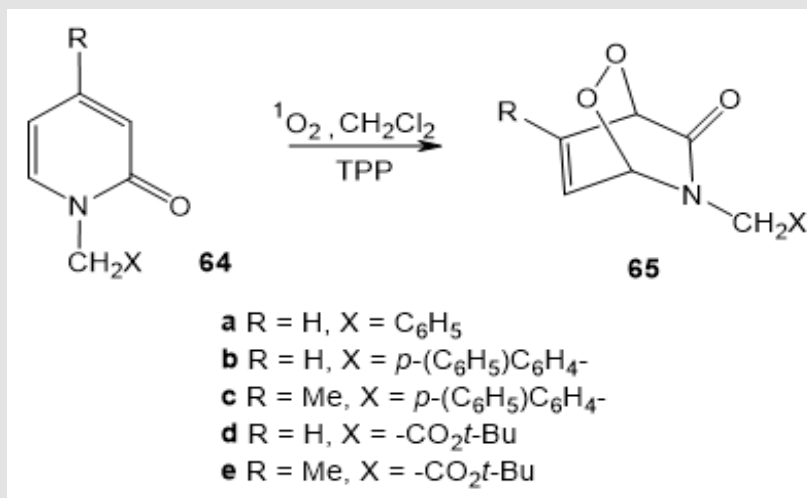
Scheme 23: Synthesis 4,5-dioxatetrahydropyridazines.



Scheme 24: Photochemical reactions of the pyrazine-2-ones under an oxygen atmosphere.

Irradiation of a solution of N-benzyl-2-pyridinones **64** in dichloromethane with a Na-lamp (940 W) in the presence of a catalytic amount of Tetraphenylporphin (TPP) in an oxygen

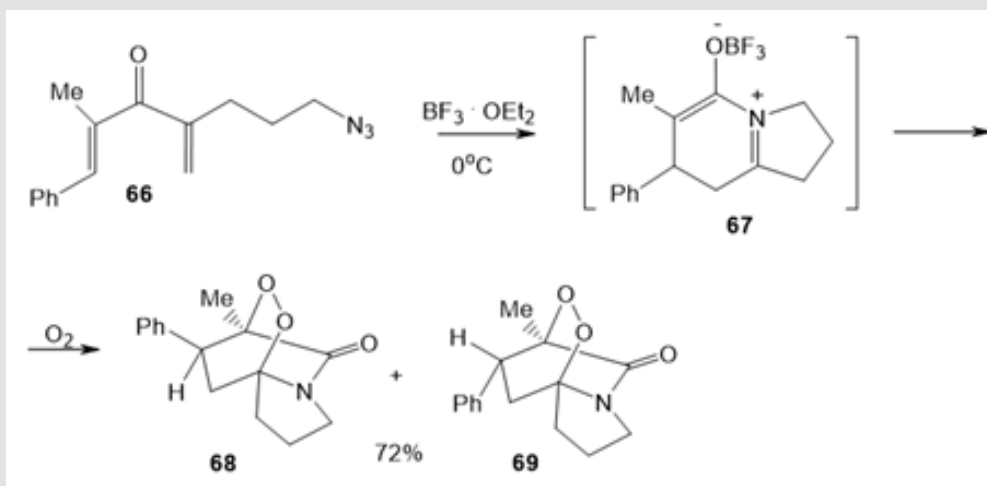
atmosphere at  $-78^{\circ}\text{C}$  for 2 h yielded exclusively 1,4-endoperoxides **65** (Scheme 25) [46].



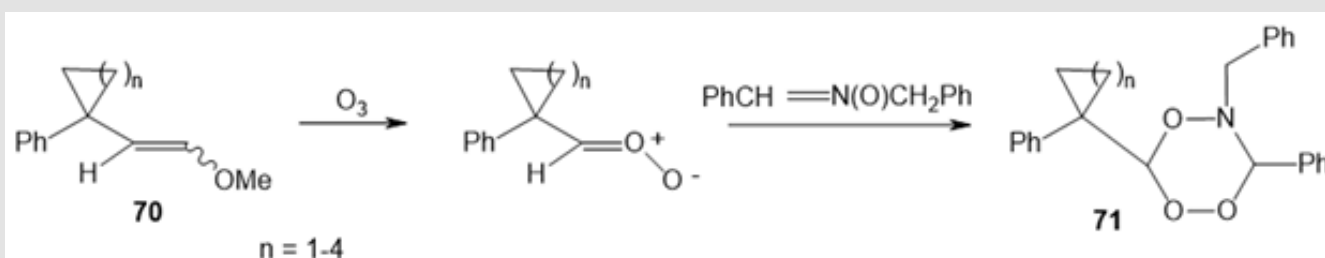
**Scheme 25:** Formation of endoperoxides by singlet oxygen addition.

The oxidation of alkadienone **66** at  $0^{\circ}\text{C}$  catalyzed by boron trifluoride etherate gave an intermediate betaine complex with Lewis acid **67**, which rearranged on further oxidation to a mixture of diastereomeric endoperoxides **68** and **69** in a total yield of 72% (Scheme 26) [47]. The ozonolysis of vinyl ethers **70** in the presence of  $\alpha$ -phenyl-N-benzylnitron afforded six-membered peroxides,

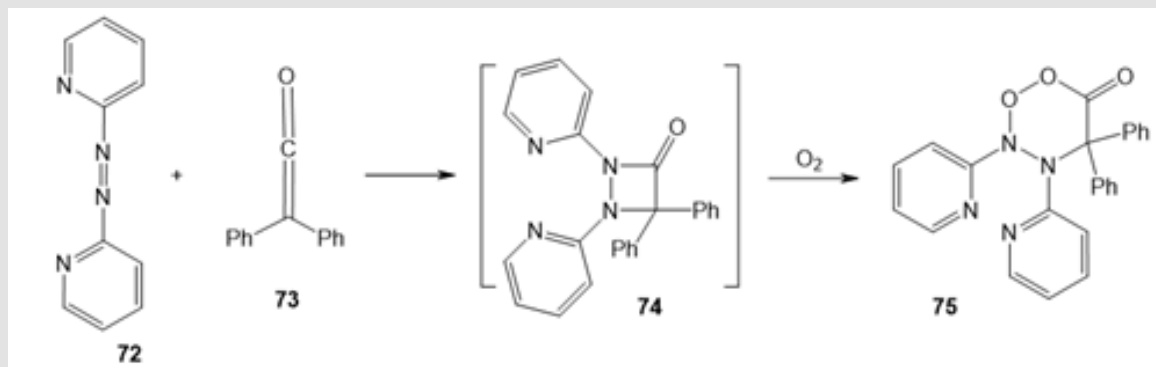
5-benzyl-6-phenyl-3-(1-phenylcycloalkyl)-5,6-dihydro-1,2,4,5-trioxazines **71**, in 79-95% yields (Scheme 27) [48]. The cycloaddition of 2,2'-azodipyridine **72** to diphenyl ketene **73**, obtained in situ, followed by self-oxidation of intermediate 1,2-diazetidione **74** furnished target dihydro-5,5-diphenyl-3,4-bis(2-pyridyl)-1,2,3,4-dioxadiazin-6-one **75** (Scheme 28) [49].



**Scheme 26:** Azide trapping and peroxide formation.



**Scheme 27:** Treatment of the vinyl ethers with ozone in the presence of  $\alpha$ -phenyl-N-benzylnitron.

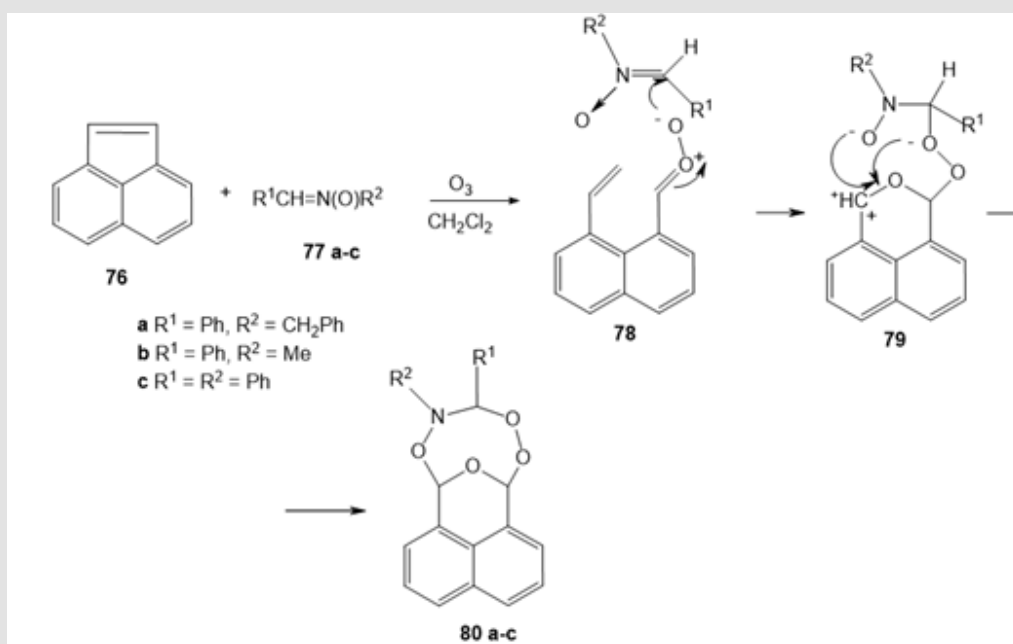


Scheme 28: Autooxidation of the 1,2-azetidione.

### Eight-Membered Aza-Peroxides

Ozonolysis of acenaphthylene 76 in the presence of nitrones 77a-c is an efficient route to polycyclic amino-peroxides 80 a-c containing the dihydro-1,2,5,7,4-tetraoxazocine ring. The reaction

proceeds as the [3+3+2]-cycloaddition between the carbonyl oxide moiety, nitron, and aldehyde group via intermediates 78 and 79 (Scheme 29) [50]. The yields of eight-membered amino-peroxides 80a-c are 11, 30, and 45%, respectively (Figure 1).



Scheme 29: The formation of the nitron-incorporated cyclic peroxides.

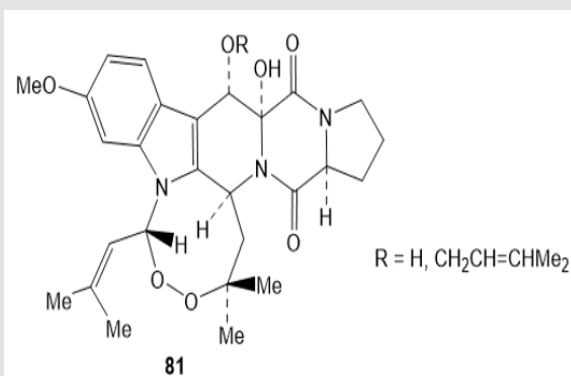
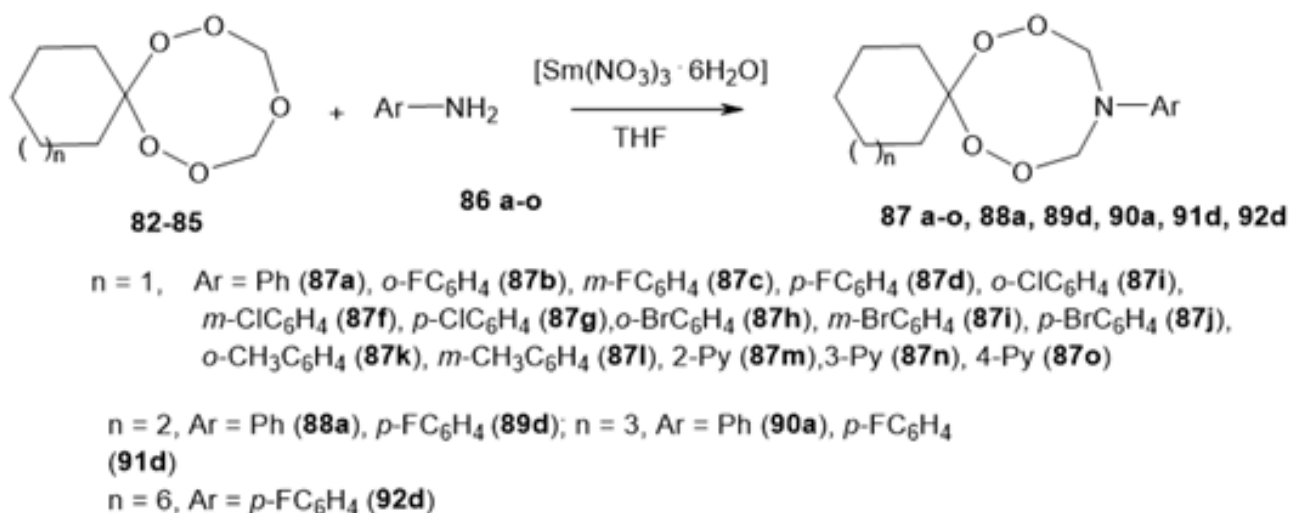


Figure 1.

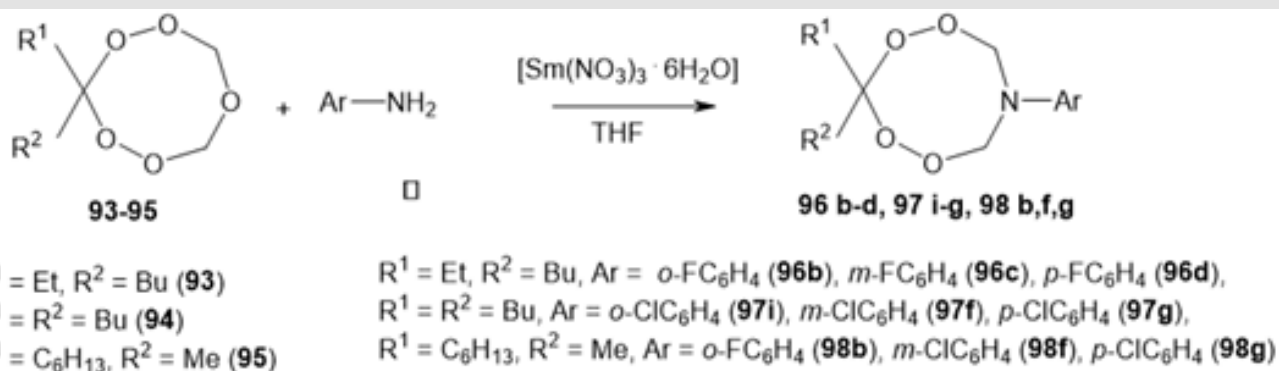
An eight-membered cyclic amino-peroxide moiety is present in Verruculogen 81, a metabolite of *Penicillium verrucosum* [51], and in the mycotoxins of several strains: *Aspergillus caepitosus* [52], *A. fumigatus* [53], *A. fisheri* [54], *Penicillium piscarium* [55], *P. paxilli* [56], *P. estinogenum* [57], *P. simplicissimum*, *P. piceum*, *P. nigricans*, *P. raistricki* [58], *Eupenicillium sp.* [59], and *Neosartorya fisheri* [60]. A Sm(NO<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O-catalyzed process was developed for the synthesis of N-substituted tetraoxazaspiroalkanes by ring transformation of pentaoxaspiroalkanes with primary amines at room temperature in THF [61]. Aryl- 87a-l and hetaryl-amines 87m-o undergo the ring transformation reaction to give N-aryl(hetaryl)-tetraoxazaspiroalkanes in 70-99% yields (Scheme 30).



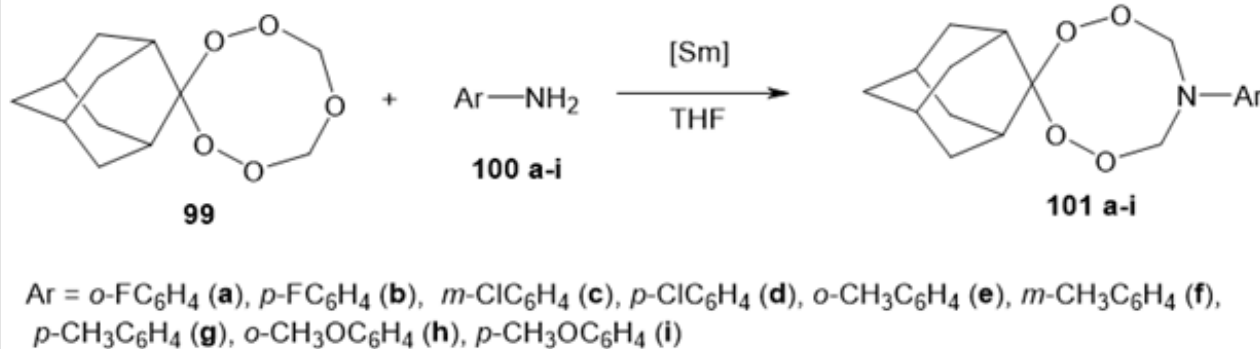
Scheme 30: Synthesis of N-substituted tetraoxazaspiroalkanes.

The yield of amino-peroxides depends little on the structure of the starting monomers and reagents, which made it possible to perform the Sm(NO<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O-catalyzed reaction for primary amines and pentaoxacanes, resulting in the selective formation of 3,3-dialkyl-7-(*o,m,p*-halophenyl)-1,2,4,5,7-tetraoxazocanes 96b-d, 97i-g, 98b,f,g in 75-90% yields (Scheme 31) [62]. Spiro{ad-

amantane-[2,3']-(1',2',4',5',7'-pentaoxacane)} 99 reacts with aryl(*o,p*-fluorophenyl, *m,p*-chlorophenyl, *o,p*-methoxyphenyl, *o,m,p*-methylphenyl)amines in the presence of the Sm(NO<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O catalyst (5 mol. %) (~ 20°C, THF) to give 7'-arylspiro{adamantane-[2,3']-(1',2',4',5',7'-tetraoxazocanes)} 101a-i in 80 - 99% yields (Scheme 32) [63].



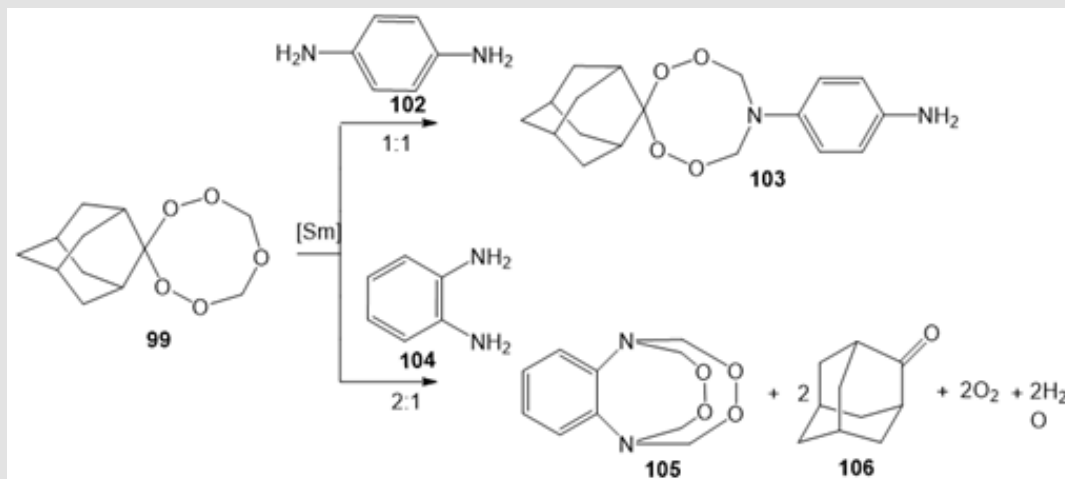
Scheme 31: Ring transformation of pentaoxacanes.



Scheme 32: 7'-Arylspiro{adamantane-[2,3']-(1',2',4',5',7'-tetraoxazocanes)}.

Apart from arylamines, aromatic diamines (o,m,p-phenylenediamines) were also reacted with spiro{adamantane-[2,3']-(1',2',4',5',7'-pentaoxacane)} 99. The ring transformation of compound 99 involving p-phenylenediamine 102 (5 mol.% of  $\text{Sm}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ , 20°C, 6 h, THF) also yielded the target 4-spiro{adamantane-2,3'-[1',2',4',5',7']tetraoxazacane}-7'-yl)

aniline 103, whereas the reaction with m-phenylenediamine produced a precipitate insoluble in organic solvents. Spiro{adamantane-[2,3']-(1',2',4',5',7'-pentaoxacane)} 99 reacted with o-phenylenediamine 104 to give adamantanone 106 and 2H,5H-1,6-(methanedioximethano)benzo[e][1,2,4,7]-dioxazocine 105 (Scheme 33) [63].

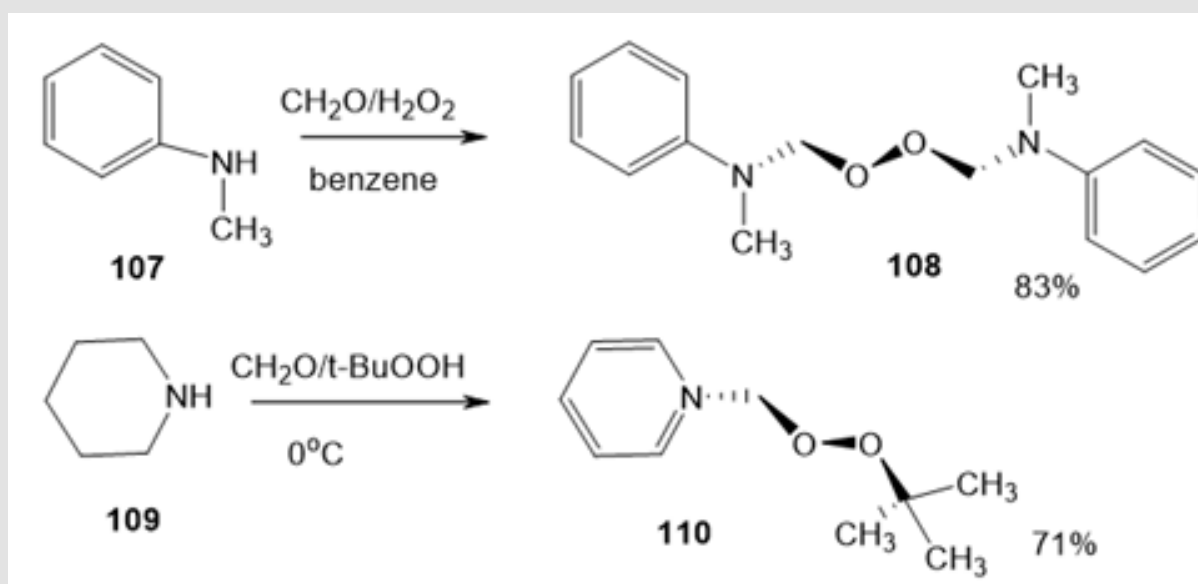


**Scheme 33:** Ring transformation of spiro{adamantane-[2,3']-(1',2',4',5',7'-pentaoxacane)} with aromatic diamines.

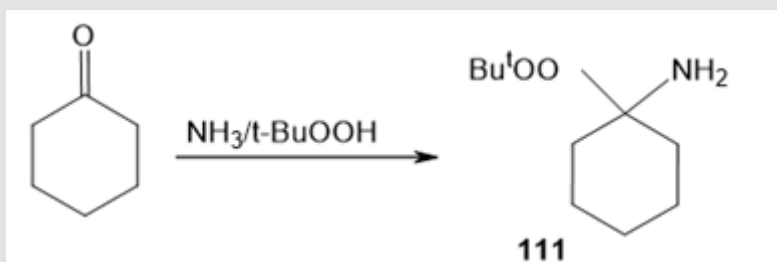
### Acyclic Amino-Peroxides

There are few published cases of preparation of alicyclic amino-peroxides 108 and 110 by oxidative peroxyformylation of methylaminobenzene 107 and piperidine 109 (Scheme 34) [64,65]. Treatment of cyclohexanone with ammonia and tert-butyl hydroperoxide produces 1-tert-butylperoxycyclohexylamine 111 (Scheme 35) [66]. Whereas cyclic amino-peroxides are synthesized by oxidative transformations, the peroxides with a side-chain

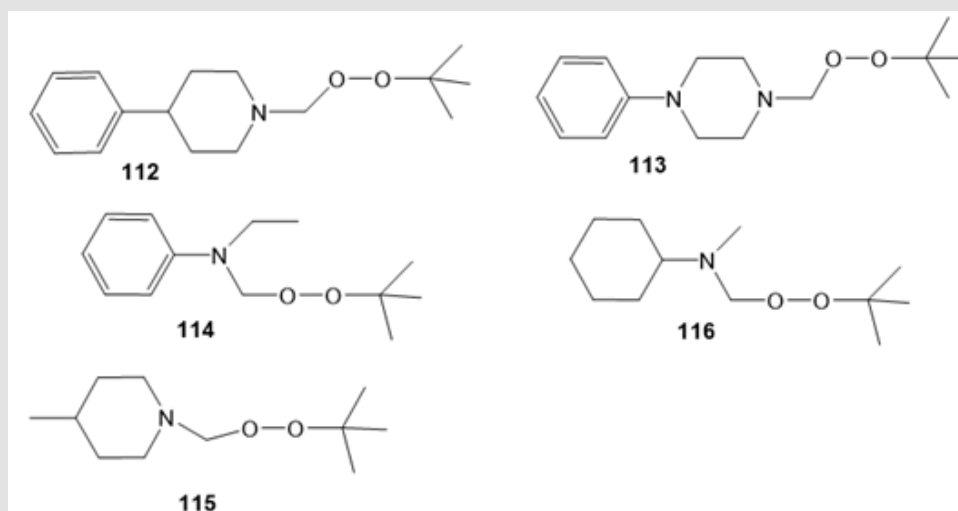
nitrogen atom are prepared via non-oxidative reactions. The most widely used method is the Rieche version of the Mannich formylation. In this case, tert-butyl hydroperoxide acts as a very potent nucleophile. J. Vennerstrom and co-workers used this protocol to synthesize tert-butylamino-peroxides 112-116 [67]. Amines were selected in such a way that the target amino-peroxides had endocyclic, exocyclic, and aliphatic or aromatic nitrogen atom. Amino-peroxides 112-116 showed a higher activity in vitro towards *Plasmodium falciparum* than artemisinin (Scheme 36).



**Scheme 34:** Alicyclic amino-peroxides.



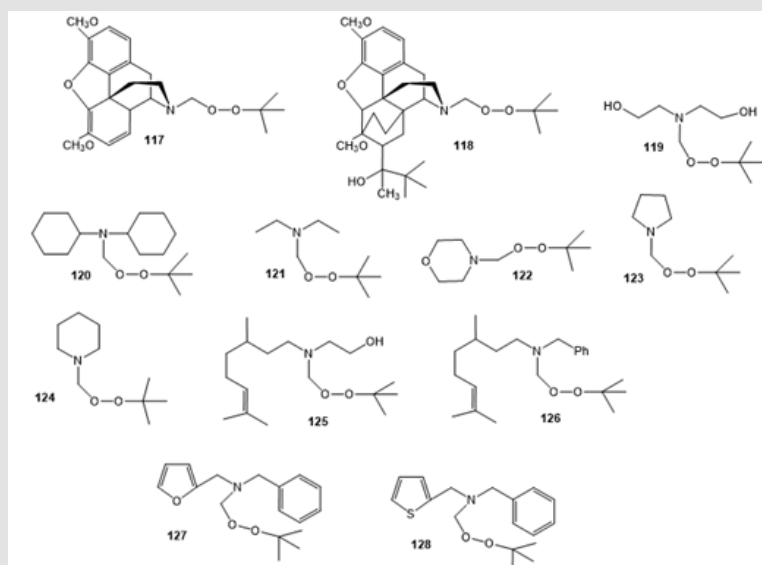
**Scheme 35:** Synthesis of 1-tert-butylperoxycyclohexylamine.



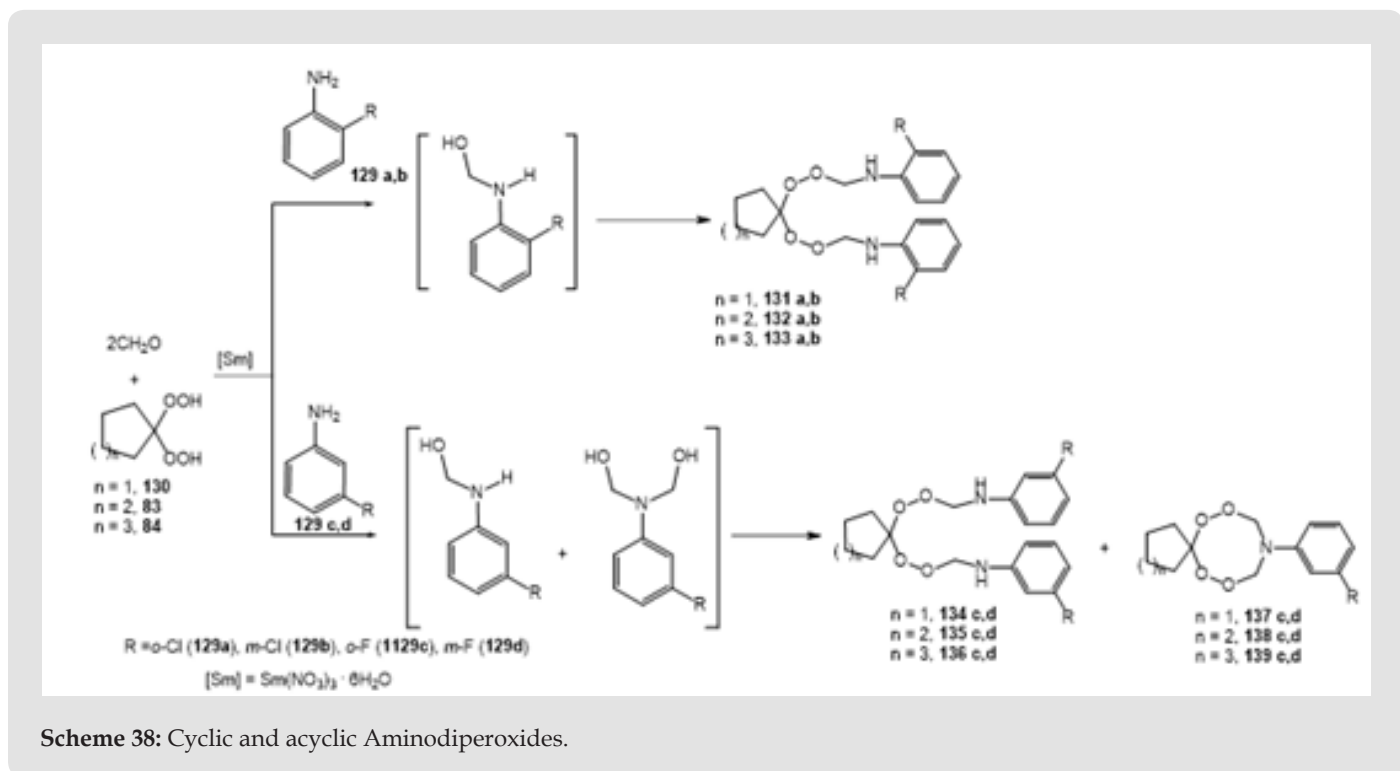
**Scheme 36:** Structure of aminoperoxides.

In 2001, N. Sundar and co-workers used a similar reaction to prepare tert-butyl peroxyamines 118-128, which were tested for antimalarial properties against the *P. berghei* and *P. falciparum* strains of malaria (Scheme 37) [68]. Acyclic diaminodiperoxides were prepared by the reaction of 1,1-bis(hydroperoxy)cycloalkanes with formaldehyde and primary arylamines catalyzed by Sm compounds ( $\text{SmCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{Sm}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{SmCl}_3/\gamma\text{-Al}_2\text{O}_3$ ,  $\text{Sm}(\text{NO}_3)_3/\gamma\text{-Al}_2\text{O}_3$ ) [62]. The reactions of ortho-aryl(chlorophenyl, fluorophe-

nyl)amines 129a,d with formaldehyde and 1,1-bis(hydroperoxy)cycloalkanes 130, 83, and 84 afford acyclic 1,1-bis[N-(peroxymethyl)-N-arylamino]cycloalkanes (131-133)a,d in 63-75% yields. The replacement of ortho-arylamines 129a,d by meta-aryl(chlorophenyl, fluorophenyl)amines 129c,d results in the formation of a mixture of acyclic (134-136)c,d and cyclic (137-139)c,d amino-peroxides in 1 : 1 ratio (Scheme 38).



**Scheme 37:** Aminoperoxides as potential antimalarials.



## Conclusion

Analysis of the literature demonstrates that the recent advances in the synthesis of organic amino-peroxides have been stimulated by their practical use, first of all, with the prospects for development of efficient medicinal drugs based on these compounds. Relatively low degree of exploration of amino-peroxides is caused by the lack of efficient methods for their synthesis. Today, photochemical ozonolytic oxidation of nitrogen-containing compounds is the method of choice for the synthesis of cyclic amino-peroxides. This method provided considerable progress in the synthesis of five-membered 1,2,4-dioxazolidine derivatives. The successful development of catalytic methods for the synthesis of aza-diperoxides in recent years is noteworthy. Of particular interest and practical value are recent studies on the synthesis of amino-diperoxides by one-pot ring transformation of pentaoxaspiroalkanes to tetraoxazaspiroalkanes on treatment with primary amines and by cyclocondensation of 1,1-bis(hydroperoxy) cycloalkanes with formaldehyde and primary amines catalyzed by lanthanide salts and complexes.

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