Ain-Shams University
Faculty of Science
Chemistry Department

Studies on the synthesis and chemical reactions of some new nitrogen heterocyclic compounds for biological evaluation.

THESIS SUBMITTED
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M. Sc. Organic Chemistry (2009)

To Chemistry Department, Faculty of Science

Ain-Shams University

For Ph. D. Degree in Organic Chemistry

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Introduction

CHEMISTRY OF EPOXIDES

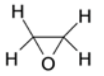
BIOLOGICAL ASPECTS:

All keto-epoxides possess significant biological activities (**Thirunarayanan and anangamudi, 2011**). The basic skeleton of epoxy ring, present widely in natural products is known to have multi-pronged activity (**Jayasinghe *et al*., 2006)**. Various multipronged activities such as, anti-microbial **(Contelles *et al*., 2004; Yongbo *et al*., 2001),** anticancer and anti-tumour **(Misra et al., 2008)** have been studied by bio-chemists and chemists on oxiranes and their derivatives. Oxiranes are more important in steroid, mammalian biosynthesis for cholesterol **(Nelson *et al*., 1981),** marine organisms **(Gerrwick *et al*., 1980)** and toxin for some species fungi **(Buchi *et al*., 1973).** Generally epoxides possess many biological activities such as vasoactivity **(Carroll *et al*., 1987),** cardiovascular activity (**Imig *et al*., 2009**), EETs **(Inceoglua *et al*., 2007),** mutagenicity **(Wu *et al*., 1993)**, K-region cure property **(Swaisland *et al*., 1973),** regulators of blood pressure, hypertension, pain, inflammation **(Morisseau *et al*., 2008 and Fang *et al*.,**

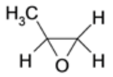
2006), anti-analgesic activity **(Inceoglua *et al.,* 2008)**, cytotoxicity (**Yu *et al.,* 1998),** mutagenic and cell-transforming activities **(Glatt *et al.,* 1986)** and tumorigenicity **(Kumar et al., 2002 and Kumar *et al.,* 2001).**

NOMENCLATURE:

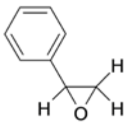
Three membered cyclic ethers are important as reactive intermediates in organic synthesis. These substances are often named individually as alkene oxide; collectively they are called oxiranes or epoxides (IUPAC) (**Roberts and Caseiro, 1965**).



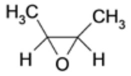
Ethylene oxide
(oxirane)



Propylene oxide
(2-methyloxirane)



Styrene oxide
(phenyloxirane)



Cis 2-butene oxide
(2,3-dimethyloxirane)

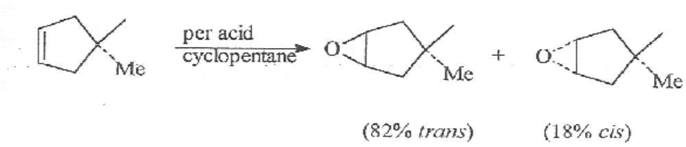
SYNTHESIS OF EPOXIDES:

α,β-Epoxy carbonyls are key building blocks in organic synthesis, as these versatile functionalities are readily and stereoselectively transformed by ring opening into a variety of oxyfunctionalized compounds **(Saumen *et al.,* 2010; Nemoto *et al.,* 2000 and Yang *et al.,* 1999).**

1- From Alkenes:

The majority of oxiranes synthesis involves the electrophilic reagent as peroxy acids. It was shown that

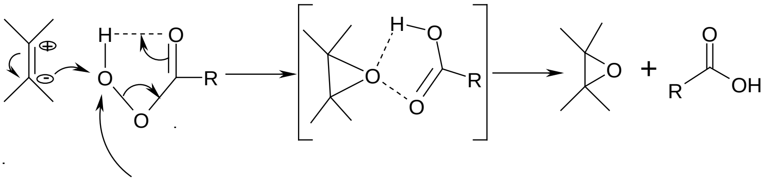
(Henbest, 1963) 85% epoxidation could occur at the α-face (side away from the substituent) of a cyclic 3-substituted olefin **1**. This has been shown to be a steric effect of the substituent in alkyl cyclopentenes **(Mousseron *et al.*, 1964).**



1 **2** **3**

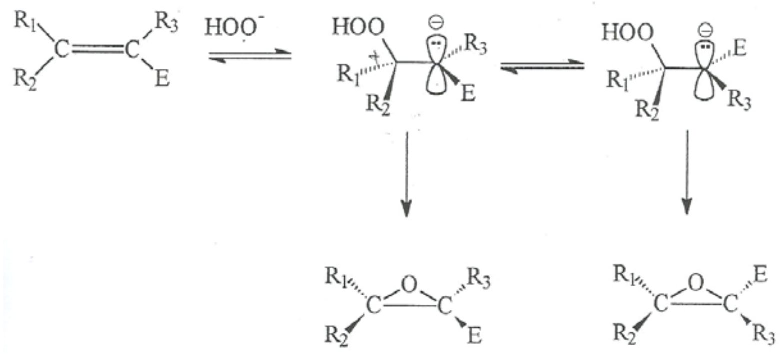
2-<u>Epoxidation by peracids:</u>

Epoxidation rates with per acids appear to be the same in almost every solvent (**Schwartz and Blumbergs, 1964**) thus suggest intramolecular hydrogen bonding (**Suhara, 1964**).



Site of nucleophilic attack by alkene

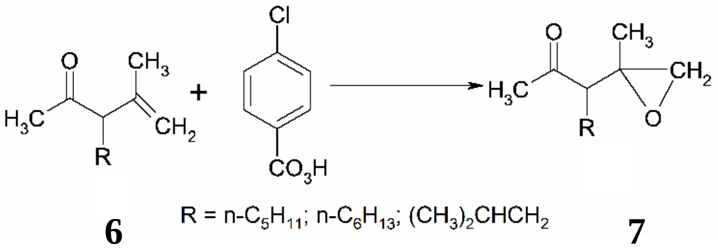
The most widely used reagent is hydroperoxide ion, which proceeds through an intermediate α-carbanion (**Betti *et al.*, 1973).**



4 **5**

a) By p-chloroperbenzoic acid:

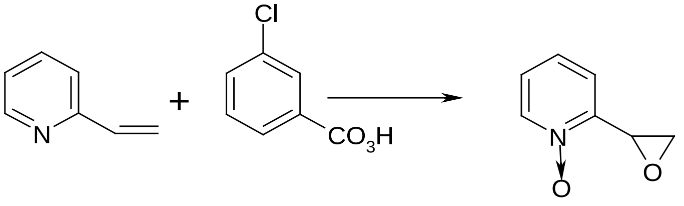
β,γ-Unsaturated ketones **6** react with *p*-chloroperbenzoic acid and gave the corresponding β,γ-epoxyketone **7** (**Fujita** ***et al.*****, 1977**).



6 **7**

b) By m-chloroperbenzoic acid:

Oxidation of 2-vinylpyridine **8** with excess *m*-chloroperbenzoic acid in methylene chloride at reflux temperature afforded 2-epoxyethylene pyridine-1-oxide **9** (**Abraham** ***et al.*****, 1978).**

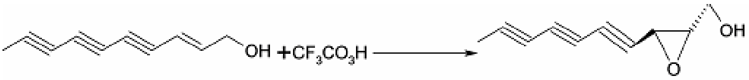


8

9 (60%)

c) By trifluoroperacetic acid:

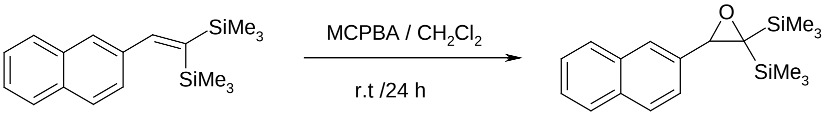
Trifluoroperacetic acid used to oxidation of deca-2-en-4, 6, 8-triyn-1-ol **10** to give epoxide **11** (**Jones *et al.*, 1963).**



10 **11**

***d) By m*-chloroperoxybenzoate anion:**

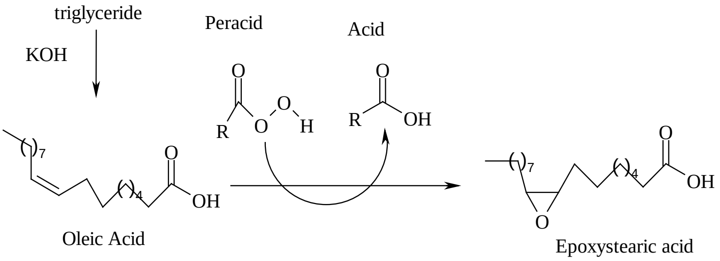
Epoxidation of 1, 1-Bis (trimethylsilyl)-2-(2-naphthyl) ethane **12** with *m*-CPBA in CH_2Cl_2 at room temperature gave 3-(naphthalen-2-yl)-2, 2-bis (trimethylsilyl) oxiran **13 (Safa *et al.*, 2011)**.



12 **13**

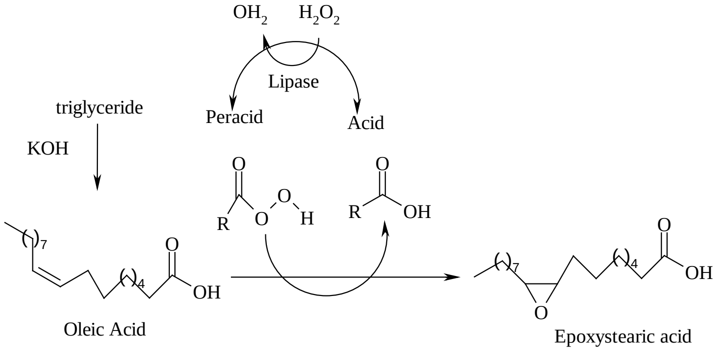
e) Epoxidation of fatty acid ester:

The most used procedure to produce deoxidized fatty acid esters currently consists of two steps involving alcoholysis of triglycerides/fatty acids using KOH as catalyst followed by epoxidation of peroxyacetic acid esters or peroxyformic **(Flavia *et al.*, 2012 and Witnauer *et al.*, 1955).**



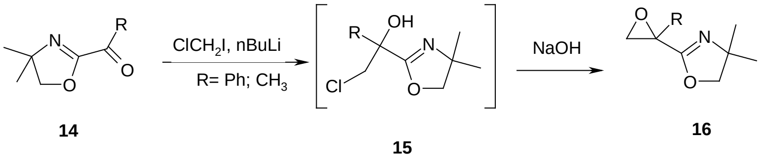
3-Chemo-enzymatic epoxidation:

In the chemo-enzymatic epoxidation reaction, the enzyme normally catalyzes the peracid formation from the corresponding fatty acid and hydrogen peroxide (**Kotlewska *et al.*, 2011)**. Then the peracid spontaneously transfers oxygen to the double bond forming the epoxide **(Tornvall *et al.*, 2007)**.



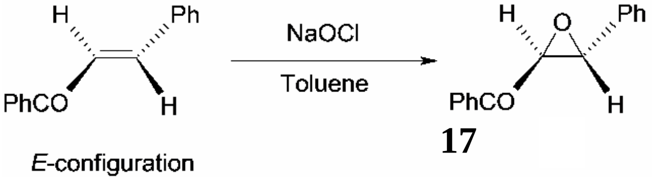
4-Epoxidation by dehydrohalogenation:

Treatment of 2-acyl-2-oxazolines **14** with $ClCH_2Li$, generated from $ClCH_2I$ and n-BuLi in THF at 78 ^{0}C, gave chlorohydrins **15** (not isolated) which converted into epoxides **16** (50–60% yield) upon treatment with NaOH (**Degennaro *et al.*, 2009**).



5-Epoxidation of olefin by oxidation:

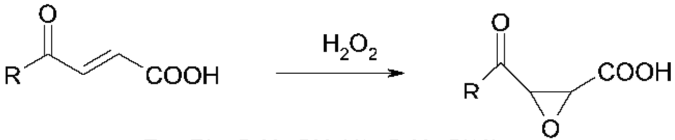
Epoxide **17** was prepared stereo specifically by treatment of *E*-PhCOCH=CHPh with NaOCl (**Hummelen and Wynberg, 1978**) at room temperature, 72 h.



Another oxidation systems has been used; NaOCl-Al_2O_3 for the oxidation of the electron-poor enyne **18** to give compound **19** (**Hopf and Kreutzer, 1990; Chemla and Ferreira, 2002**).

6-Epoxidation of olefin by using hydrogen peroxide:

Olefin oxides were prepared by the catalytic epoxidation of olefins at 0-120°C by H_2O_2 with continuous removal of H_2O. Epoxide **20** were prepared by oxidizing R-CO-CH=CH-COOH by using hydrogen peroxide (**El-Hashash and El-Kady, 1978**).

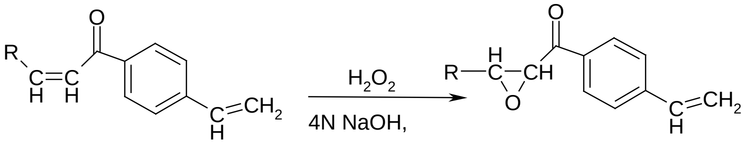


R = Ph; $C_6H_4.CH_3(4)$; $C_6H_4.Cl(4)$

20

7-Epoxidation by using alkaline hydrogen peroxide:

The vinyl chalcones **21** were epoxidized to the benzyl oxiranes **22** by treatment with H_2O_2 in 4N NaOH at 0°C (**Roshke *et al.*, 1974).**

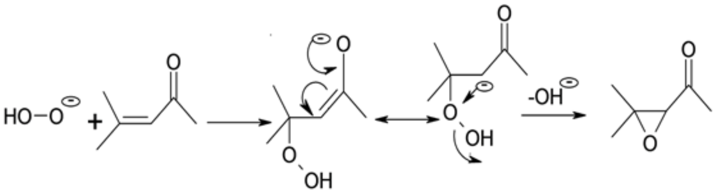


21

22

R = Ph; $Cl-C_6H_4$; $Br-C_6H_4$; $Cl_2-C_6H_3$; $I-C_6H_4$; $O_2N-C_6H_4$;

The α,β-unsaturated ketone react with H_2O_2 in alkaline media to give α-keto-oxiranes (**Zwanenburg and Terwiel, 1970** ; **Coffen and Korzan, 1971**) which proceed through an intermediate α-carbonyl anion.

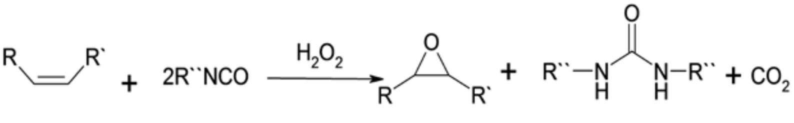


8-Epoxidation by using mixture of acetic acid and hydrogen peroxide:

Unsaturated esters were epoxidized (**Utkin and Ermakov, 1975**) in AcOH/H_2O_2 in 1:3:1.5 ratios by heating in the presence of styrene divinyl benzene copolymer as catalyst.

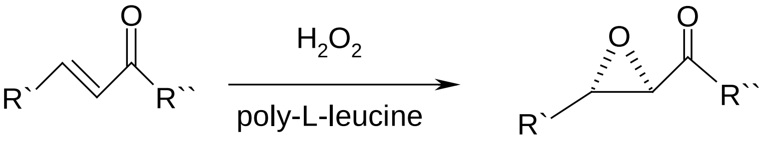
9-Epoxidation by using hydrogen peroxide and isocyanate:

Epoxides may be obtained in reasonable yields under neutral conditions by treatment of alkenes with hydrogen peroxide and an aryl isocyanate (**Matsumura *et al.*, 1970**). Best results were obtained when a non-polar solvent and 2:1 molar ratio of isocyanate to alkene were used.



10-Epoxidation by using hydrogen peroxide and polyleucine-catalysed:

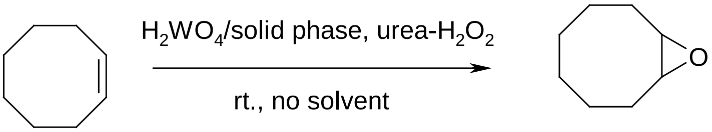
The epoxide **23** may also be prepared by poly-L-leucine-catalysed oxidation of enones (**Pena and Roberts, 2003**) in presences of H_2O_2.



23

11-Epoxidation by tungstic acid:

It was found that tungstic acid catalyst dispersed on apatite solid phase (H_2WO_4/ apatite) is effective as the environmentally benign solid catalyst for the epoxidation of alkenes and allylic alcohols with solid urea-hydrogen peroxide complex (**Ichihara, 2001**).



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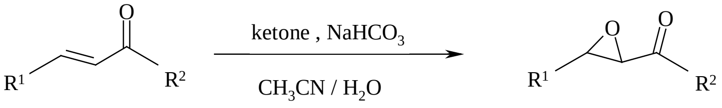
12-Epoxidation by different Ketone:

The chalcones were epoxidized to the oxiranes **25** by treatment with Ketone, $NaHCO_3$ and CH_3CN/H_2O at 25°C (**Hajra and Bhowmick, 2010**).

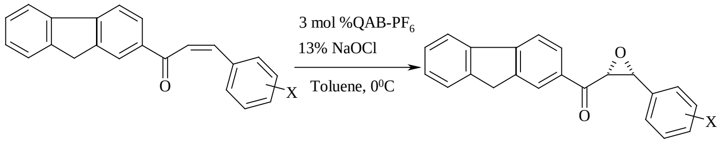


25

R^1 = 4-MeOC_6H_4; Ph; Me R^2 = OMe; Ph

13-Epoxidation of α,β-unsaturated ketone:

Appropriate mixture of substituted styryl 9H-fluorene-2-yl ketones **26** (0.10 mmol) and a chiral quaternary ammonium bromide- PF6 catalyst (6 mg, 0.003 mmol, 3 mol %) in toluene (3 mL) was added to 15% aqueous sodium hypochlorite (NaOCl, 0.15 mL). This mixture was stirred for 14 h (minimum 10 h) at 0 ◦C under inert atmosphere afforded 2-(9H)-fluorene-4-yl[3-(substituted phenyl)oxiran-2-yl] methanones **27** **(Thiruarayanan *et al.*, 2011).**



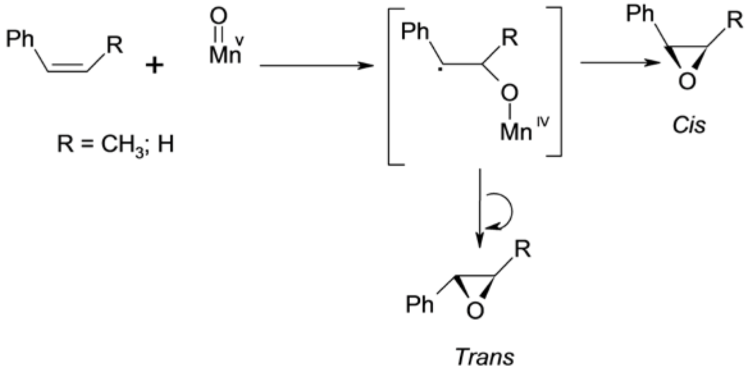
26 **27**

14-Epoxidation by nitric acid:

The use of 90-100% nitric acid on tetra-(p-nitrophenyl) ethylene at 0°C gave the corresponding epoxide (**Gorwin, 1963**). This is the first reported case of this type of epoxidation and it is undoubtely due to the high electrophilicity of the double bond.

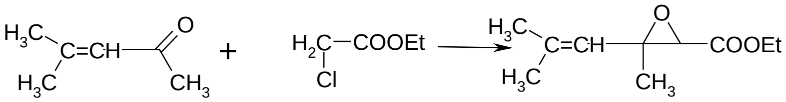
15- Epoxidation by metal- catalyzed:

Epoxidation of conjugated olefins observed to proceed through a radical intermediate that causes isomerization by rotation about the resulting carbon-carbon single bond so that acyclic conjugated olefins gave a mixture of *Cis* and *Trans* epoxides (**Srinivasan *et al.*, 1986; Irie *et al.*, 1990**).



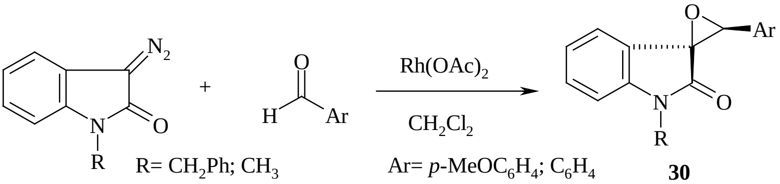
16- Epoxidation by ethyl chloroacetate:

The reaction of mesityl oxide **28** as an enone with ethyl chloroacetate using methoxide anion as catalyst gave oxirane derivative **29** (**Casagrande and Ferrari, 1966**).



17-Epoxidation by rhodium(II)acetate:

Reaction of cyclic diazoamides and aromatic aldehydes having electron-donating or -withdrawing groups in the presence of rhodium(II) acetate catalyst at room temperature afforded spiro-oxiranes **30** **(Muthusamy *et al.*, 2011)**.



30

18-Epoxidation of methyl oleate withH_2O_2:

Currently, epoxy fatty acid compounds **31** are mainly obtained on the industrial scale by the Prileshajew reaction, in which the unsaturated oils **32** are converted with percarboxylic acids, such as peracetic or performic acid. This route suffers from several drawbacks: (I) in the acidic reaction media, the selectivity for epoxides is relatively low due to oxirane ring opening, (II) the handling of peracids and highly concentrated hydrogen peroxide solutions is strongly hazardous, and (III) the aqueous solutions of C1–C3 carboxylic acids formed as by products are strongly corrosive **(Nicole *et al.*, 2012; Camblor *et al.*, 1997 and Debal *et al.*, 1993).**

31

methyl 9,10-epoxy stearate

32