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VOLUME **106**

Editor

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PREFACE

Professor Mikael Begtrup (University of Copenhagen, Denmark) has provided a masterly overview which for the first time brings together extensive knowledge on diazole, triazole and tetrazole N-oxides, much of which has been obtained by his own group in Denmark. This whole field is still moving forward at a rapid pace, and the review is most timely.

The synthesis and structural diversity of heteroporphyrins is overviewed by Professor K. Singh together with Dr. A. Sharma and Dr. S. Sharma, all of Guru Nanak Dev University, Amritsar, India. Porphyrins continue to be of immense interest in a wide variety of areas including pigments of diverse applications and great progress has been made recently in the diversification of porphyrin structures, especially those containing expanded systems and core modification. This whole subject has now been updated.

The final chapter in this volume deals with a very different topic. Professor H. Wamhoff of the University of Bonn, Germany, and Professor G. W. Gribble of Dartmouth College in New Hampshire have documented the fascinating subject of the occurrence of heterocyclic components in wine. The authors, experts in both oenology (wine-making) and in heterocyclic chemistry, have provided us with a most fascinating account of the tremendous diversity of heterocycles which occur in wine and which must in many cases be responsible for the quality, flavor, and color of a wine as well as the bouquet and the flavor which characterize one of the most ancient cultural drinks of the world. Enjoy!

Alan Katritzky

CHAPTER 1

Diazole, Triazole, and Tetrazole *N*-Oxides

Mikael Begtrup

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Application of *N*-oxides in chemistry and biology has attracted increasing interest. General trends in chemical properties are emerging but further investigations are needed to exploit the full potential of these multifaceted and useful compounds.

The azole *N*-oxides display enhanced reactivity and complementary regioactivation as compared to the parent azoles. They can undergo unique reactions making them highly versatile by regiocontrolled functionalization of 5-membered azaheterocycles, when functionalization is followed by removal of the *N*-oxide oxygen atom. *O*-Alkylation or acylation further activates both ring and lateral positions for subsequent transformations in one pot into substituted azoles.

KEYWORDS

1. INTRODUCTION

a								
b								
c								
Known:	a, b, c	a, b, c	a, b	b, c	5	6	7	8
	9	10	11	12	13	14	15	16
Known:	a, b, c	a, b, c	a, b, c	a	a	c		

Scheme 1

Diazole, triazole, and tetrazole *N*-oxides **1a–16a** form a subset of the azole *N*-oxides **1a–c–16a–c**, which has given rise to the majority of the publications dealing with azole *N*-oxides. The azole *N*-oxides have been shown to be activated in a regioselective fashion toward a series of reaction types among which several are unique and by which a great variety of substituents can be introduced both into the heteroaromatic ring and into lateral positions. The facile, multivariate, and selective introduction of substituents in azole *N*-oxides provides them with a great potential for application in synthesis calling for a comprehensive analysis and rationalization of available data in order to describe characteristic features and to establish predictive models for reactivity and regioselectivity.

The present review covers all the literature on diazole, triazole, and tetrazole *N*-oxides until 2011. Previous cumulative reviews are found in (1971MI1, 1990MI1, 1991MI1, 1992H1011). Previous reviews dedicated to specific diazole or triazole *N*-oxides are cited in the individual sections. The aim of the review is to give reference to all published original papers and previous reviews searching for general trends and accentuating common traits. Less emphasis has been put on lists of compounds, exact yields, and experimental details. Reaction conditions and yields are given when unpublished experiments are cited.

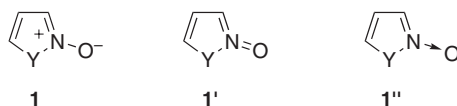
1.1. Structure of azole *N*-oxides

In azole *N*-oxides the bond between the nitrogen and the oxygen atom is formed by an overlap of a lone pair orbital at the N-atom with an empty p-orbital at the oxygen atom. In the literature the N–O bond has been depicted as a dipolar single bond, a double bond, or as an arrow as shown in [Scheme 2](#). The dipolar representation is used here. The double bond representation is usually applied in literature search engines.

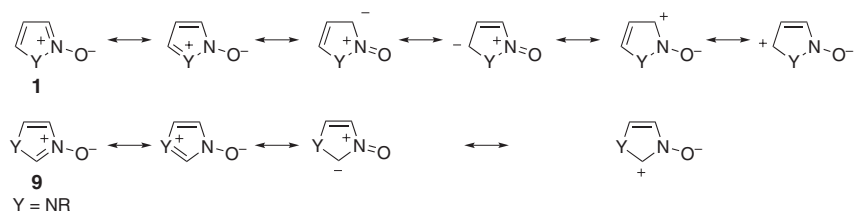
1.1.1. 1,2-Type and 1,3-type azole *N*-oxides

Structurally, the azole *N*-oxides can be divided into two distinct types. In the 1,2-type ([Scheme 1](#), upper row) the oxygen-substituted nitrogen atom and the heteroatom contributing two electrons to the aromatic π -electron sextet of the azole are situated in a 1,2-position. In the 1,3-type these atoms are situated in a 1,3-position ([Scheme 1](#), lower row).

The two types are stabilized by resonance as shown in [Scheme 3](#).



Scheme 2



Scheme 3

1.2. Physical characteristics of azole *N*-oxides

Warning: Azole N-oxides should be handled with care and not be heated neat above room temperature. Azole N-oxides should never be distilled. The N-oxides contain a weak N–O bond. The energy stored in the structures increases with the number of nitrogen atoms. The potential hazard also appears from differential scanning calorimetry and thermogravimetric analysis. At room temperature the azole N-oxides are usually crystalline compounds, being more polar than the parent azoles, and frequently being hygroscopic. The azole N-oxides act as weak bases, being protonated at the N-oxygen atom. Hydroxy-substituted N-oxides are weak acids. The 1,3-type N-oxides are more polar and stronger as bases than the 1,2-type N-oxides.

1.3. Reactions of azole *N*-oxides

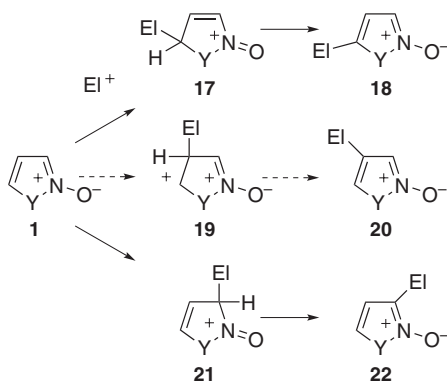
The azole *N*-oxides can react by electrophilic substitution, nucleophilic substitution, proton–metal exchange, or halogen–metal exchange to be followed by addition of an electrophile or by cross-coupling. Halogen substituents or suitable leaving groups in the *N*-oxides can be activated by palladium catalysts to undergo cross-coupling reactions. Certain azole *N*-oxides can act as 1,3-dipoles in cycloaddition reactions. Azole *N*-oxides can be deoxygenated. *N*-Alkylazol-*N*-oxides can be dealkylated to give *N*-hydroxyazoles. Photochemical, electrochemical, and single electron transfer reactions are also known.

1.4. Reactivity of azole *N*-oxides

Due to the polar nature of the N–O bond and due to enhanced charge delocalization the *N*-oxides are more reactive than the parent azoles toward electrophiles, nucleophiles, and bases. The activated positions in a given azole *N*-oxide can usually be pointed out by comparison of the stability of the putative intermediates. There are distinct differences between the 1,2- and 1,3-type *N*-oxides.

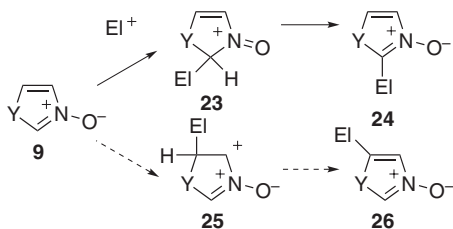
1.4.1. Electrophilic aromatic substitution

In 1,2-type azole *N*-oxides, the 3- and 5-positions are activated toward electrophilic aromatic substitution since attack at these positions gives rise to intermediates **17** and **21** in which only one positive charge remains while attack at C4 would lead to an intermediate **19** with three charges (Scheme 4).



Scheme 4

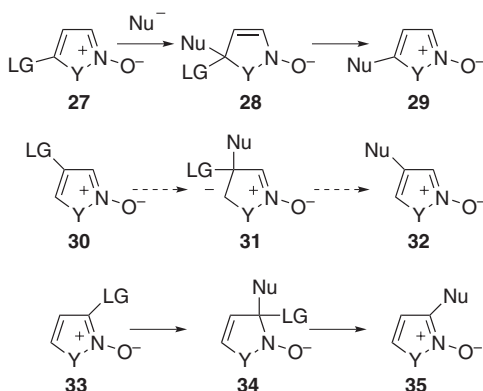
In 1,3-type *N*-oxides, electrophiles preferentially attack at the 2-position since attack at this position renders an intermediate **23** with one positive charge mesomerically delocalized to the pyrrole nitrogen atom. Attack at C4 or C5 would give rise to intermediates like **25** without such mesomeric delocalization of their positive charge (Scheme 5).



Scheme 5

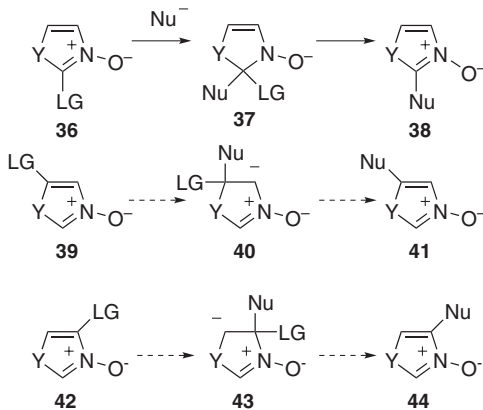
1.4.2. Nucleophilic aromatic substitution

In 1,2-type azole *N*-oxides, leaving groups at the 3- and 5-positions are activated toward nucleophilic aromatic substitution since nucleophilic attack at these positions renders intermediates **28** and **34** in which the positive *N*-oxide nitrogen atom adopts the negative charge brought to the adduct by the nucleophile. Nucleophilic attack at the 4-substituted isomer **30** would give rise to intermediates like **31** in which such stabilization is impossible (Scheme 6).



Scheme 6

In 1,3-type azole *N*-oxides, leaving groups at the 2-position are most activated toward nucleophilic attack since the negative charge brought by the nucleophile is neutralized by the positive nitrogen atom furnishing the monocharged intermediate **37**. In contrast, nucleophilic substitution of a leaving group at C4 or C5 would pass through intermediates **40** and **43** possessing three charged atoms (Scheme 7).



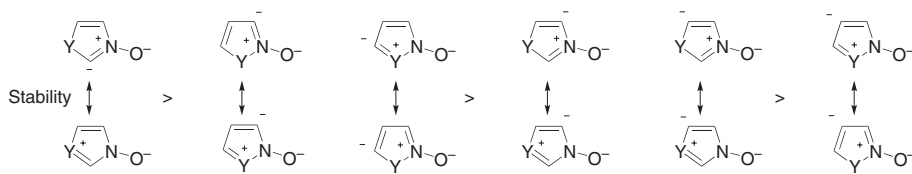
Scheme 7

1.4.3. Deprotonation

1.4.3.1. Abstraction of ring protons

Abstraction of ring protons leads to aromatic anions in which the negative charge is situated in an orbital, which is coplanar with the azole ring, and thus do not overlap with the aromatic π -orbitals. Therefore, the anion

electron pair cannot be delocalized mesomerically but only be stabilized by inductive effects. Since a positive nitrogen atom stabilizes better than a neutral, ring protons of azole *N*-oxides are more acidic than the corresponding protons in the parent azoles. The order of acidity of the aromatic protons in azole *N*-oxides can be predicted and explained as follows: (i) H2 of 1,3-type compounds is the most acidic since the corresponding anion is stabilized by two adjacent positive nitrogen atoms. (ii) H4 of 1,2-type compounds is the least acidic since the corresponding anion is not stabilized by adjacent nitrogen atoms. (iii) Inductive stabilization is transmitted better through a double bond than a single bond, hence H3 and H5 of 1,2-type compounds are predicted to be more acidic than H4 and H5 of 1,3-type compounds (Scheme 8).

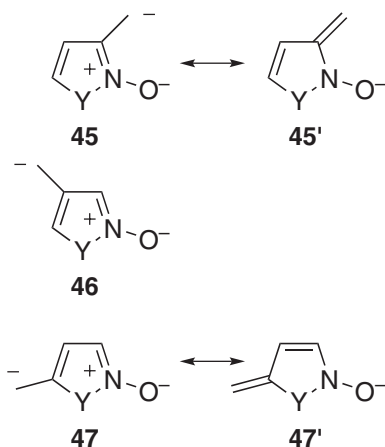


Scheme 8

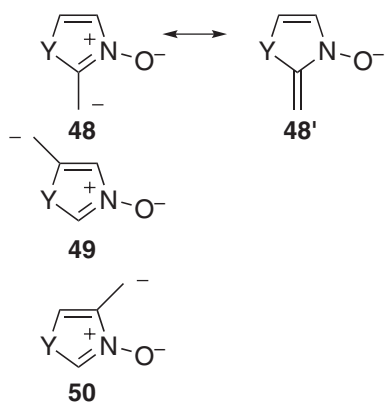
1.4.3.2. Abstraction of Lateral Protons

Abstraction of lateral protons of azole *N*-oxides gives rise to carbanions with the negative charge situated in an orbital, which can overlap with the aromatic π -orbital. Carbanions at the lateral 3- and 5-positions of 1,2-type azole *N*-oxides are stabilized by mesomeric delocalization involving the positively charged *N*-oxide nitrogen atom giving rise to resonance structures 45' and 47' in which a positive and a negative charge counterbalance each other (Scheme 9). Therefore, lateral protons at the 3- and 5-positions of the 1,2-type *N*-oxides are expected to be more acidic than lateral protons at the 4-position as well as the lateral protons in the parent 2-substituted azole since charge counterbalancing is impossible in these carbanions.

For 1,3-type azole *N*-oxides, only abstraction of a lateral proton at the 2-position gives an anion in which charge counterbalancing is possible as apparent from resonance structure 48'. This explains why protons at this position are more acidic than lateral protons at the 4- and 5-positions of the *N*-oxide and more acidic than the lateral protons in the parent 3-substituted azole where charge counterbalancing is impossible (Scheme 10).



Scheme 9



Scheme 10

1.5. Reactions of *N*-alkyloxazolium and *N*-acyloxazolium salts

Both type 1 and type 2 azole *N*-oxides like **1** and **9** upon alkylation, acylation, sulfonylation, phosphorylation, or silylation at the oxygen atom give rise to highly reactive *N*-alkyloxazolium or *N*-acyloxazolium salts, etc., (abbreviated common term: oxyazolium salts) which can undergo a series of exquisite and useful reactions with nucleophiles, bases, and electrophiles. In most cases the whole sequence can be run in one pot. Reactions of this kind are discussed in the sections dealing with the individual azole *N*-oxides. A brief overview, listing the reactions of this kind that have been observed in the azole *N*-oxide series, is presented below. Some of these reaction types have been observed in a few cases only and

further systematic investigations are required for getting insight into the full potential of these reactions.

1.5.1. Reactions leading to introduction of substituents into the azole nucleus

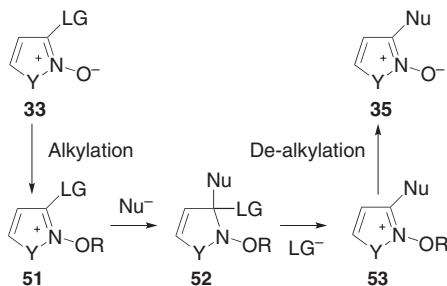
Reactions of *N*-alkyloxyazolum and *N*-acyloxyazolum salts, which lead to the introduction of substituents in the nucleus, are:

- (i) Nucleophilic displacement of a leaving group by an addition–elimination (AE) mechanism
- (ii) Deprotonation followed by addition of an electrophile
- (iii) Nucleophilic addition followed by elimination of HOR (R = Alkyl or Acyl)
- (iv) Allylic nucleophilic displacement of HOR
- (v) Nucleophilic addition followed by elimination of XOR (X = Halogen)

These reaction types are discussed in the following sections with *N*-alkyloxyazolum salts as an example.

1.5.1.1. Nucleophilic displacement of a leaving group by an AE mechanism

Nucleophilic displacement of a leaving group in an alkoxyazolum salt by an AE mechanism is exemplified in [Scheme 11](#).

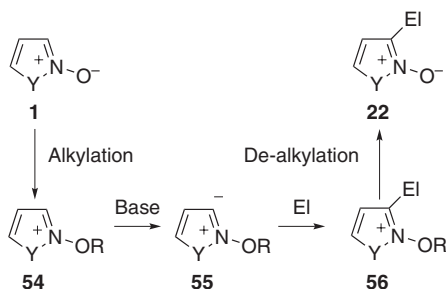


Scheme 11

The order of reactivity of the individual positions in 1,2-type and 1,3-type azole *N*-oxides can be predicted by comparison of the relative stability of the intermediate adducts similar to the analyses presented in [Schemes 6 and 7](#). The total sequence including alkylation and final dealkylation constitutes a nucleophilic displacement of a leaving group in an azole *N*-oxide, which can be run in a telescoped protocol.

1.5.1.2. Deprotonation followed by addition of an electrophile

The acidity of the ring protons of alkyloxyazolum salts is greatly enhanced as compared to the *N*-oxide precursors and these protons can be abstracted using a tertiary amine as the base.

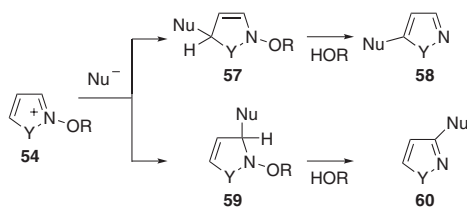


Scheme 12

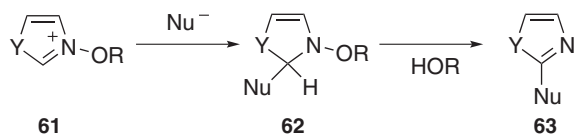
The relative acidity of the activated positions runs parallel with the trends illustrated in [Scheme 8](#). Subsequent trapping of the anions with an electrophile followed by hydrolysis renders substituted *N*-oxides. The full sequence, which encompasses substitution of a heteroaromatic H with an electrophile, can frequently be performed in one pot ([Scheme 12](#)).

1.5.1.3. Nucleophilic addition followed by elimination of ROH

Even weak nucleophiles may add at C3 or C5 of 1,2-type or at C2 of 1,3-type *N*-alkoxyazolium salts. Subsequent elimination of methanol leads to substituted azoles. The net result is replacement of hydrogen at the heteroaromatic nucleus with a nucleophile ([Scheme 13](#) and [14](#)). The entire sequence, including *O*-alkylation of the *N*-oxide, can be performed in one pot.



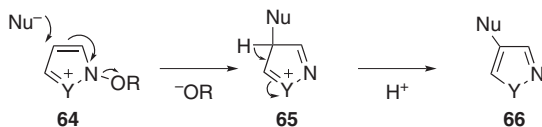
Scheme 13



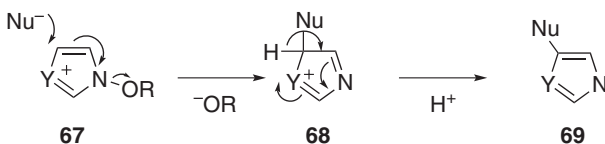
Scheme 14

1.5.1.4. Allylic nucleophilic displacement of ROH

Nucleophiles can be introduced at C4 of 1,2-type **64** (Scheme 15) and at C4 or C5 of 1,3-type *N*-alkoxyazolium salts **67** (Scheme 16) by an allylic displacement of ROH and loss of a proton. This reaction mode competes with the nucleophilic addition followed by elimination of ROH described in Section 1.5.1.3. Consequently all ring protons in 1,2-type and 1,3-type azoles become activated but predictions of product distribution turn difficult. In all cases the net result is replacement of hydrogen at the heteroaromatic nucleus with a nucleophile. The sequence can be performed in one pot.



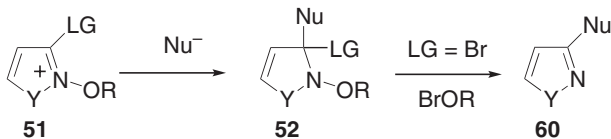
Scheme 15



Scheme 16

1.5.1.5. Nucleophilic addition followed by elimination of LGOR

N-Oxyazolium salts possessing a leaving group (LG) like bromide **51** are activated toward nucleophilic addition to be followed by elimination of alkylhydrobromite (Scheme 17).



Scheme 17

If the nucleophilic addition is the rate limiting step, the order of reactivity of the individual ring positions should run parallel to the order found by nucleophilic addition followed by elimination as discussed in Section 1.5.1.3. With azole *N*-oxide as the starting material, the net result

of the sequence is displacement of a heteroaromatic bound leaving group with a nucleophile with concurrent deoxygenation.

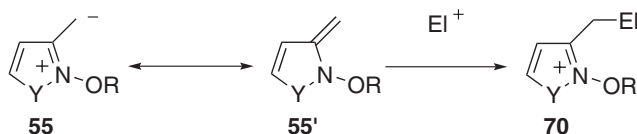
1.5.2. Reactions involving lateral positions of the azole

Reactions involving lateral positions of the azole are:

- (vi) Abstraction of laterally situated protons followed by addition of an electrophile
- (vii) Abstraction of laterally situated protons followed by allylic nucleophilic displacement of HOR

1.5.2.1. Abstraction of laterally situated protons followed by addition of an electrophile

The acidity of lateral protons of alkoxyazolum salts is enhanced as compared to the corresponding protons in azole *N*-oxides. Strongest acidity is predicted for protons located laterally at C3 and C5 in 1,2-type and at C2 of 1,3-type *N*-oxyazolum salts since the corresponding anions through mesomeric delocalization give rise to neutral species. The lateral anion may react with an electrophile as shown in [Scheme 18](#). The overall outcome of the sequence, which can be run in one pot, is replacement of a lateral H with an electrophile.



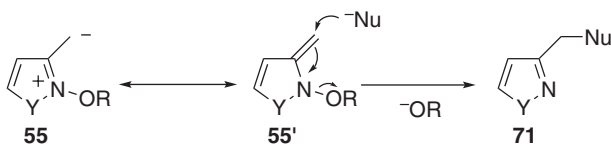
Scheme 18

1.5.2.2. Abstraction of laterally situated protons followed by allylic nucleophilic displacement of ROH

The neutral species formed by abstraction of protons located laterally at C3 and C5 in 1,2-type and at C2 of 1,3-type *N*-oxyazolum salts discussed in [Section 1.5.2.1](#) are prone to react with nucleophiles in an allylic type substitution with elimination of -OR . The reaction is facilitated by the easy cleavage of the weak N-O bond ([Scheme 19](#)). The global reaction is displacement of specific lateral protons with a nucleophile. The entire sequence can be run in one pot.

Regiocontrol in these useful reactions is achieved by a careful selection of alkylation or acylation reagent, base, nucleophile, solvent, and reaction temperature. Reactions of oxyazolum salts are useful for regioselective introduction of substituents both at ring positions and at lateral positions. The alkylation or acylation followed by reaction with nucleophile, base, or

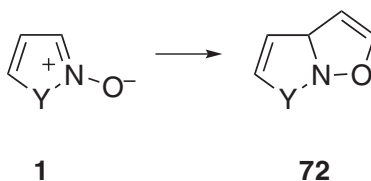
electrophile, which often can be run in one pot, opens access to a number of substituted azoles.



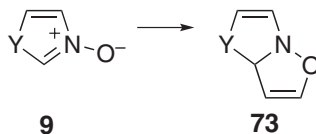
Scheme 19

1.6. 1,3-Dipolar cycloaddition

The azole *N*-oxides contain an embedded nitron type 1,3-dipole. 1,3-Dipolar cycloadditions for certain azole *N*-oxides have been described. The 1,2-type *N*-oxide **1** furnishes bicyclic **72**, while the 1,3-type *N*-oxide **9** gives bicyclic **73** (Schemes 20 and 21).



Scheme 20



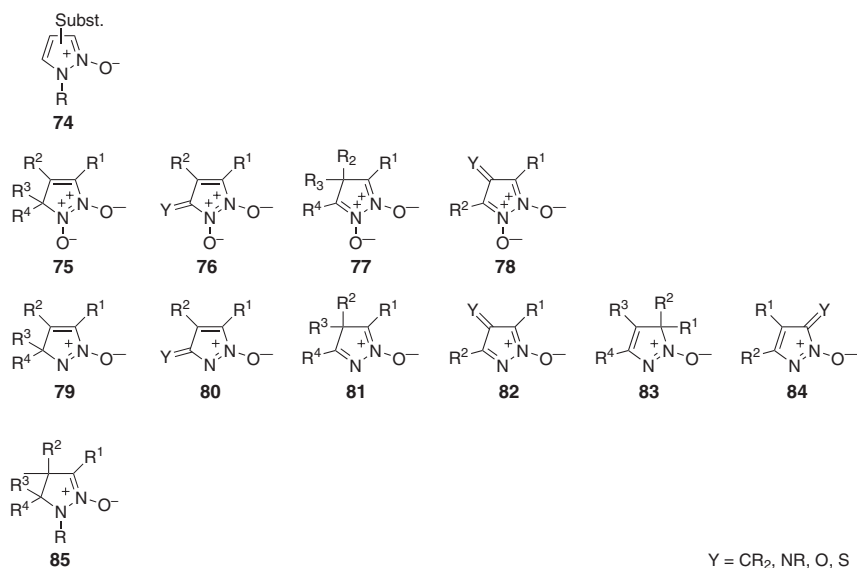
Scheme 21

In the following sections the individual *N*-oxides will be discussed.

2. PYRAZOLE *N*-OXIDES

The aromatic 2-substituted pyrazole 1-oxides **74** are derived from pyrazoles **89** by appending an oxygen atom to the pyridine type ring nitrogen atom of the pyrazole nucleus. The second nitrogen atom of the pyrazole ring can be attached to an alkyl, aryl, hydroxy, or amino group.

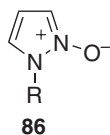
Section 2.1 is devoted to the aromatic pyrazole 1-oxides. Further structures derived from pyrazole and embedding an N–O bond are the nonaromatic 1,2-dioxides also called diazapentalene 4,4'-dioxides **75–78**, the pyrazoline 1-oxides also called diazapentalene 4-oxides **79–84**, and the 2-substituted pyrazoline 1-oxides represented in Scheme 22 by the parent structure **85**. Structures **77**, **78**, **79**, **81**, and **82** are known and are discussed in Section 2.2 but since the present review deals with aromatic *N*-oxides the nonaromatic *N*-oxides will only be discussed when their chemistry relates them to the aromatic pyrazole *N*-oxides.



Scheme 22

2.1. 2-Substituted pyrazole 1-oxides

See Scheme 23.



R = Alkyl, Aryl, OR or NR₂

Scheme 23

2.1.1. Molecular structure

The parent structure **87** constitutes a tautomeric form of 1-hydroxypyrazole **88** (Scheme 24). 1-Hydroxypyrazoles **88** make up a self-contained group of compounds, which will not be covered in the present review.



Scheme 24

The first pyrazole 1-oxide **74** was isolated in 1957 during an investigation of the degradation of a pyrazole when treated with H_2O_2 in HOAc (1957JA3175). Until 2011, about 215 2-substituted pyrazole 1-oxides **74** with a variety of substituents at C3, C4, and C5 have been reported. A review appeared in 1989 (1989H1615). Examples of the use of pyrazole 1-oxides in synthesis have been discussed (1988BSB573).

The resonance structures of the 2-substituted pyrazole 1-oxides **74** are discussed in Section 1.1.1. According to IUPAC nomenclature, structure **86** is a 1-substituted 1*H*-pyrazole 2-oxide since the rules dictate that when $\text{R}=\text{H}$ the indicated hydrogen position takes numbering precedence. Other names found in the literature are 1-substituted pyrazole 2-oxides or 1-substituted 2-oxo-1*H*-pyrazoles. Frequently the numbering is switched to give the names 2-substituted 2*H*-pyrazole 1-oxide, 2-substituted pyrazole 1-oxides, or 2-substituted 1-oxo-2*H*-pyrazoles. In the present review the most commonly used naming, which is accepted by IUPAC, *Chem. Abstr. Autonom.*, is used calling structure **86** a 2-substituted pyrazole 1-oxide. Consistently, structure **86** ($\text{R}=\text{OH}$, OAlk, or NH_2) is named 2-hydroxy, 2-alkoxy-, or 2-aminopyrazole 1-oxide, respectively.

2.1.2. Physical properties

The 2-alkyl- or aryl-substituted pyrazole 1-oxides are usually stable, crystalline, semipolar, and slightly hygroscopic compounds. 2-Substituted pyrazole 1-oxides are weak bases, being subject to protonation at the negatively charged oxygen atom. 2-Hydroxypyrazole 1-oxides **74** ($\text{R}=\text{OH}$) are acids, no pK_a values seem to have been reported.

2.1.3. Theoretical calculations

Calculations with neglect of differential overlap (INDO calculations) have been performed on radical ions derived from the nonaromatic diazapentalene 4,4'-dioxides (1979JOC3211).

2.1.4. Molecular spectroscopy

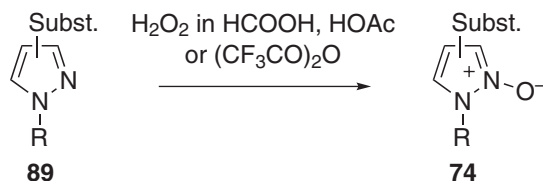
UV and IR data are only available for 2-hydroxypyrazole 1-oxides **74** ($R=OH$) (1979JOC3211). H and C NMR have been used routinely for characterization. A more systematic NMR investigation revealed that in 2-substituted pyrazole 1-oxides **74** $\delta_{H5} > \delta_{H3} > \delta_{H4}$, and $J_{H3,H4}$ is larger than $J_{H4,H5}$. δ_{C3} and δ_{C5} are similar but larger than δ_{C4} . All two- and three-bond C–H couplings are 5.0–7.5 Hz and C3 couples with lateral protons situated at N2 (1992ACSA972). Only standard mass spectra of pyrazole 1-oxides have been published. The X-ray spectrum of a 2-acylaminopyrazole 1-oxide has been reported (2006SL2731).

2.1.5 Preparation of 2-substituted pyrazole 1-oxides

2-Substituted pyrazole 1-oxides **74** can be prepared by *N*-oxidation of 1-substituted pyrazoles **89**, by *N*-alkylation of 1-hydroxypyrazoles **90**, or by cyclization of 1,3-oximinines, conjugated oximenamines, or conjugated 1,3-nitrosoimines.

2.1.5.1 *N*-Oxidation of pyrazoles

N-Oxidation of pyrazoles **89** into 2-substituted pyrazole 1-oxides **74** has been effected with hydrogen peroxide (1992ACSA972), or hydrogen peroxide in combination with formic acid (1992ACSA972, 1993JCS(P1)625), acetic acid (1957JA3175, 1992ACSA972), acetic anhydride (1992ACSA972), trifluoroacetic acid (TFA) (1992ACSA972), or trifluoroacetic anhydride (1970JHC455) (Scheme 25). In addition, dichloropermaleic anhydride and 3-chloroperoxybenzoic acid have been used (1992ACSA972). Yields were invariably low since the pyrazole 1-oxides are deoxygenated by the peracids (1992ACSA972). Therefore, procedures and conditions are crucial. Mainly 1-alkyl-pyrazoles have been subjected to *N*-oxidation and yields tend to decrease when the starting material possesses electron-withdrawing substituents (1992ACSA972).

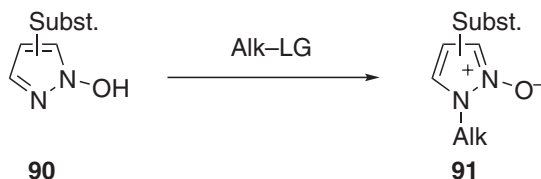


Scheme 25

2.1.5.2 *N*-Alkylation of 1-hydroxypyrazoles

N-Alkylation of 1-hydroxypyrazoles **90** produces 2-substituted pyrazole 1-oxides **91** (Scheme 26). Competing *O*-alkylation of the

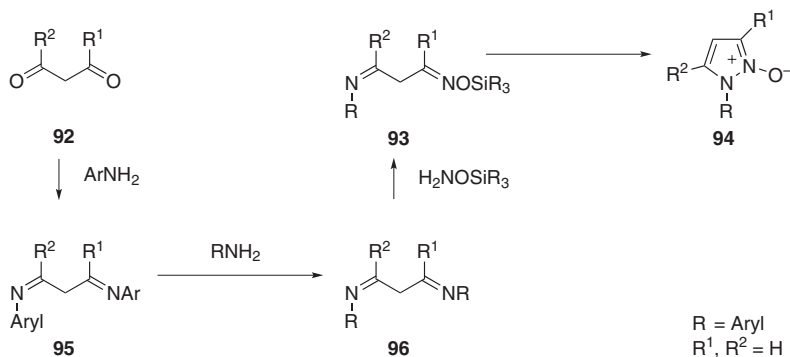
1-hydroxypyrazoles is suppressed by omitting addition of base during the alkylation (1996ACSA549, 2001S1053, 2002JOC3904, 2007USP7226930). Alkylbromides serve best and yields are high, except for the 2-*iso*-propylpyrazole 1-oxide. When the alkyl group is a benzyl or 4-methoxybenzyl the alkylating species can be generated in situ from the corresponding alcohol and either TFA or a strong acidic ion exchanger (2001JOC8654).



Scheme 26

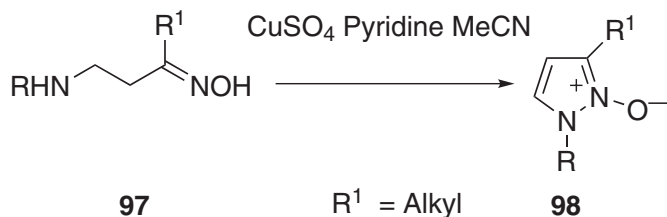
2.1.5.3. Cyclization

2-Alkyl- or aryl-substituted pyrazole 1-oxides **94** can be obtained in acceptable yields by oxidative cyclization of *O*-silylated 3-oximimines like 1-*tert*-butyldimethylsilyloxy-4-methylamino-1-azabuta-1,3-diene **93** using copper(II) sulfate as the oxidant and pyridine and acetonitrile as the solvent. The oximimines are prepared from 1,3-dicarbonyl compounds **92** in a one-pot process. The method also gives access to 2-alkyl and arylpyrazole 1-oxides **94** $R=H$ devoid of substituents at the ring carbon atoms (**94**; $R^1=R^2=H$) (1995JCS(P1)2773) (Scheme 27).



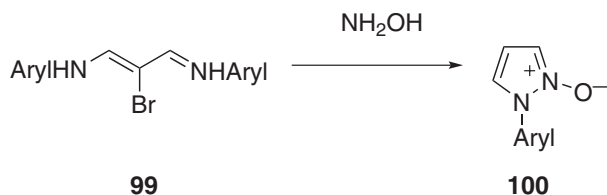
Scheme 27

Treatment of 1-benzylamino-5-methylhexan-3-one oxime **97** with copper(II) sulfate in pyridine acetonitrile yields 2,5-disubstituted pyrazole 1-oxides **98** (1994JHC281) (Scheme 28).



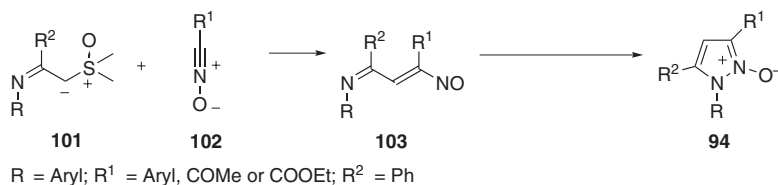
Scheme 28

Reaction of 3-bromo-1,5-di-(4-tolyl)-1,5-diazapenta-1,3-diene **99** with hydroxyamine affords 2-substituted pyrazole 1-oxides **100** (1995JCS(P1)2773) (Scheme 29).



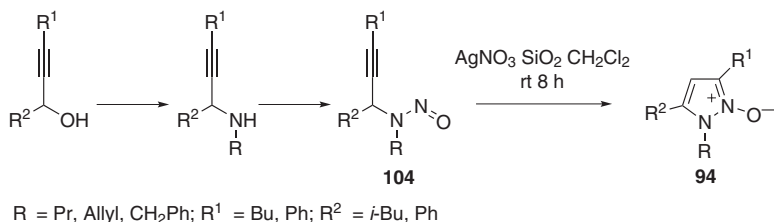
Scheme 29

N-Aryloxosulfonium ylides **101** react with nitriloxides to give 2-substituted pyrazole 1-oxides **94**. Conjugated nitrosoimines **103** have been suggested as intermediates (1977JCS(P1)1196) (Scheme 30).



Scheme 30

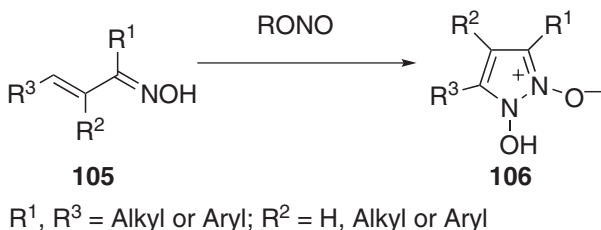
5-*endo*-Dig cyclization of readily accessible *N*-nitroso derivatives of homopropargylic amines **104**, catalyzed by silver nitrate on silica gel renders 2-substituted pyrazole 1-oxides **94**. The cyclization occurs in dichloromethane or chloroform at ambient temperature. Yields of 2-substituted pyrazole 1-oxides **94** are essentially quantitative (2008SL2188) (Scheme 31).



Scheme 31

2.1.6. Preparation of 2-hydroxypyrazole 1-oxides

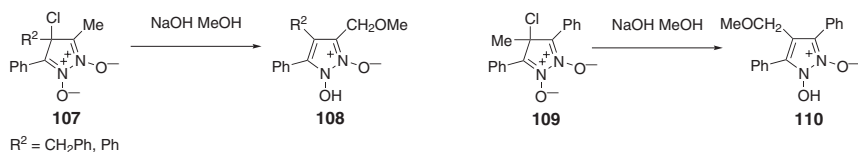
2-Hydroxypyrazole 1-oxides **106** can be prepared by treatment of α,β -unsaturated β -oximes **105** with nitrosation agents like nitrous acid (HONO) and alkyl nitrites in the presence of cobalt(II) (1991IJC(B)749) or copper(II) ions (1994JHC1481). The 2-hydroxypyrazole 1-oxide is trapped by chelation with the metal ions to give a slightly soluble chelate, which separates and thus is protected against further transformation to diazapentalene 4,4'-dioxide (Scheme 32).



Scheme 32

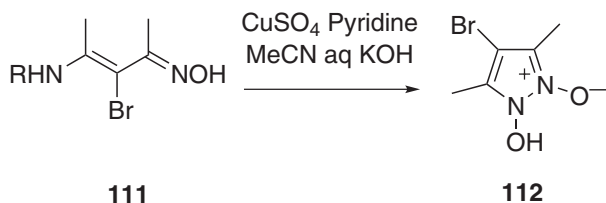
In the absence of transition metal ions, the initially formed 2-hydroxypyrazole 1-oxide **106** reacts further with HONO to give diazapentalene 4,4'-dioxides **75**. These can, however, be converted back to the

2-hydroxypyrazole 1-oxides **108** and **110** by chlorination followed by treatment with sodium hydroxide in methanol (1977JOC177) (Scheme 33).



Scheme 33

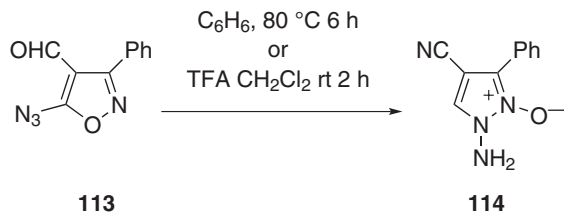
3-Bromo-3-penten-2-one oxime **111** is converted into 2-hydroxypyrazole 1-oxides **112**, when treated first with copper sulfate using pyridine as the solvent and then with butyl nitrite and aq KOH (1994JHC281, 1994JHC1487) (Scheme 34).



Scheme 34

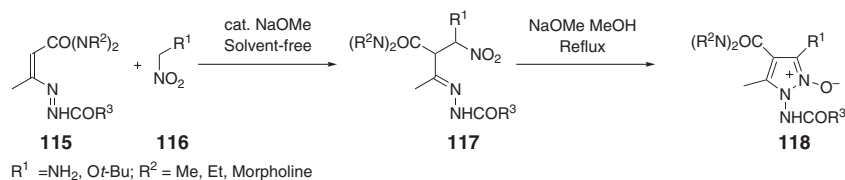
2.1.7. Preparation of 2-aminopyrazole 1-oxides

2-Aminopyrazole 1-oxide **114** is one of the products formed by heating a solution of 5-azidoisoxazole **113** in benzene to reflux or by keeping a solution of **113** and TFA in CH_2Cl_2 at room temperature. A mechanism encompassing ring opening, rearrangement, and ring closure has been proposed. IR and H NMR data were recorded (1995JHC1189) (Scheme 35).



Scheme 35

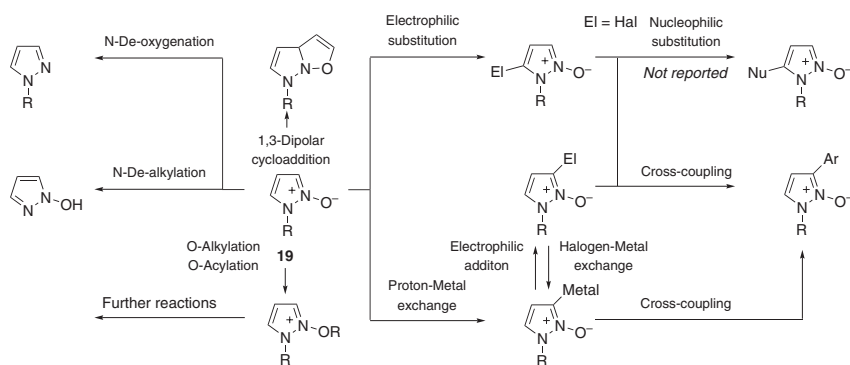
Acylated 2-aminopyrazole 1-oxides **118** were prepared in excellent yields by heating β -nitroacylhydrazones **117** to reflux with sodium methoxide in methanol (2006SL2731). The nitroacylhydrazones **117** were synthesized by treatment of 2-diaza-1,3-butadienes **115** with nitroalkanes **116** and catalytic amounts of sodium methoxide under solvent-free conditions at room temperature. The nitroalkane anion adds to the hydrazone **115** in a conjugated fashion producing diastereomeric mixtures of nitroacylhydrazone **117** in high yields (Scheme 36).



Scheme 36

2.1.8. Reactions of 2-substituted pyrazole 1-oxides

An overview of the reactions of 2-substituted pyrazole 1-oxides **86** is shown in Scheme 37. 2-Substituted pyrazole 1-oxides **86** have been reported to undergo electrophilic aromatic substitution and be subject to debromination, proton–metal exchange, and halogen–metal exchange followed by electrophilic addition, transmetalation, or cross-coupling. In addition, pyrazole 1-oxides **86** react with *O*-alkylation, acylation, silylation, or phosphorylation, which can be followed by reaction with a nucleophile. Furthermore, 2-substituted pyrazole 1-oxides **86** can undergo deoxygenation, dealkylation, and rearrangement.



Scheme 37

Halogen at ring positions of pyrazole 1-oxides can be activated by palladium toward cross-coupling reactions. However, no examples of nucleophilic displacement of such halogen have been reported.

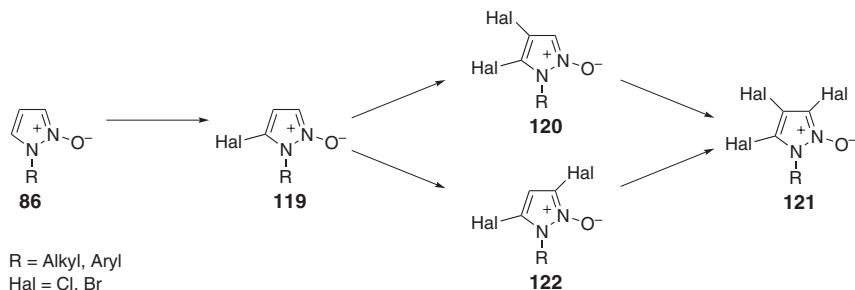
2.1.8.1. Electrophilic aromatic substitution

Bromination of 2-alkyl-substituted pyrazole 1-oxides **86** (R=Alk) has been performed using bromine (1992ACSA972, 2001JOC8654) or *N*-bromosuccinimide (NBS) in acetonitrile (2002T7635, 2002JOC3904). The first bromine enters the 3-position to give **119**, which can be obtained in high yields. Under similar conditions the parent pyrazoles are first attacked at the 4-position. In competition experiments 1-benzyl-pyrazole **89** (R=CH₂Ph) and the derived 1-oxide **86** (R=CH₂Ph) reacted at the same rate with bromine producing the 4- and the 3-bromoderivative, respectively (1992ACSA972). This complementary regioselectivity is most useful by regioselective introduction of substituents in pyrazoles (Scheme 38).

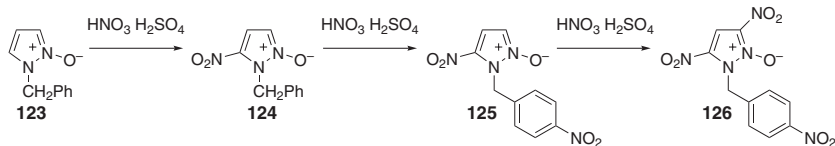
Further bromination of 3-bromo-substituted pyrazole 1-oxide **119** proceeds readily but with low regio and monoselectivity producing a mixture of 3,4-, 3,5-, and 3,4,5-halogen-substituted pyrazole 1-oxides **120**, **122**, and **121** (1992ACSA972). Exhaustive bromination gives tribromo-substituted pyrazole 1-oxide **121** (Hal=Br) in high yields (1992ACSA972). 4-Bromo-substituted pyrazole 1-oxide **129** was brominated regioselectively at C3 (1992ACSA972). The bromination of 5-aryl-substituted pyrazole 1-oxide **86** was neither regio nor monoselective but exhaustive bromination afforded the 3,4-dibromo compound **120** (2002JOC3904).

Chlorination of 2-substituted pyrazole 1-oxides **86** using chlorine in tetrachloromethane (1992ACSA972) and sulfonyl chloride in dichloromethane follows the same trend (1992ACSA972).

The regioselectivity by electrophilic aromatic substitution is conserved when switching to acidic reaction conditions. Thus 2-substituted pyrazole 1-oxide **123** was nitrated regio and monoselectively at C3 by HNO₃–H₂SO₄ to give **124** in quantitative yield (1992ACSA972). Further nitration takes place first at the benzyl 4-position, and then at the pyrazole 5-position (Scheme 39).



Scheme 38

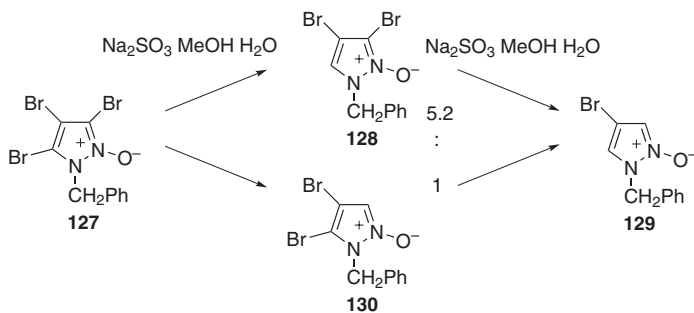


Scheme 39

Nitration of 3-chloropyrazole 1-oxide **119** ($\text{R}=\text{CH}_2\text{Ph}$, $\text{Hal}=\text{Cl}$) gave the 4-nitro derivative, which was unstable, rearranging to 1-benzyl-3-hydroxy-4-nitro-5-chloropyrazole apparently *via* an intermolecular reaction (1992ACSA972).

2.1.8.2. Debromination

Bromine at C3 and C5 of 2-substituted pyrazole 1-oxides is readily removed by treatment with aqueous-methanolic Na_2SO_3 without removing the *N*-oxygen atom (1992ACSA972, 2002T7635). The debromination occurs stepwise but with moderate regioselectivity. Thus 2-benzyl 3,4,5-tribromopyrazole 1-oxide **127** produces a 5.2:1 mixture of the 4,5- and the 3,4-dibromo compounds **128** and **130**, both of which are debrominated into the 4-bromo compound **129** (1992ACSA972) (Scheme 40).



Scheme 40

Debromination has been achieved by metallation followed by protonation (2002JOC3904). Finally, debromination has been effected using PCl_3 , which in addition caused deoxygenation. Thus 2-benzyl-3,

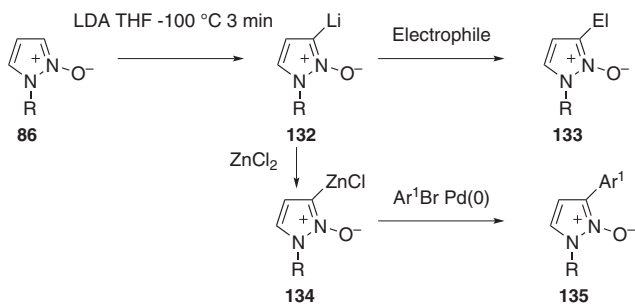
4-dibromopyrazole 1-oxide **130** afforded 93% of 1-benzyl-4-bromopyrazole **131** (1992ACSA972) (Scheme 41).



Scheme 41

2.1.8.3. Proton–metal exchange

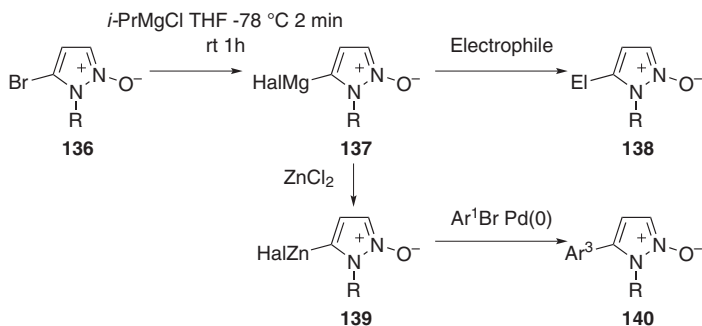
Protons at positions 3 and 5 of pyrazole 1-oxides **86** are more acidic than the corresponding protons in the parent pyrazoles since the anionic negative charge is stabilized inductively by the adjacent positive nitrogen atoms. The activated protons can be abstracted by treatment with strong bases. Deprotonation using KOD in D₂O revealed that in 2-benzyl-pyrazole 1-oxide **86** (R=CH₂Ph) H5 was exchanged 1.07 times faster than H3 (1992ACSA1096). The first screening of bases showed that sodium hydride in CH₂Cl₂ at 70°C worked better than NaOH in H₂O–toluene, lithium diisopropylamide (LDA) in tetrahydrofuran (THF), lithium tetramethylpiperidide (LiTMP) in THF, KO^{*t*}-Bu in *t*-BuOH, or KNH₂ in liquid ammonia. However, substantial decomposition took place in all cases (1992ACSA1096). Later it was demonstrated that H5 is subject to smooth proton–magnesium exchange at –78°C using *i*-PrMgCl in THF as the base. Proton–lithium exchange using BuLi, LDA, or LiTMP in THF as the base gave the best results at –100°C (2002JOC3904). Protons at position 4 of 2-substituted pyrazole 1-oxides **86** are not activated since the anionic negative charge is distant from the positively charged nitrogen atoms and their abstraction has not been reported (Scheme 42).



Scheme 42

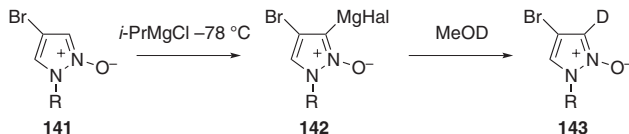
2.1.8.4. Halogen–metal exchange

Bromine–metal exchange has been achieved at all ring positions of 2-substituted pyrazole 1-oxides **86**. Bromine at C3 was exchanged with magnesium using *i*-PrMgCl in THF (2001JOC8654, 2002JCS(P1)428, 2002JOC3904, 2002T7635). The 3-magnesiated species **137** was stable at low temperatures while the corresponding 3-lithio compound, generated by metallation with *n*-BuLi in THF, was thermally unstable (Scheme 43).



Scheme 43

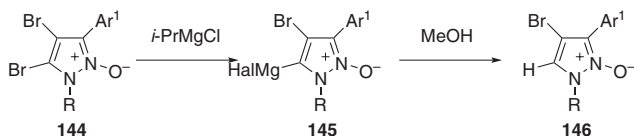
Bromine at the 4-position was replaced with magnesium using *i*-PrMgCl in THF (2002JOC3904). However, bromine–magnesium exchange at C4 is slower than proton–magnesium exchange at C5 since metallation of the 4-bromopyrazole 1-oxide **141** followed by quenching with MeOD furnished the 5-deuterated derivative **143** (Scheme 44).



Scheme 44

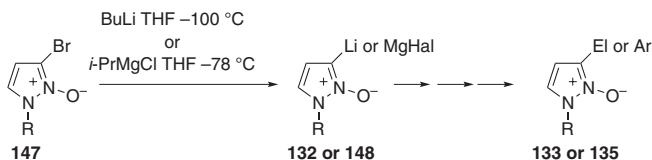
Exchange of bromine at C4 with lithiation was abandoned due to the instability of the 4-lithio species (2002JOC3904).

Magnesiumation of 3,4-dibromopyrazole 1-oxide **144** proceeded regioselectively at the 3-position since subsequent quenching with methanol gave rise to the 4-bromo compound **146** (2002JOC3904) (Scheme 45).



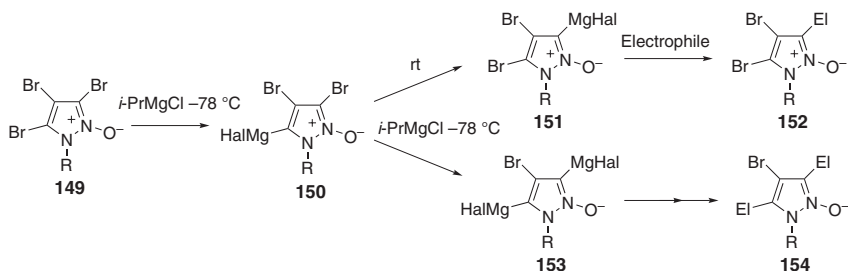
Scheme 45

Bromine at C5 was exchanged with lithium using BuLi in THF at -100°C or with magnesium using *iso*-propylmagnesium chloride in THF at -78°C (2002JOC3904) (Scheme 46).



Scheme 46

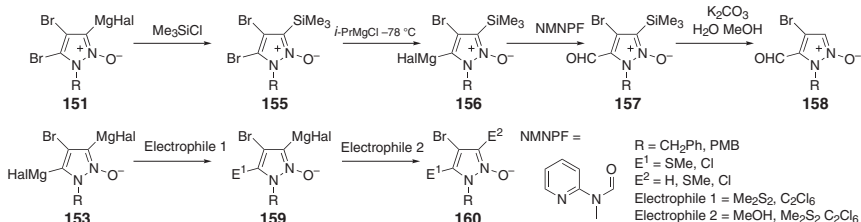
Magnesiumation of 3,4,5-dibromopyrazole 1-oxide **149** at -78°C proceeded regioselectively at C3 to give slightly soluble **150**, which upon heating to room temperature rearranged to the readily soluble C5 magnesiated isomer **151**. When using two equivalents of *i*-PrMgCl, the manipulable crystalline 3,5-dimagnesiated pyrazole 1-oxide **153** was formed and could be trapped with one or two electrophilic reagents as shown in Scheme 47 (2002T7635).



Scheme 47

2.1.8.5. Metallation followed by electrophilic addition

C3, C4, and C5 metallated 2-substituted pyrazole 1-oxides, generated by proton–metal or halogen–metal exchange, add to electrophiles. Thus the anions have been protonated (2002T7635), deuterated (2002T7635), methylated (1992ACSA1096), alkylated (1992ACSA1096), hydroxybenzylated (2002JOC3904), acylated (2002T7635), (2002JCS(PI)428), halogenated (1992ACSA1096, 2002T7635), methylthiolated (1992ACSA1096, 2002T7635), or silylated (1993JCS(PI)625, 2002T7635). In this way a great number of substituents can be introduced regioselectively in the pyrazole nucleus. The regioselectivity can be controlled by combining metallation with introduction of temporary protection groups or by stepwise introduction of the electrophiles as illustrated in Scheme 48 (2002T7635). Such sequences can often be carried out in one pot.



Scheme 48

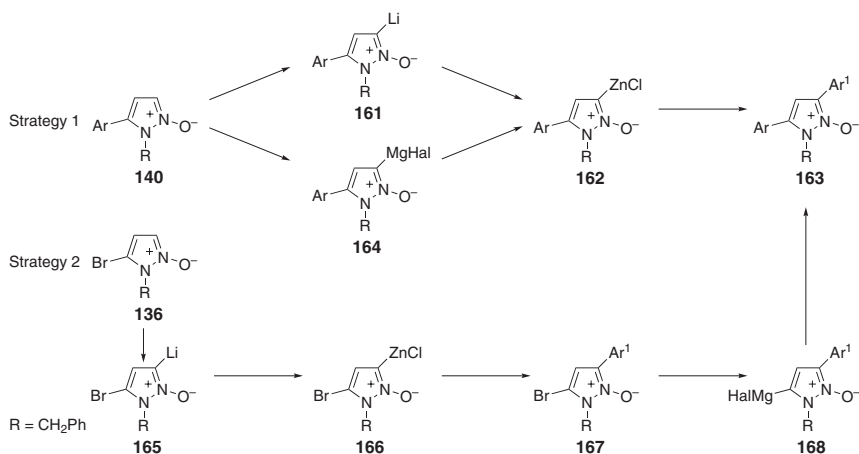
2.1.8.6. Transmetallation

The lithiated and magnesiated 2-substituted pyrazole 1-oxides undergo metal–metal exchange by treatment with zinc chloride (2001JOC8654, 2002JOC3904) (see Scheme 43, 49 and 50).

2.1.8.7. Cross-coupling with pyrazole donors

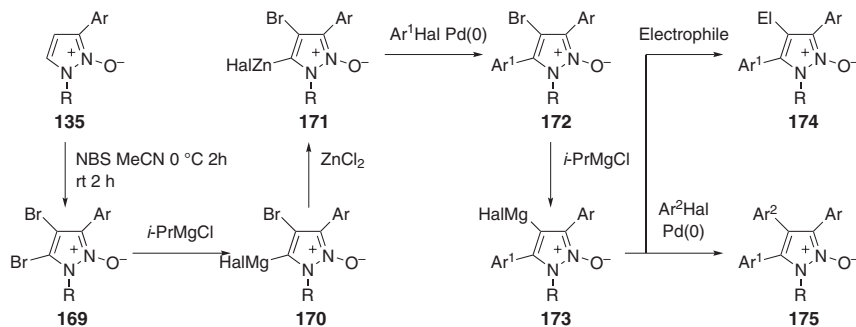
C3, C4, and C5 zincated 2-substituted pyrazole 1-oxides react with aryl and heteroaryl halides and palladium catalysis under Negishi–Miyaura conditions to give cross-coupling products in high yields (2002T7635). Lately, also Sonogashira reactions have been performed successfully (2010UP3). In this way a great number of aryl and heteroaryl groups can be introduced regioselectively into the pyrazole nucleus. Sequences of proton–metal exchange, halogen–metal exchange, addition of an electrophile, or transmetallation followed by palladium-catalyzed cross-coupling give access to a broad range of functionalized pyrazoles. Two strategies for the

synthesis of 3,5-disubstituted pyrazole 1-oxides **163** have been described (2002JOC3904) (Scheme 49).



Scheme 49

The synthesis of 3,4,5-trisubstituted pyrazoles **174** and **175** was initiated by metallation followed by arylation at the 5-position, as described above, to give **135**. Subsequent dibromination using NBS in MeCN gave **169**, which was magnesiated regioselectively at the 3-position. Magnesium–zinc exchange followed by palladium-catalyzed cross-coupling produced the 4-bromo-3,5-diarylated pyrazole **172**, which then was subject to magnesiation, magnesium–zinc exchange, and palladium-catalyzed cross-coupling (2002JOC3904) (Scheme 50).



Scheme 50

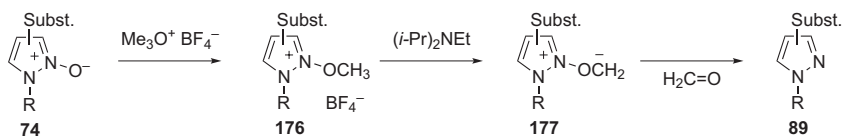
In these sequences it is recommended that the most sensitive aryl group be introduced in the last step. Nitro-, formyl-, and cyanoaryl groups could be introduced.

2.1.8.8. Nucleophilic substitution

Although leaving groups at C3 and C5 of pyrazole 1-oxides **74** are predicted to be activated toward nucleophilic substitution (Section 1.5.1.1), such displacement reactions have not yet been reported. However, bromo and chloro substituents can be activated by palladium catalysis. The resulting pyrazolyl palladium halogenide reacts smoothly with arylboronates under Suzuki conditions (2001JOC8654, 2002T7635, 2002JOC3904) or arylzinc halogenides under Negishi conditions providing cross-coupling products in good yields. The 3-, 4- (2002T7635), and 5-halogeno 2-substituted pyrazole 1-oxides undergo this reaction and protocols for stepwise regioselective arylation at the 3-, 4-, and 5-position of 2-substituted pyrazole 1-oxides **86** have been developed extending the flexibility when selecting a sequence for the preparation of substituted pyrazole 1-oxides.

2.1.8.9. O-Alkylation

The 2-substituted pyrazole 1-oxides **74** were alkylated at the oxygen by trimethyloxonium tetrafluoroborate using liquid sulfur dioxide as the solvent or by methyl triflate generated in situ from iodomethane and silver triflate (1992JCS(P1)2555). The hygroscopic 2-substituted 1-methoxypyrazolium salt **176**, formed in high yield, could be deformylated upon treatment with diisopropylethylamine precluding the anion **177**. The corresponding trideuteriomethyloxypyrazolium salt produced 5-monodeuteriomethyl-pyrazole. This indicates that the initially formed C5 anion rearranges to the thermodynamically more stable anion **177** through a six-membered cyclic transition state. In order to exclude abstraction of OCH-protons, a prerequisite for deformylation, O-tritylation, and O-4-nitrophenylation was attempted but was found inefficient (Scheme 51).

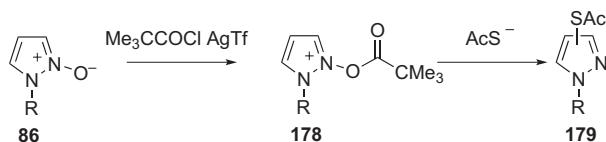


Scheme 51

2.1.8.10. O-Acylation

Except for the brief statement that 2-methyl-3-nitropyrazole 1-oxide reacts with acetyl chloride to give 1-methyl-5-chloro-4-nitropyrazole apparently no reports on the reaction between 2-substituted pyrazole 1-oxides **86** and acetylchloride or acetic anhydride exist (1977JCS(P1)672).

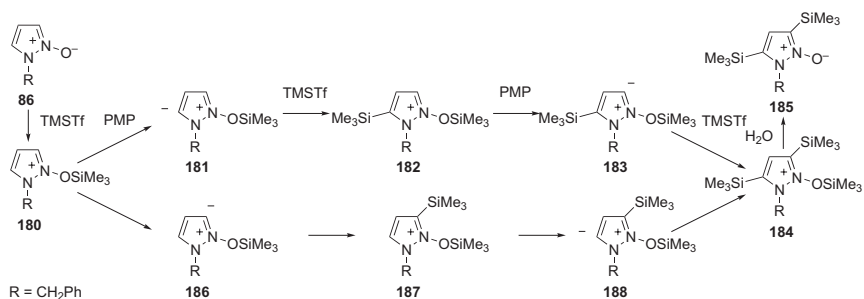
Pivaloylation of **86** using pivaloyl chloride and silver triflate afforded the unstable 1-pivaloyloxypyrazolium salt **178** in quantitative yield. When the salt was treated with potassium thioacetate only products resulting from attack at the ring positions were detected. No details are given (1992JCS(P1)2555) (Scheme 52).



Scheme 52

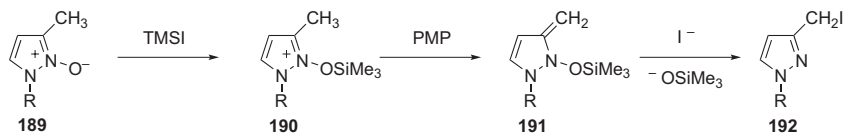
2.1.8.11. O-Silylation

O-Silylation of 2-substituted pyrazole 1-oxides **86** has been effected using iodotrimethylsilane, trimethylsilyl (TMS) triflate, or *t*-butyldimethylsilyl triflate producing moisture sensitive, unstable silyloxypyrazolium salts **180** in good yields. In these salts, the protons at the 3- and 5-position are highly activated since the anion formed by the proton abstraction is inductively stabilized by an adjacent positive nitrogen atom. The silyloxypyrazolium salts **180** were not isolated but deprotonated in situ using 1,2,2,6,6-pentamethylpiperidine (PMP) as the base. After hydrolytic workup the 3,5-disilylated pyrazole 1-oxide **185** was isolated in 74% yield resulting from sequential deprotonation of H3 and H5, followed by silylation of the anions and final hydrolytic desilylation (1992JCS(P1)2555) (Scheme 53).



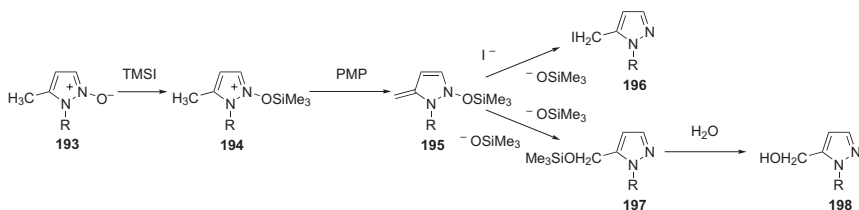
Scheme 53

O-Silylation of 2-substituted pyrazole 1-oxides also activates lateral protons at the 3- and 5-positions. Thus the 5-methyl derivative **189** upon silylation furnishes the silyloxypyrazolium ion **190**, which is deprotonated at the methyl group by PMP giving rise to a neutral species **191**. Next, the iodide ion replaces the trimethylsilyloxy group of the intermediate **191** in an allylic type substitution to give iodomethyl-substituted pyrazole **192**. The whole sequence **189** → **192** takes place in one pot (1992JCS(P1)2555) (Scheme 54).



Scheme 54

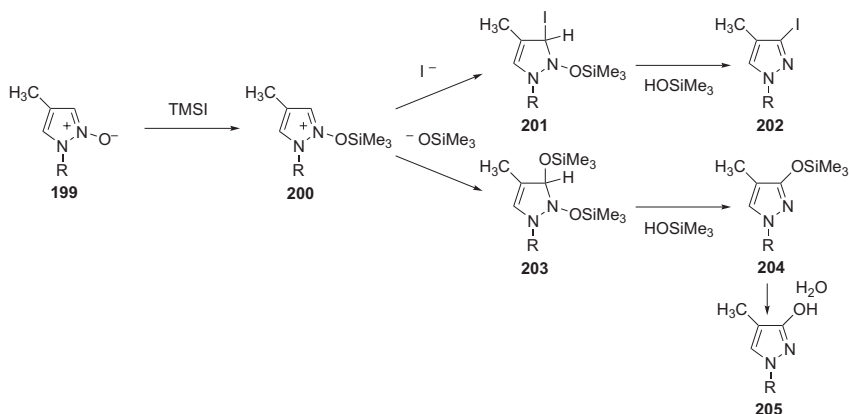
The isomeric 2-benzyl-3-methyl-pyrazole 1-oxide **193** reacts similarly to give the 3-iodomethyl-pyrazole **196**. In this case, the 3-trimethylsilyloxy-methyl compound **197** is formed as a by-product. Most likely, the silyloxymethyl compound **197** arises when the liberated silyloxyanion acts as a nucleophile replacing the silyloxy group in a regenerative fashion. The silyloxy compound **197** is readily hydrolyzed to hydroxymethyl-pyrazole **198**. The 3-methyl-pyrazole 1-oxide **193** reacts five times faster than the 5-methyl isomer **189** as shown by a competition experiment (1992JCS(P1)2555). The iodomethyl-pyrazoles **192** and **196** are versatile starting materials for further transformations in the pyrazole side chain (Scheme 55).



Scheme 55

The lateral protons of the isomeric 4-methyl-pyrazole 1-oxide **199** are not activated, since lateral deprotonation does not give rise to a neutral species. Under similar conditions the 4-methyl isomer **199** reacts at the 3-position producing 1-benzyl-3-iodo-4-methyl-pyrazole **202** and

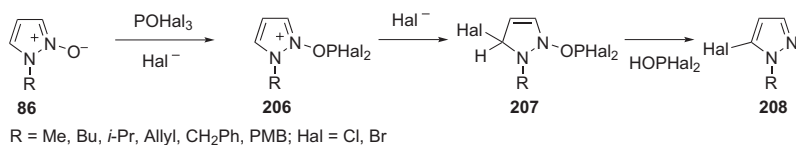
1-benzyl-3-hydroxy-4-methyl-pyrazole **205**. Most likely, deprotonation at the 3-position is followed by nucleophilic addition of iodide ion and elimination of trimethylsilyloxy anion furnishing the 5-iodo-4-methyl-pyrazole **202**. The liberated silyloxyanion competes with the iodide ion reacting in an AE sequence liberating the silyloxyanion in a regenerative fashion. The silyloxy pyrazole **204** formed is hydrolyzed during the aqueous workup producing the hydroxypyrazole **205** (Scheme 56).



Scheme 56

2.1.8.12. O-Phosphorylation

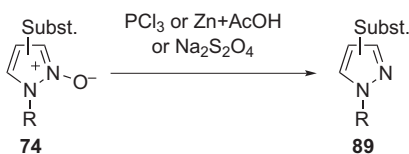
2-Substituted pyrazole 1-oxides **86** react with $POCl_3$ or $POBr_3$ in $CHCl_3$ solution producing 1-substituted 5-chloro or 5-bromopyrazoles **208** in high yields (2001S1053, 2007USP7226930). Most likely, initial O-phosphorylation is followed by nucleophilic addition of the halogenide ions liberated by the phosphorylation. Subsequent elimination of $HOPHal_2$ restores aromaticity affording halogen-substituted pyrazole **208** (Scheme 57).



Scheme 57

2.1.8.13. Deoxygenation

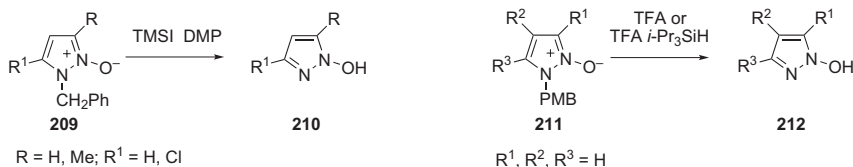
2-Substituted pyrazole 1-oxides **74** can be deoxygenated to give the corresponding pyrazoles **89** by heating with PCl_3 to 60°C for 2–5h (1992ACSA972, 2008SL2188). Deoxygenation using Zn and HOAc also works well (1991IJC(B)749, 1995JHC1189, 1969JOC187), as does heating with aqueous $\text{Na}_2\text{S}_2\text{O}_4$ (1980JOC76, 1991IJC(B)749). A large number of specific functionalized pyrazoles can be prepared by introduction of the substituents into the activated *N*-oxides followed by removal of the *N*-oxygen atom (Scheme 58).



Scheme 58

2.1.8.14. *N*-Dealkylation

2-Benzyl-pyrazole 1-oxides **209** were debenzylated when heated with iodo-trimethylsilane and 2,6-dimethylpyridine at 70°C for 14h (1996ACSA549) (Scheme 59).



Scheme 59

2-(4-Methoxybenzyl)pyrazole 1-oxides **211** are dealkylated by TFA affording 1-hydroxypyrazoles **212** (2002JCS(PI)428). The dealkylation is facilitated by addition of triisopropylsilane (2002JOC3904, 2001JOC8654). Many specifically functionalized 1-hydroxypyrazoles have been obtained by introducing the substituents in the activated 2-(4-methoxybenzyl)-substituted *N*-oxides followed by removal of the 4-methoxybenzyl group (1992JCS(P1)2555).

2.1.8.15. Rearrangement

The rearrangement of azidoisoxazoles into 2-aminopyrazole 1-oxides is discussed in Section 2.1.7. No skeletal rearrangements of 2-substituted

pyrazole 1-oxides **74** have been reported. The O to C migrations of the acyl group of *N*-acyloxy-substituted pyrazoles are discussed in [Section 2.1.9.2](#).

2.1.8.16. 1,3-Dipolar cycloaddition

An unpublished test experiment showed that 2-benzyl-pyrazole 1-oxide **86** ($R = \text{CH}_2\text{Ph}$) when treated with diethyl acetylene dicarboxylate acts as a 1,3-dipole yielding highly unstable bicyclic **213** ($R = \text{CH}_2\text{Ph}$), which degrades quickly at room temperature (2009UP2) ([Scheme 60](#)).

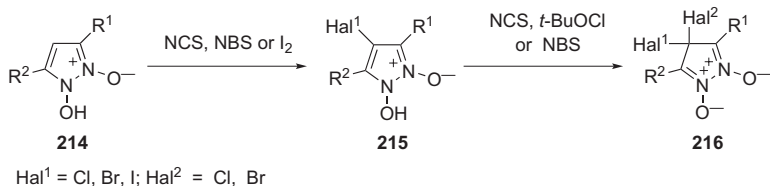


Scheme 60

2.1.9. Reactions of 2-hydroxypyrazole 1-oxides

2.1.9.1. Electrophilic aromatic substitution

2-Hydroxypyrazole 1-oxides devoid of substituents at C3 and C5 are unknown. If devoid of a 4-substituent, bromination at this site occurs using bromine (1980JOC76) or NBS (1980JOC76). Upon addition of a second equivalent of NBS, a second halogen is introduced at the 4-position with formation of dihalogen-substituted **216** ($\text{Hal}^1 = \text{Hal}^2 = \text{Br}$) ([Scheme 61](#)).



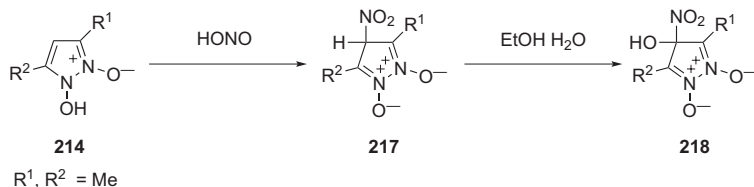
Scheme 61

2-Hydroxypyrazole 1-oxides are chlorinated at C4 using *N*-chlorosuccinimide (NCS) (1980JOC76) to give 4-chloro derivatives **215** ($\text{Hal}^1 = \text{Cl}$), which can be further chlorinated at C4 using a second equivalent of NCS or *t*-BuOCl (1980JOC76).

Iodination of 2-hydroxypyrazole 1-oxides **214** with iodine leads to the 4-iodo-substituted derivatives **215** ($\text{Hal}^1 = \text{I}$) (1980JOC76).

2-Hydroxypyrazole 1-oxides devoid of 4-substituents **214** were nitrated at the 4-position by HONO or *n*-butyl nitrite giving rise to the

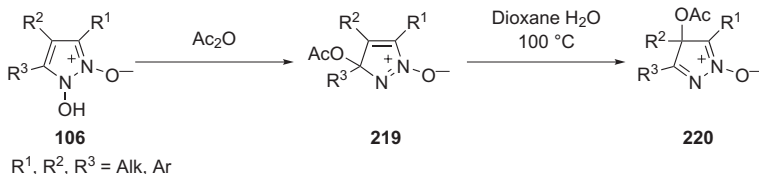
nitro compound **217**, which readily undergoes hydrolysis, affording the hydroxy-nitro compound **218** (1969JOC187, 1994JHC1481) (Scheme 62).



Scheme 62

2.1.9.2. O-Acylation

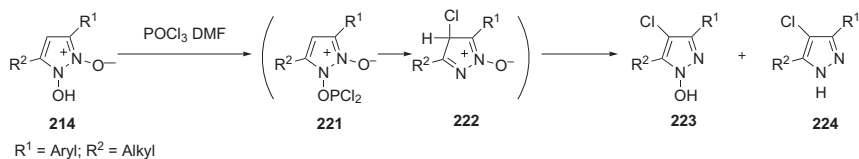
When 2-hydroxypyrazole 1-oxide **106**, possessing a substituent at the 4-position, is reacted with acetic anhydride the acetoxy compound **219** is formed and can be isolated (1974JOC2663). Presumably, acetylation of the OH group of **106** is followed by nucleophilic addition of the liberated acetate ions followed by elimination of acetic acid. By heating **219** in dioxane solution, the acetoxy group migrates to the 4-position giving rise to **220** (Scheme 63).



Scheme 63

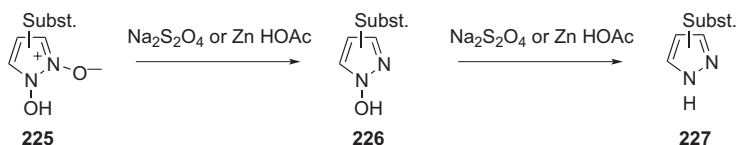
Attempts to formylate 2-hydroxypyrazole 1-oxides **214** by electrophilic substitution with use of POCl_3 and dimethylformamide (DMF) under Vilsmeier conditions gave rise to 1-hydroxy-4-chloropyrazole **223** together with minor amounts of the corresponding deoxygenated 4-chloropyrazole **224** (1979JOC4438). The reaction is in accord with initial phosphorylation of the hydroxy group of **214**. Subsequently, the liberated chloride anions replace the phosphoryloxy group by allylic substitution to give **222**. Final proton migration leads to the aromatic product **223**. The mechanism is similar to that believed to operate when 2-substituted pyrazole 1-oxides

74 are treated with acylating or silylating reagents as described in [Section 2.1.8.10–12](#) (Scheme 64).



Scheme 64

2-Hydroxypyrazole 1-oxides **225** are *N*-deoxygenated by treatment with zinc in acetic acid or with sodium dithionite affording the parent pyrazole **227** as the final product ([1969JOC187](#), [1974JOC2663](#), [1975JOC816](#), [1976JOC2871](#)). When using dithionite under mild conditions, the intermediate 1-hydroxypyrazole **226** could be isolated in certain cases ([1976JOC2871](#)) (Scheme 65).



Scheme 65

2.1.9.3. Rearrangement

The rearrangement of azidoisoxazoles **113** into 2-aminopyrazole 1-oxides **114** is discussed in [Section 2.1.7](#).

2.1.10. Reactions of 2-aminopyrazole 1-oxides

No particular reactions of 2-aminopyrazole 1-oxides **114** have been reported.

2.2. Diazapentalene *N*-oxides and *N,N'*-dioxides

In addition to the aromatic 2-substituted pyrazole 1-oxides **74**, a series of nonaromatic diazapentalene 4,4'-dioxides **75–78** and diazapentalene 4-oxides **79–84** (Scheme 22) have been described and reviewed ([1989H1615](#)). The properties and chemistry of these compounds are related to those of the 2-substituted pyrazole derived *N*-oxides have been described in [Section 2.1.9.1](#).

2.2.1. Molecular structure

2.2.2. Theoretical calculations

INDO calculations have been performed on radical ions derived from the nonaromatic diazapentalene 4,4'-dioxides **75–78** (1979JOC3211).

2.2.3. Physical properties

The diazapentalene *N*-oxides and *N,N'*-dioxides **75–84** are stable polar compounds. The compounds **77**, **79**, and **81** in which R² = Halogen are sensitive to water and undergo hydrolysis, while compounds **79**, **81**, and **82** are sensitive to oxygen.

2.2.4. Molecular spectroscopy

In addition to spectroscopic data needed for characterization, more details about UV spectra (1969JOC194, 1972CC961, 1980JOC76, 1979JOC3211), IR spectra (1979JOC3211, 1972CC961, 1969JOC187, 1975JOC816, 1976JOC2871, 1980JOC76), mass spectrometry (MS) data (1972CC961), and H NMR data (1980JOC76) have been published. Electron paramagnetic resonance (ESR) spectra of radical anions derived from diazapentalene *N,N'*-dioxides have been recorded and the observed couplings compared with INDO calculations (1979JOC3211).

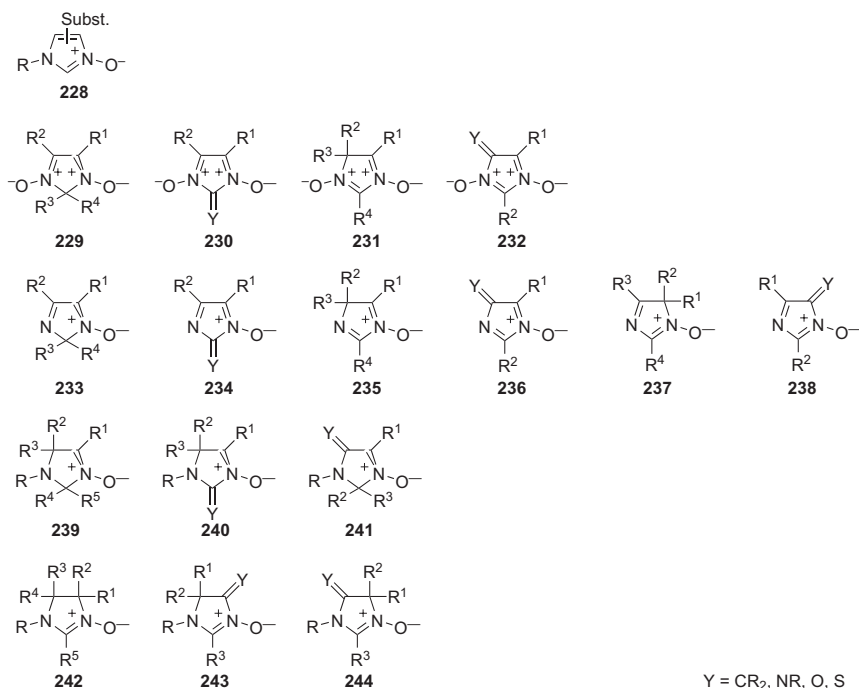
2.2.5. Applications of pyrazole 1-oxides

The palette of regio and monoselective reactions of pyrazole *N*-oxides makes them attractive for tailored synthesis of substituted pyrazoles decorated with specific substituents at specific positions, at ring or at lateral positions. This feature also makes pyrazole *N*-oxides well suited for annulation reactions as demonstrated in (2002T7635). The pyrazole 1-oxides have been used as ligands for chelation of Cu⁺², Co⁺², and Ni⁺² ions (1989JINC493, 1991DOK360, 1979ICA107, 1985POL947). Pyrazole *N*-oxides have been employed for the synthesis of aryl and heteroaryl-pyrazoles, which acted as selective phosphodiesterase 4 (PDE4) inhibitors with higher activity than Rolipram and showed selectivity with regard to inhibition of other classes of PDEs (2007USP7226930). More examples can be found in (1997MI1).

3. IMIDAZOLE *N*-OXIDES

The aromatic imidazole 1-oxides **228** discussed in Section 3.1 are derived from imidazoles **248** by appending an oxygen atom to the pyridine type ring nitrogen atom of the imidazole nucleus. The second nitrogen atom of the imidazole ring can be attached to an alkyl or aryl group or to a

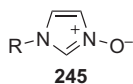
hydroxy or an amino group. A series of nonaromatic imidazoline 1,3-dioxides **229–232**, imidazoline 1-oxides **233–238**, and 3-substituted imidazoline 1-oxides **239–244** can be envisaged. Of these **229**, **231**, **239**, **241**, and **242** have been reported but are not discussed further because nonaromatic *N*-oxides are beyond the scope of the present review and since no ties between the chemistry of the aromatic and nonaromatic imidazoles have been manifested (Scheme 66).



Scheme 66

3.1. 3-Substituted imidazole 1-oxides

See Scheme 67.



R = Alkyl, Aryl, OR or NR₂

The formula for the parent 3-substituted imidazole 1-oxide **245** is shown in Scheme 67

3.1.1. Molecular structure

The aromatic imidazole *N*-oxides have structure **245**. The parent compound **246** displays tautomerism between the *N*-oxide tautomer **246** and the 1-hydroxyimidazole tautomer **247** (Scheme 68). 1-Hydroxyimidazole **247** and substituted 1-hydroxyimidazoles **249** belong to a separate group of compounds, which is not discussed in the present review.



Scheme 68

The resonance structures of the 3-substituted imidazole 1-oxides **245** are discussed in Section 1.1.1. According to IUPAC nomenclature, structure **245** is a 1-substituted 1*H*-imidazole 3-oxide since the rules dictate that when R=H the indicated hydrogen position takes numbering precedence. Other names found in the literature are 1-substituted imidazole 3-oxides or 1-substituted 3-oxo-1*H*-imidazoles. Frequently the numbering is switched to give the names 3-substituted 2*H*-imidazole 1-oxide, 3-substituted imidazole 1-oxides, or 3-substituted 1-oxo-3*H*-imidazoles. In the present review the most commonly used naming, which is accepted by IUPAC, *Chem. Abstr. Autonom.*, is used calling structure **245** a 3-substituted imidazole 1-oxide. Consistently, structure **245** (R=OH, OAlk, or NH₂) is named 3-hydroxy, 3-alkoxy, or 3-aminoimidazole 1-oxide, respectively.

The first imidazole 1-oxide was prepared in 1905 but thought to be a 1,2,5-oxadiazine (1905CB3363). The correct imidazole 1-oxide structure was proven in 1964 (1964JOC1620). Before that La Parola in 1945 obtained **267** (R¹=Ph, R²=R³=Me) (1945G216). About 560 3-substituted imidazole 1-oxides **228** with a variety of substituents at C3, C4, and C5 have been reported. A review appeared in 1970 (1970AHC103), 1981 (1981AHC241), and 1993 (1993CHE127). Imidazole 1-oxides are used by the regiocontrolled synthesis of important and otherwise difficult accessible substituted imidazoles. Imidazole 1-oxides have been used as catalysts or ligands for catalysts and for the preparation of ionic liquids. Imidazole 1-oxides have biologically interesting properties.

3.1.2. Physical properties

The 3-hydroxyimidazole 1-oxides **267** should be handled with care because they undergo violent decomposition upon heating (1971RZC1747, 1998HCA1585). At room temperature imidazole 1-oxides **228** are usually stable, crystalline, polar, and hygroscopic compounds. An exception is imidazole 1-oxides devoid of substituents at the 2-position, which may rearrange to

imidazolinones **289**. Imidazole 1-oxides lose the *N*-oxygen at elevated temperatures. Complete drying of imidazole 1-oxides has been attempted without success (2006HCA1304). X-ray crystallography has shown that 2 mol of water tie 2 mol of imidazole 1-oxide together in the crystal (2006HCA1304). Imidazole 1-oxides are good nucleophiles and weak Lewis bases, being subject to protonation at the negatively charged oxygen atom (2005TL1859). The pK_a values for proton addition are in the range 3.3–4.1 (1971JCS(B)2350, 1964CI(L)1837). Protons at the 2-position of 3-substituted imidazole 1-oxides **228** are acidic and can be abstracted in basic and even weakly acidic aqueous solution (2004S2678). No pK_a values for this process have been published. 3-Hydroxyimidazole 1-oxides are acids. The pK_a value for proton dissociation is 4.0 for the parent compound **245** ($R=OH$), while substituted derivatives display values from 4.3 to 6.7 (1964JOC1620, 1992ZOR154).

3.1.3. Theoretical calculations

Calculations of the energy of the individual tautomeric forms **246** and **247** have been performed (2006T5474).

3.1.4. Molecular spectroscopy

Standard IR spectra and data of 3-substituted imidazole 1-oxides have been published. The IR spectra point at the existence of strong hydrogen bonds (1971JCS(B)2350, 1977JOC2748, 1989S773, 1993TL7961, 2006HCA1304). UV spectra have been recorded for representative imidazole 1-oxides **228** (1977JCS(P1)672, 2004APMC259) and have been used for the determination of pK_a values (1971JCS(B)2350).

Mass spectra show a strong signal from the molecular ion and characteristic peaks at M^+-16 and M^+-17 (1971JCS(B)2350, 1993TL7961). In addition, H and C NMR have been applied routinely for characterization (1964JOC1620, 1977JOC2748, 1989S773, 1993TL7961, 1995JCS(P1)2467, 2004S2678, 2006HCA1304). In a more detailed ^{13}C NMR study, assignment of the individual signals revealed that for 3-substituted imidazole 1-oxides **95** the three ring carbon signals and the lateral carbon atoms at C2 and C4 exhibit a high-field shift as compared to the corresponding signals in the parent 1-substituted imidazoles **248** (average shift difference 10.4ppm for C2, 7.0ppm for C4, 2.7ppm for C5, 5.2ppm for 2-CH₃, and 5.4ppm for 4-CH₃). Only the 5-CH₃ signal is not shifted. The one-bond $^{13}C-H$ coupling constants of the ring carbon atoms are larger in the imidazole 1-oxides **228** than in the imidazoles reflecting lower electron density in the former species. The two- and three-bond $^{13}C-H$ couplings point at a better charge delocalization in the *N*-oxides **228** (1998JCS(P1)296).

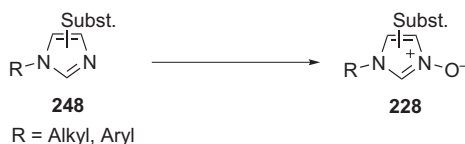
X-ray spectra of a number of imidazole 1-oxides **228** have been published (1999JCS(P1)615, 1974JHC615, 2006HCA1304, 2007ZN(A)295, 2008TA1600, 2008ZN447).

3.1.5. Preparation of 3-substituted imidazole 1-oxides

3-Substituted imidazole 1-oxides **228** can be prepared by *N*-oxidation of imidazoles **248**, by *N*-alkylation of 1-hydroxyimidazoles **249**, or by cyclization using suitable starting materials derived from a 1,2-dicarbonyl compound, an aldehyde, an amine, and hydroxyamine. The substituents at the three first starting materials are transferred to the product and make control over the substituents in the imidazole 1-oxide **228** possible depending on the protocol used by the synthesis. The synthesis of 3-hydroxyimidazole 1-oxides is presented in Section 3.1.6.

3.1.5.1. *N*-Oxidation of imidazoles

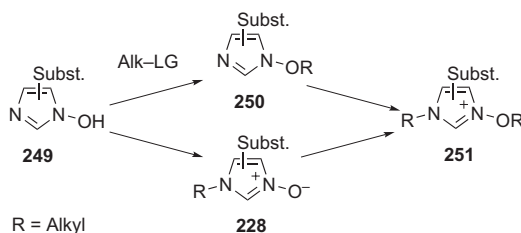
N-Oxidation of 1-methyl-imidazole **248** (R=Me, Subst.=H) with 30% aqueous H₂O₂ in THF solution affords 3-methyl-imidazole 1-oxide **228** (R=Me, Subst.=H) in 95% yield (2005TL1859). However, other attempts to oxidize 1-substituted imidazoles **248** resulted in low yields (1970ZC211, 1990S795, 1995JCS(P1)243, 1998BMCL625), decomposition, or an extremely slow reaction giving complex mixtures of products (2009JA3291) (Scheme 69).



Scheme 69

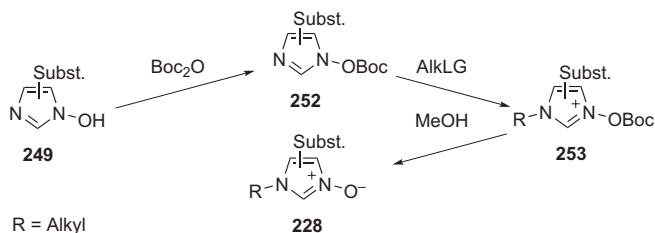
3.1.5.2. *N*-Alkylation of 1-hydroxyimidazoles

N-Alkylation of 1-hydroxyimidazoles **249** produces 3-substituted imidazole 1-oxides **228** (R=Alk) in low yields due to competing *O*-alkylation and dialkylation leading to 1-alkoxyimidazoles **250** and 1-alkyl-3-alkyloxyimidazolium salts **251**, respectively (1970ZC211, 1990S795) (Scheme 70).



Scheme 70

This issue was addressed taking into advance that butyloxycarbonyl (Boc)protection of **249** takes place regioselectively at the oxygen atom to give **252**. Subsequent alkylation finds only N-3 accessible for attack (1990S795). Subsequent methanolysis and neutralization afforded the 3-substituted imidazole 1-oxide **228** (Scheme 71).

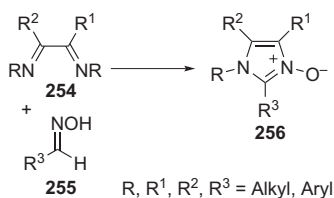


Scheme 71

3.1.5.3. Cyclization

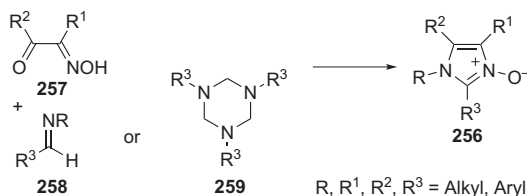
The building blocks for the synthesis of 3-alkyl and 3-aryl-imidazole 1-oxides **228** by cyclization are a 1,2-dicarbonyl compound, an aldehyde, an amine, and hydroxylamine. These are used in different sequences in order to gain control over reactivity and regioselectivity. Versatile and flexible protocols have been developed based on cyclization of 1,2-diimines, 2-oxo oximes, 2-amino oximes, or a three-component cyclization.

3.1.5.3.1. 1,2-Diimines and aldoximes Imidazole 1-oxides **256** can be obtained by reaction of 1,2-diimine (1,3-diazabuta-1,3-diene) **254** with aldoxime **255** (1995JCS(P1)2467). This method provides good control over substituents in the product **256** since both aldoximes and 1,2-diimines with a variety of aliphatic and aromatic substituents are accessible. When aromatic diimines **254** (R = Ar) are employed, the reaction can be run with microwave heating omitting the solvent by mixing the starting materials with montmorillonite KSF or silica gel (1996H1465). When unsymmetric diimines are used as starting materials regioselectivity becomes an issue. Thus diimine derived from methylglyoxal **254** ($\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$) gives an inseparable mixture of 4-methyl and 5-methyl 3-hydroxyimidazole 1-oxide **256** ($\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$) and **256** ($\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$) (Scheme 72).



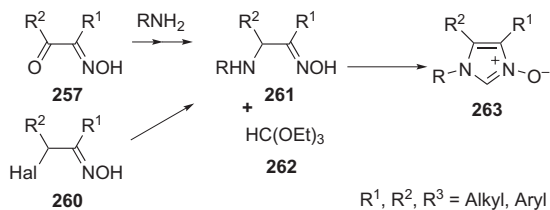
Scheme 72

3.1.5.3.2. 2-Oxooximes and aldimines Imidazole 1-oxides **256** can be accessed by reaction of 2-oxooxime **257** with aldimine **258** (1998HCA1585). This method allows for the introduction of aliphatic and aromatic substituents at C2, C4, and C5 of the product **256** since aldimines can be obtained by reaction of aldehydes with amines and 2-oxooximes can be prepared by several complementary routes (1986S704, 2009JA3291). The aldimines can be replaced with 1,3,5-trisubstituted triazane **259** serving as an aldimine precursor. By use of triazinanes the difficulties of handling sensitive or volatile aldimines can be circumvented (1998HCA1585, 2002AG(E)2290, 2004JMC6311, 2006HCA1304, 2007HCA1765, 2009JA3291, 2011H765). The aldimines can be generated in situ from aldehyde and amine (2004JMC6311, 2009TA1073, 2011IC451) and chiral amines have been used to prepare homochiral 3-substituted imidazole 1-oxides (2007ZN(A)295, 2008HCA232, 2008TA1600, 2009TA1073, 2011EJOC2542) (Scheme 73).



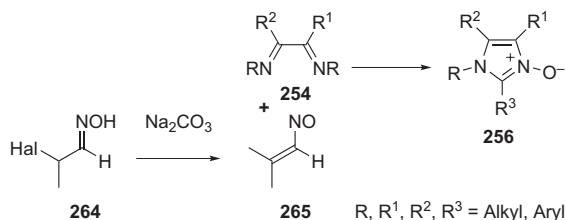
Scheme 73

3.1.5.3.3. 2-Aminooximes and *ortho* esters Heating to reflux 2-aminooximes **261** and trimethyl orthoformate in acetic acid solution furnishes 3-substituted imidazole 1-oxides **263** (2004S2678). The 2-aminooximes **261** are conveniently prepared by reductive amination using 2-oxoimine **257** and amine as starting materials. Alternatively, α -halogenooximes **260** are treated stepwise with one equivalent of amine and hydroxyamine (2004S2678). The substituents can be tracked back to simple starting materials and imidazole 1-oxides **263** with a range of substituents can be synthesized (Scheme 74).



Scheme 74

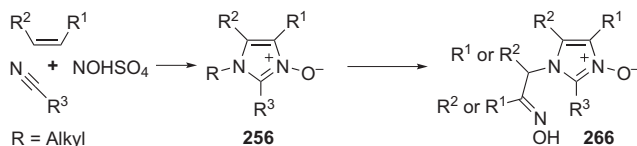
3.1.5.3.4. 1,2-Diimines and nitrosoalkenes [3+2]Cycloaddition between 1,2-diimines (1,3-diazabuta-1,3-dienes) **254** and nitrosoalkenes **265**, generated in situ from 2-halogen-substituted oximes **264** and Na_2CO_3 , leads to nitrones in a regioselective fashion. Subsequent heating of the nitrones to 140–150°C in benzene solution causes loss of amidine with simultaneous formation of 3-substituted imidazole 1-oxide **256** (1993TL7961, 1974JHC615). The protocol allows for variations in the 4- and 5-substituents in the imidazole 1-oxide **256** since they originate from the 1,2-diimine. The influence of the substituents at the diimine backbone on reaction rate, regioselectivity, and product composition has been studied by theoretical calculations at semiempirical AM1 and *ab initio* 12 HF/6-31G* levels (2006T5474) (Scheme 75).



Scheme 75

3.1.5.3.5. Miscellaneous cyclization reactions based on 1,2-dicarbonyl compounds Related processes for preparation of imidazole 1-oxides **228** are condensation of 2-ketooximes with in situ generated formimides (1998HCA1585), condensation of 1,2-diimines with formaldoxime, 1,3-oximimines, conjugated oximenamines, or conjugated 1,3-nitrosoimines (1995JCS(P1)2467, 1996H1465).

3.1.5.3.6. Three-component cyclization 3-Substituted imidazole 1-oxides **266** are formed in the three-component one-pot reaction between a nitrile, an alkene, and nitrosylsulfuric acid (1969JCP746). Most likely, the alkene is nitrosated to give a nitrosocarbenium ion, which then alkylates the nitrile at the α -position. Subsequent cyclization gives rise to a 1-hydroxyimidazole **256**, which is then alkylated by nitrosoalkene formed by nitrosation of the alkene. The protocol allows for variations in substituents at C2 brought by the nitrile and at C4 and C5 coming from the alkene. The 3-substituent is restricted to be a β -oximino group (Scheme 76).



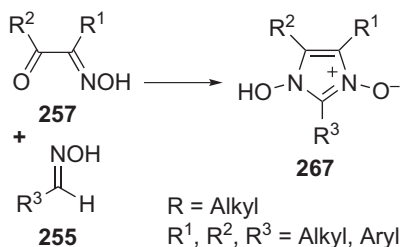
Scheme 76

3.1.6. Preparation of 3-hydroxyimidazole 1-oxides

Several of the methods used for synthesis of 3-alkyl or aryl-imidazole 1-oxides **228** can be modified to produce 3-hydroxyimidazole 1-oxides **267** by replacing an amine or imine functionality in the starting materials with an oxime group.

3.1.6.1. 2-Oxooximes and aldoximes

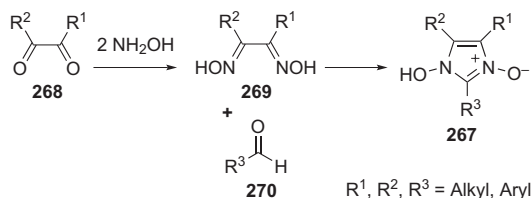
3-Hydroxyimidazole 1-oxides **267** can be synthesized following the protocol shown in Scheme 73 by replacing the imine entity with an oxime entity. Thus, 2-oxooximes **257** react with aldoximes **255** yielding 3-hydroxyimidazole 1-oxides **267** (1945G216, 1964JOC1620, 1967AG(E)947, 1965AP293, 1975CB3900, 2004APMC259, 2009OBMC4221) (Scheme 77).



Scheme 77

3.1.6.2. 1,2-Dioximes and aldehydes

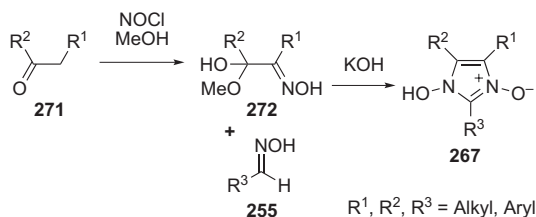
1,2-Dioximes (2-hydroxyiminooximes) **269**, which are readily accessible (1986S704), can be reacted with an aldehyde (1964JOC1620). The 2-hydroxyiminooximes **269** can be generated in situ providing a protocol by which 1,2-dicarbonyl compound **268** and aldehyde **270** are reacted with two equivalents of hydroxyamine (1989S773, 1998JOC12, 2002JMC3230). The latter protocol works well with glyoxal and formaldehyde giving easy access to the parent unsubstituted 3-hydroxyimidazole 1-oxide **245** (R=OH) (Scheme 78). The aldehyde may be replaced by aldoxime (1974A1399).



Scheme 78

3.1.6.3. Cyclization of 2-hydroxy-2-methoxyoxime

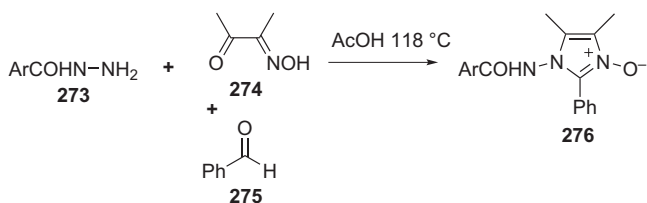
The 2-hydroxy-2-methoxyoxime **272**, prepared by α -nitrosation of the ketone **271** using nitrosyl chloride in dry methanol solution, upon treatment with KOH gives rise to 3-hydroxyimidazole 1-oxide **267** (1977JOC2748). Only one example is reported but the sequence could have a broader preparative potential (Scheme 79).



Scheme 79

3.1.7. Preparation of 3-aminoimidazole 1-oxides

3-Acylaminoimidazole 1-oxide **276** was prepared like 3-hydroxyimidazole 1-oxide **267** replacing amine with hydrazine. Only one example has been reported but other reactions for preparation of 3-hydroxyimidazole 1-oxide **267** offer opportunities for synthesis of analogues of **276** after replacement of amine with hydrazine as the starting material (2004USP248958) (Scheme 80).



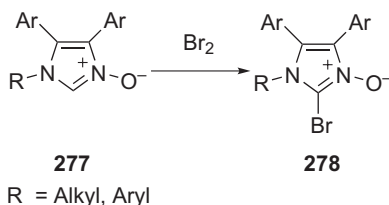
Scheme 80

3.1.8. Reactions of 3-substituted imidazole 1-oxides

3-Substituted imidazole 1-oxides **228** are predicted to be activated toward electrophilic aromatic substitution, nucleophilic aromatic substitution, and metallation as described in Section 1. Nevertheless little information about the reactivity of imidazole 1-oxides in these processes exists. The reason for this lack may be the high polarity of the imidazole 1-oxides, which makes it difficult to find suitable reaction solvents. Another obstacle is that no method for complete drying of imidazole 1-oxides exists and dry starting material is instrumental for successful metallation. Well documented and useful is the reaction of imidazole 1-oxide **228** with alkylation and acylation reagents, their function as 1,3-dipoles in cycloadditions, and their palladium-catalyzed direct arylation.

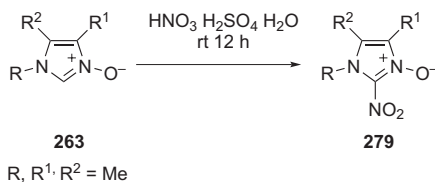
3.1.8.1. Electrophilic aromatic substitution

Bromination of the parent 1-substituted imidazoles **248** (Subst.=H) proceeds with poor regio and monocontrol (1924JCS1564). 3-Substituted imidazole 1-oxides **277** have been chlorinated and brominated at the 2-position yielding **278** (2002AG(E)2290). Since the starting material **277** possesses substituents at the 4- and 5-positions, no information about regioselectivity of the imidazole 1-oxides can be extracted from the halogenation experiments (Scheme 81).



Scheme 81

3,4,5-Trimethyl-imidazole 1-oxide **263** could be nitrated at the 2-position. According to reaction kinetics it is the neutral imidazole species which undergoes nitration (1977JCS(P1)672) (Scheme 82).



Scheme 82

The reaction of imidazole 1-oxides **245** with silylating, acylating, or phosphorylating agents does not follow a classical electrophilic aromatic substitution course. Initial attack takes place at the *N*-oxygen atom and is followed by rupture of the N–O bond and migration of the acyloxy group to a new position. The mechanism for these substitution–deoxygenation reactions is discussed in [Section 3.1.8.8](#) and [3.1.8.9](#).

3.1.8.2. Proton–metal exchange

Protons at C2 of imidazole 1-oxides **228** are acidic and are exchanged with deuterium even in weakly acidic solution. The exchange rate increases with increasing pH ([2004S2678](#)). Although the mechanism is not fully understood, the palladium-catalyzed direct arylation of imidazole 1-oxides most likely involves deprotonation so that the observed regioselective arylation reflects the propensity to proton abstraction found to decrease in the order C2 > C5 > C4 ([2009JA3291](#)).

3.1.8.3. Metallation followed by electrophilic addition

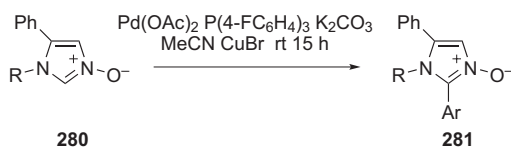
Although protons at C2 of imidazole 1-oxides **228** are fairly acidic as shown by their facile exchange with deuterium in deuterium oxide solution ([2004S2678](#)), subsequent trapping of the anion with electrophiles has not been exploited.

3.1.8.4. Transmetallation

The palladium-catalyzed and the copper-cocatalyzed direct arylation of imidazole 1-oxides **280** shown in [Scheme 83](#) may involve transmetallation ([2008JA3276](#), [2009JA3291](#)). However, classical transmetallation like conversion of imidazolyl lithium compounds to imidazolyl zinc compounds has not been reported.

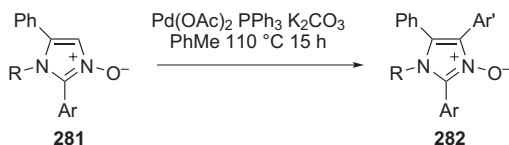
3.1.8.5. Cross-coupling with imidazole donors

Imidazole 1-oxides can be arylated regio and monoselectively with aryl-bromides in the presence of palladium as the catalyst ([2009JA3291](#)). 4-Substituted imidazole 1-oxides **280** are arylated monoselectively at C2, while 2,4-disubstituted imidazole 1-oxides **281** are arylated at C5 ([Schemes 83 and 84](#)). Aryl groups with electron-attracting or -donating substituents or sterically demanding aryl groups can be introduced in good to



Scheme 83

high yields at slightly elevated temperatures. The arylation proceeds at room temperature upon addition of copper(I) bromide and pivalic acid as cocatalysts. In these arylations the *N*-oxides display higher reactivity than the corresponding parent azoles. Direct arylation at the 4-position has not been reported (2009JA3291).



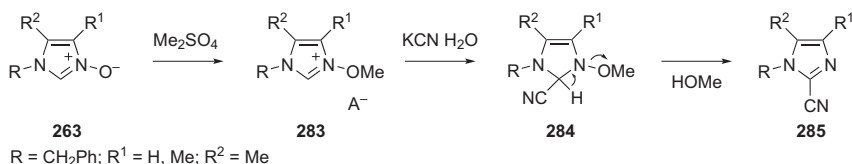
Scheme 84

3.1.8.6. Nucleophilic substitution

Only few imidazole 1-oxides possessing leaving groups like compound **278** are known. Although predicted to be apt to undergo nucleophilic aromatic substitution (see Section 1.4.2) such reactions have not been reported.

3.1.8.7. O-Alkylation

3-Substituted imidazole 1-oxides **263** upon treatment with dimethyl or diethyl sulfate furnish 1-alkoxy-3-substituted imidazolium salts **283** that were converted to the tetrafluoroborate **283** ($A^- = BF_4^-$) or hexafluorophosphates **283** ($A^- = PF_6^-$) by treatment with sodium tetrafluoroborate or hexafluorophosphate (2007ZN(A)295). The tetrafluoroborates **283** ($A^- = BF_4^-$) reacted with cyanide ion to give 2-cyanoimidazoles **285** (1975JCS(P1)275). The reaction probably follows a mechanism similar to that suggested to be operative in the pyrazole series encompassing *O*-alkylation succeeded by nucleophilic addition and elimination of methanol (Scheme 85).

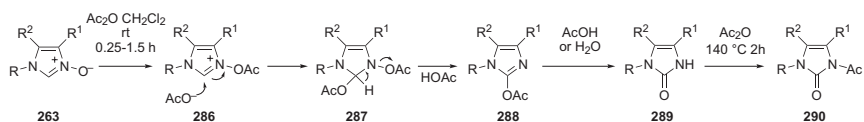


Scheme 85

Since all except one of the imidazolium salts **283** were oils, a potential as ionic liquids was envisaged and a series of homochiral imidazole 1-oxides **228** were transformed into homochiral 1-methoxyimidazolium salts **283** (2009TA1073, 2007ZN(A)295). When using 1,3-dibromopropane as the alkylating reagent, a 1,3-diimidazoliumpropane was formed.

3.1.8.8. O-Acylation

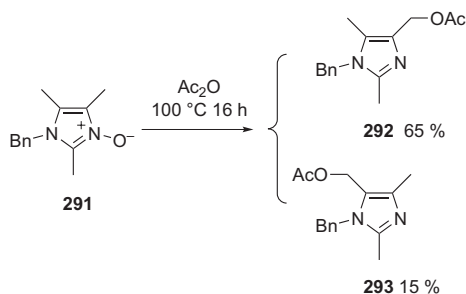
Treatment of 3-substituted 4,5-disubstituted imidazole 1-oxide **263** devoid of a 2-substituent with acetic anhydride at room temperature yields 1,3-dihydroimidazole 2-one **289** (2000HCA728, 2007HCA1765). The 3-alkyl compounds are more reactive than the 3-aryl analogues, while the 3-hydroxy analogues **263** ($R=OH$) do not rearrange under similar conditions (1970Z462, 1963CPB1375). In all probability, mechanism (iii) (Section 1.5.1.3) is operating: initial O-acylation is followed by addition at C2 of acetate ion liberated by the acylation with formation of the adduct **287**, which then by elimination of acetic acid produces the aromatic imidazole **288**. The intermediacy of an azadioxolenium ion in a sequence analogous to that outlined in Scheme 119 would also explain the observed transformation of **263** into **289**. Subsequent acetolysis or hydrolysis converts **288** into **289** that is the isolated product. If the reaction of imidazole 1-oxide **263** and acetic anhydride is performed at elevated temperatures, the isolated product is the *N*-acetyl-imidazolinone **290** (Scheme 86).



Scheme 86

If the 2-position possesses a substituent, hydrogen atoms situated at lateral positions at C3 and C4 can be replaced with an acyl group. Thus 2,4,5-trimethyl-imidazole 1-oxide **291** reacted with acetic anhydride to give a 4.3:1 mixture of the 3-acetoxymethyl **292** and 5-acetoxymethyl-imidazoles **293** (2010UP1) (Scheme 87).

Presumably, **292** and **293** are formed by mechanism (vii) (Section 1.5.2.2). Reaction at the lateral 2-methyl group was not observed. Combining the information provided by the experiments depicted in Schemes 86 and 87,

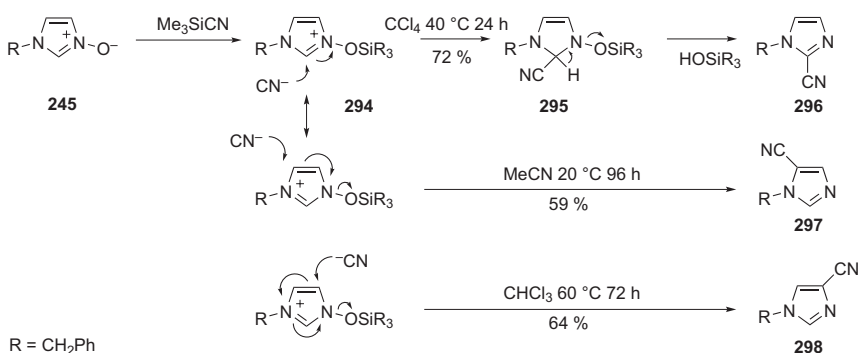


Scheme 87

it can be deduced that when imidazole 1-oxides **228** react with acetic anhydride the reactivity decreases in the order $C2 \gg CH_3-C3 > CH_3-C5 \gg CH_3-C2$.

3.1.8.9. O-Silylation

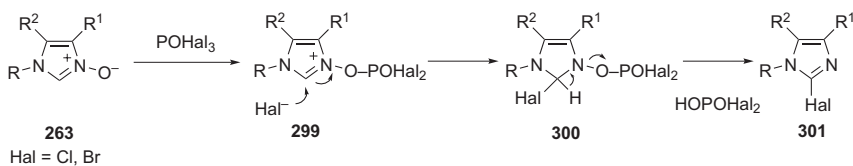
Reaction of 4,5-disubstituted imidazole 1-oxide with trimethylsilyl cyanide (TMSCN) leads to 2-cyanoimidazole. If devoid of substituents at C4 and C5, the cyano (CN) group also enters these positions (1996JOC6971). The reactivity of the 2-, 4-, and 5-position is comparable and **245** reacts with TMSCN affording the isomeric cyanoimidazoles **296–298** in a ratio that depends on the nature of the 3-substituent, solvent polarity, and reaction temperature. These parameters could be optimized to give each of the three cyano compounds as the major product. Mechanisms (iii) and (iv) (Section 1.5.1.3 and 1.5.1.4) account for the formation of **296–298** (Scheme 88).



Scheme 88

3.1.8.10. O-Phosphorylation

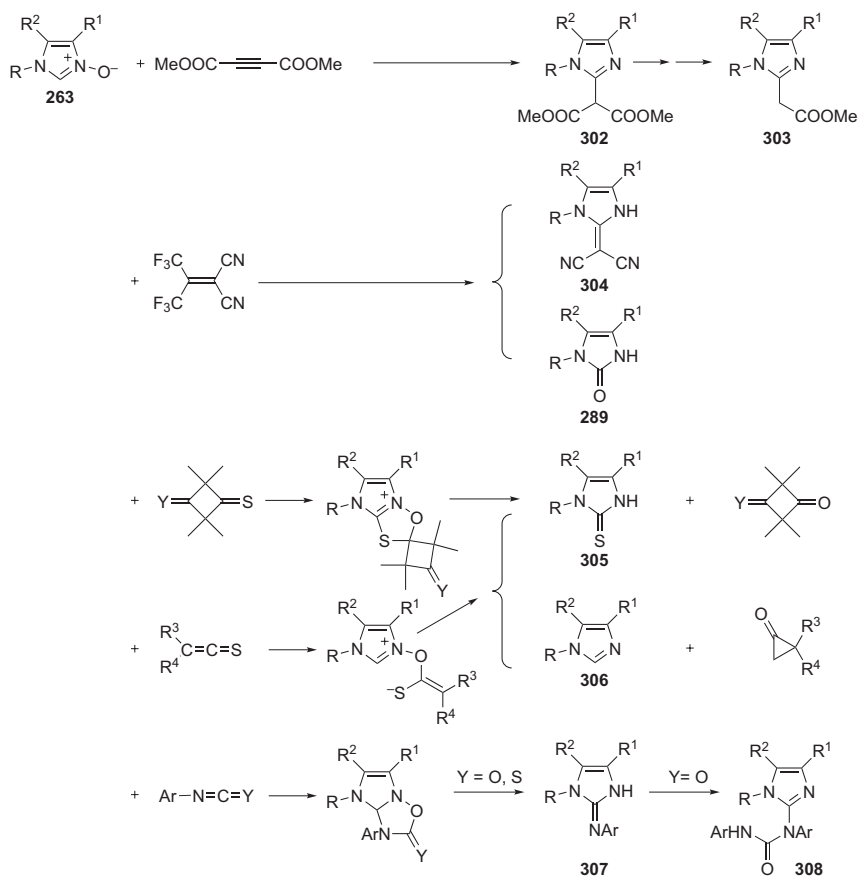
Reaction of 4,5-disubstituted imidazole 1-oxides **263** with POCl₃ or POBr₃ produces 2-chloro or 2-bromimidazole **301** (Hal=Cl or Br) (1975JCS(P1)275, 2002AG(E)2290). A possible mechanism in line with that in play by acylation comprises O-phosphorylation to be followed by addition of halogenide ion and subsequent elimination of halophosphoric acid as outlined in Scheme 89.



Scheme 89

3.1.8.11. 1,3-Dipolar cycloaddition

3-Substituted imidazole 1-oxides without substituents at the 2-position **263** react smoothly as nitrones in 1,3-dipolar cycloaddition with dialkyl acetylene dicarboxylate, activated alkenes, thioketones, thioketenes, arylisocyanates, or arylisothiocyanates as dipolarophile. The initially formed adduct then undergoes elimination with formation of 2-substituted imidazoles, **302** 1,3-dihydroimidazole 2-ones, **289** or 2-thiones **305** (1993CHE127, 1963TL1687, 1998HCA1585) (Scheme 90). Accumulating evidence indicates that at least some of these reactions are not concerted but follow an *O*-acylation–nucleophilic AE paradigm described above as mechanism (iii) (Section 1.5.1.3) (2000T5405, 2011H765).



Scheme 90

3.1.8.11.1. Cycloaddition with acetylene diesters 3-Substituted imidazole 1-oxides **263** react with dialkyl acetylenedicarboxylate to give dialkyl 2-(1,3-dihydro-2*H*-imidazol-2-ylidene)malonate (1975JCS(P1)275, 1999JCS(P1)615, 2000T5405, 2011EJOC2542). Hydrolysis of the malonates renders the imidazol-2-yl acetates **303**.

3.1.8.11.2. Cycloaddition with activated alkenes Reaction between 3-substituted imidazole 1-oxides **228** and 2,2-bis(trifluoromethyl)ethene-1,1-dicarbonitrile leads to 2-(1,3-dihydro-2*H*-imidazol-2-ylidene)malononitriles **304** (2006HCA1304).

3.1.8.11.3. Cycloaddition with thioketones 3-Substituted imidazole 1-oxides **228** react with 2,2,4,4-tetramethylcylobutane-1,3-dithione with formation of 1,3-dihydro-2*H*-imidazol-2-thiones **305** (1998HCA1585, 2011H765).

3.1.8.11.4. Cycloaddition with thioketenes 3-Substituted imidazole 1-oxides **228** react with thioketenes to give a mixture of 1,3-dihydro-2*H*-imidazol-2-thione **305** and deoxygenated starting material **306** (1998HCA1585).

3.1.8.11.5. Cycloaddition with isocyanates and isothiocyanates 3-Substituted imidazole 1-oxides **228** react with arylisocyanate with formation of 2-phenyliminoimidazole **307**, which under the reaction conditions is acylated by the isocyanate affording the urea derivative **308** (1975JCS(P1)275, 2000T5405). When the arylisocyanate was replaced with the corresponding isothiocyanate the 2-phenyliminoimidazole **307** was formed indicating that a stepwise rather than a concerted reaction course takes place (2000T5405). Indeed some of these reactions may follow the mechanism (iii) paradigm (Section 1.5.1.3).

3.1.8.12. Deoxygenation

3-Substituted imidazole 1-oxides **228** can be deoxygenated to give the corresponding imidazoles **248** by treatment with zinc and hydrochloric acid (1964JOC1620, 1977RCZ1747), zinc and acetic acid (2011IC451), zinc dust and ammonium chloride (2009JA3291), iron and acetic acid (2009JA3291), sodium hydrogen sulfite (2004APMC259), hydrogen and palladium on carbon (1989S773), ammonium formate and palladium on carbon (2009JA3291), hydrogen and freshly prepared Raney nickel (1969JPC746, 2006HCA1304, 2008HCA232, 2008TA1600), heating with PCl₃ to 60°C for 2–5 h (1971JCS(B)2350, 1975JCS(P1)275, 1998JOC12, 2002AG(E)2290), or trimethyl phosphite in DMF (2007OBMCL5514). Thermolytic deoxygenation was observed when 3-aryl-imidazole 1-oxides **228** (R = Ar) were heated to reflux in xylene solution for 1 h to give **248** (R = Ar) (1999JCS(P1)615).

A number of specific functionalized imidazoles have been prepared by introduction of the substituents in the activated *N*-oxides followed by removal of the *N*-oxygen atom (2009JA3291) (Scheme 91).



Scheme 91

3.1.8.13. *N*-Dealkylation

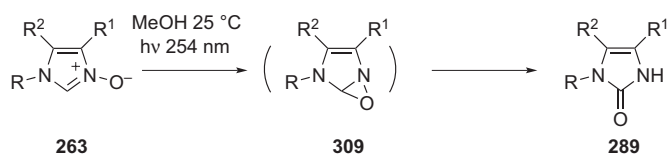
N-Dealkylation of 3-substituted imidazole 1-oxides **228** has not been reported.

3.1.8.14. Rearrangement

The rearrangements taking place when 3-substituted imidazole 1-oxides **228** are treated with acetic anhydride are discussed in [Section 3.1.8.8](#).

3.1.8.15. Photochemical rearrangement

3-Alkyl- and aryl-substituted imidazole 3-oxides lacking substituents at C2 **263** upon irradiation in solution rearrange into imidazoline 2-ones **289** ([1977RZC49](#), [1977RZC1747](#)). The reaction was blocked upon acidification to pH ca. 5.8. A reaction course passing through an **309** in accord with the rationalization of the photolysis of other heterocyclic *N*-oxides has been proposed ([1984CR43](#)) ([Scheme 92](#)).



Scheme 92

2,3,4,5-Tetraphenyl-imidazole 3-oxide **256** ($\text{R}, \text{R}^1, \text{R}^2, \text{R}^3 = \text{Ph}$) upon irradiation in methanol solution isomerized to give (*Z,Z*)-benzil diimine ([1979AJC2059](#)).

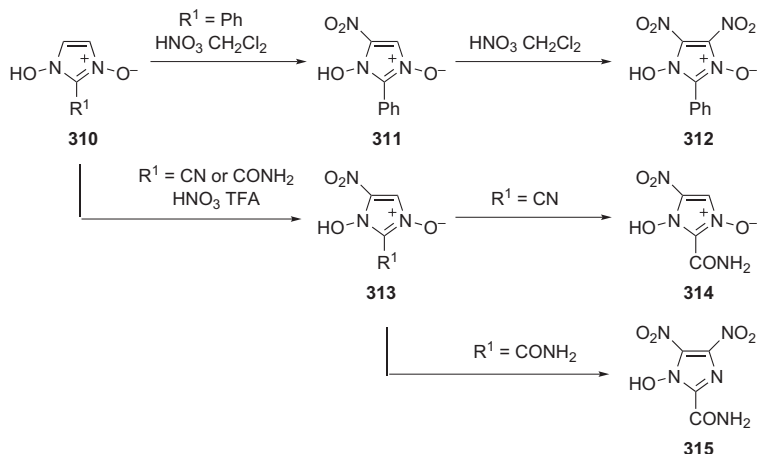
3.1.9. Reactions of 3-hydroxyimidazole 1-oxides

3.1.9.1. Electrophilic substitution

3-Hydroxyimidazole 1-oxides devoid of 2-substituents **267** ($\text{R}^1 = \text{H}$) decompose when treated with $\text{HNO}_3 + \text{H}_2\text{SO}_4$, HNO_3 , or N_2O_5 , while HNO_3 in CH_2Cl_2 , $\text{C}_2\text{H}_4\text{Cl}_2$, or TFA leads to protonation of the 3-hydroxyimidazole 1-oxide. 2-Phenyl-3-hydroxyimidazole 1-oxide **310** ($\text{R}^1 = \text{Phenyl}$) is nitrated by $\text{HNO}_3\text{--H}_2\text{SO}_4$ mixtures at the phenyl *para* position whereupon

degradation follows. HNO_3 in CH_2Cl_2 , CHCl_3 , or TFA leads to attack at the imidazole 4-position and next at the 5-position (1964CPB1290) (Scheme 93).

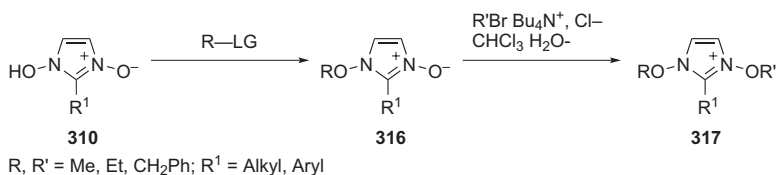
When treated with HNO_3 in TFA, 2-cyano-3-hydroxyimidazole 1-oxide **310** ($\text{R}^1 = \text{CN}$) is nitrated at the 4-position and the cyano group hydrolyzed, while the 2-carboxamido analogue **310** ($\text{R}^1 = \text{CONH}_2$) is dinitrated at the 4- and 5-position with simultaneous deoxygenation (1992ZOR2424).



Scheme 93

3.1.9.2. O-Alkylation

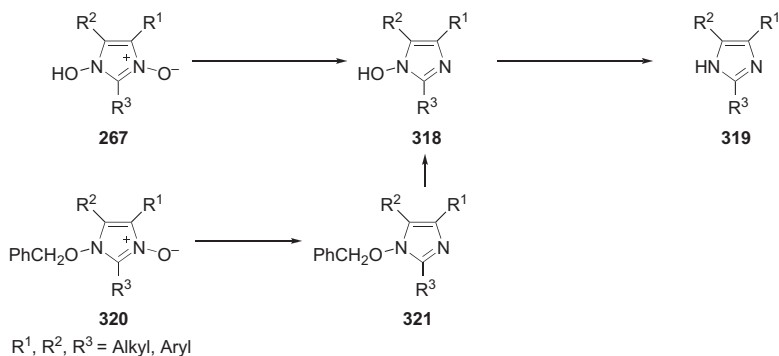
3-Hydroxyimidazole 1-oxides **310**, when treated with alkylating agents, gave rise to 3-alkoxyimidazole 1-oxides **316**, which can be isolated provided that they possess a substituent at the 2-position (1998JOC12). 1-Bromoethane, bromocyclohexane, benzyl bromide, benzyl chloride, dimethyl sulfate, diethyl sulfate, and diethyl phosphate performed well as alkylation agents (1998JOC12, 2007ZN(A)295, 2009TA1073, 2010ARK17). If the alkylation was performed under phase transfer conditions, the hydroxyimidazole 1-oxides **310** were dialkylated with formation of 1-alkyloxy-3-alkyl-imidazolium salts **317** (1990S795) (Scheme 94).



Scheme 94

3.1.9.3. Deoxygenation

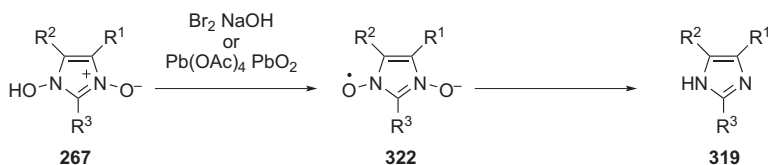
Deoxygenation of **267** by palladium-catalyzed hydrogenolysis in aqueous HCl solution proceeds stepwise *via* 1-hydroxyimidazole **318** to imidazole **319** (1979AJC2059, 1988S773). Similarly, 3-benzyloxyimidazole 1-oxides **320** are *N*-deoxygenated by treatment with PCl_3 to give 1-benzyloxyimidazole **321** (1998JOC12) (Scheme 95).



Scheme 95

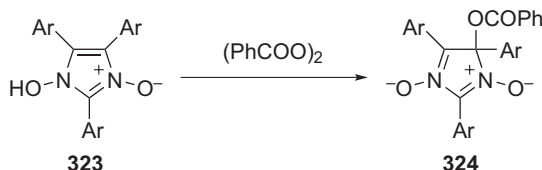
3.1.9.4. Radical oxidation

Under basic conditions 3-hydroxyimidazole 1-oxides **267** are oxidized by bromine or $\text{Pb}(\text{OAc})_4$ to give quite stable radicals **322** as shown by electron paramagnetic resonance (EPR) spectra (1968CI(L)651, 1967AG(E)947, 1970CB296) (Scheme 96).



Scheme 96

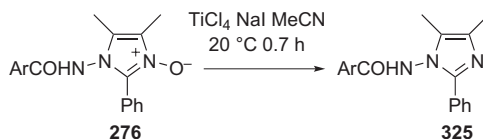
3-Hydroxyimidazole 1-oxides **323** react with dibenzoylperoxide furnishing imidazoline 1,3-dioxide **324** (1971Z62, 1993CHE127) (Scheme 97).



Scheme 97

3.1.10. Reactions of 3-aminoimidazole 1-oxides

3-Acylaminoimidazole 1-oxide **276** has been deoxygenated with $\text{TiCl}_4 + \text{NaI}$ to give the imidazole **325** (2004USP248958) (Scheme 98).



Scheme 98

3.1.11. Applications of imidazole 1-oxides

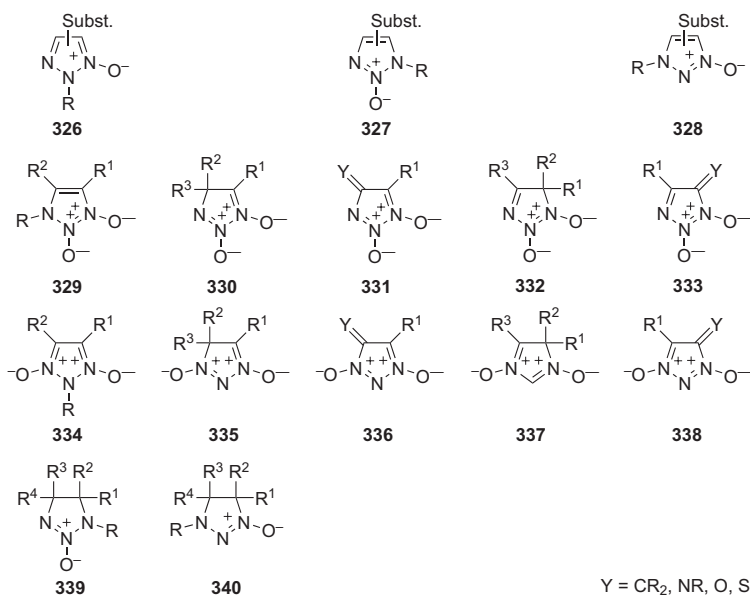
Imidazole 1-oxides react efficiently and regioselectively in a number of complementary reactions and are therefore useful for regio-controlled preparation of substituted imidazoles (1968CI(L)651, 2002AG(E)2290, 1970ZC211, 2000T5405, 1967AG(E)1967, 1970CB296). Imidazole *N*-oxides have acted as key intermediates for the synthesis of a series of biologically active imidazoles (2004APMC259, 1991PHA412, 2005MRMC409). The synthesis of a Tie2 tyrosine kinase inhibitor is a good example (2009JA3291). Imidazole 1-oxides exhibit a potential for application in Vag. Imidazole 1-oxides have been embedded in iron chelating constructs that act as hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors (2009OBMC4221). Imidazole 1-oxides are dual peroxisome proliferator-activated receptor (PPAR) α/γ agonists (2009OBML1451), inhibitors of cytokine release (2004JMC6311), inhibitors of the mitogen-activated protein kinase p38, and inhibitors of the release of the proinflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor R (TNFR) isolated from human whole blood after stimulation with lipopolysaccharide (LPS). Furthermore, imidazole 1-oxides exhibited reduced cytochrome P450 interaction in comparison with compound SB203580. Imidazole *N*-oxides have shown

antiinflammatory activity (2004JMC6311), activity as anthelmintics (2004S2678), insecticides (1973GEP(O)2254474), and as plant growth regulators (1980GEP(E)140966, 1997MI1). Imidazole *N*-oxides are of interest as chiral or achiral ionic liquids (2009TA1073, 2007ZN(A)295), chiral carbene ligands for transition metals, and as chiral Lewis base catalyst for the Morita–Bayliss–Hillman reaction between aldehydes and α,β -unsaturated ketones (2005TL1859).

In recent years, there has been a growing interest in the synthesis and applications of bis-imidazole derivatives. Especially attractive are their metal complexes as catalysts in organic synthesis (2003OM4384, 2008TA1600, 2011IC451).

4. 1,2,3-TRIAZOLE *N*-OXIDES

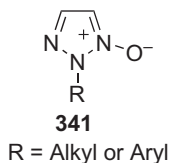
Three families of aromatic 1,2,3-triazole *N*-oxides **326**–**328** exist and are discussed separately in Section 4.1–4.3. Nonaromatic 1,2,3-triazoline *N,N'*-dioxides **329**–**338** and 1,2,3-triazoline *N*-oxides **339**–**340** seem not to have been reported (Scheme 99).



Scheme 99

4.1. 2-Substituted 1,2,3-triazole 1-oxides

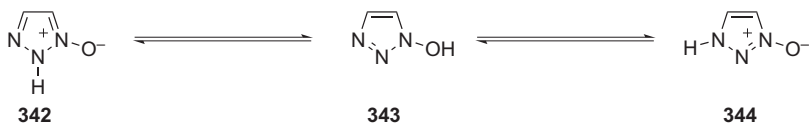
The formula for the parent 2-substituted 1,2,3-triazole 1-oxide **341** is shown in Scheme 100.



Scheme 100

4.1.1. Molecular structure

The aromatic 2-substituted 1,2,3-triazole 1-oxides are represented by the structure **341**. The parent compound **342** is one of the three possible tautomeric forms of 1-hydroxy-1,2,3-triazole **343**. 1-Hydroxy-1,2,3-triazoles **343** constitute a separate group of compounds, which are not included in the present review (Scheme 101).



Scheme 101

The resonance structures of the 2-substituted 1,2,3-triazole 1-oxides **341** are discussed in Section 1.1.1. According to IUPAC nomenclature, structure **341** is a 2-substituted 2*H*-1,2,3-triazole 1-oxide. Other names found in the literature are 2-substituted 1,2,3-triazole 1-oxides. In the present review the most commonly used naming, which is accepted by IUPAC, *Chem. Abstr. Autonom.*, has been adopted calling structure **341** a 2-substituted 1,2,3-triazole 1-oxide.

The first 1,2,3-triazole 1-oxide **326** was reported in 1898 (1898JPC160, 1898G173). It was obtained in low yield by oxidative cyclization of 2-hydroxyiminophenylhydrazones (2-oxime phenylhydrazones) using HgO as the oxidant. About 285 2-substituted 1,2,3-triazole 1-oxides **326** with a variety of substituents at C3, C4, and C5 have been reported. A review appeared in 1989 (1989CHE113). Examples of the use of 1,2,3-triazole 1-oxides in the synthesis of substituted 1,2,3-triazoles have been discussed (1988BSB573).

4.1.2. Physical properties

Due to a high content of nitrogen atoms and the presence of an N–O bond, 2-substituted 1,2,3-triazole 1-oxides **326** should be handled with care.

The 1,2,3-triazole 1-oxides **326** are usually stable, crystalline, semipolar, and colorless compounds. The lower 2-alkyl-substituted 1,2,3-triazole 1-oxides tend to be slightly hygroscopic. They act as very weak bases, protonation requiring acids like triflic acid and *O*-alkylation requiring trimethyloxonium salts. No pK_a values have been reported.

4.1.3. Theoretical calculations

4.1.4. Molecular spectroscopy

UV spectra have been run for several 2-substituted 1,2,3-triazole 1-oxides **326** (1973CHE120, 1992TL7941, 1999CHE180, 2003CHE467).

IR data for a number of 2-substituted 1,2,3-triazole 1-oxides **326** have been reported but no comparative studies have appeared (1973CHE120, 1999CHE180, 2003CHE467, 2003CHE608).

¹H NMR data have been reported in (1973CHE120, 1981JCS(P1)503, 1992TL7941, 1997T1751, 1993T5339, 2003CHE467, 2003CHE608).

Introduction of the *N*-oxygen atom into the parent 2-phenyl-triazole **382** (R=Phenyl, Subst.=H) causes high-field shift changes of 22.5ppm for C5 and 6.7ppm for C4, reflecting increased negative charge densities and activation toward electrophilic attack, particularly at C5 (1981JCS(P1)503). Simultaneous activation toward nucleophiles of the *N*-oxide as compared to 2-phenyl-triazole itself is suggested by the 10Hz (C5) and 6Hz (C4) larger one-bond C–H coupling constants in the former species. Larger coupling constants signify increased positive charge on the nitrogen atoms in heteroaromatic rings. The shift difference between phenyl C3 and C2 of 2-phenyl-1,2,3-triazole 1-oxides **326** (R=Ph) is 5.8–6.5ppm indicating that the *N*-oxygen atom slightly impedes interannular conjugation causing twisting of the phenyl and the triazole ring with respect to each other (1974ACSA(B)61). Routine ¹³C NMR spectra are found in (1997T1751, 1993T5339, 2003CHE467, 2003CHE608).

¹⁴N and ¹⁵N NMR spectra of **326** have been recorded (2003CHE608).

In the mass spectra most triazole 1-oxides, **326** gives rise to a molar peak and a M-16 peak. Many triazole *N*-oxides give rise to a M-17 peak (1981JCS(P1)503, 1986ACSA(B)262, 1993T5339, 1999CHE180, 2002CHE1475, 2003CHE467). A main fragmentation route has been outlined (1993T5339). Since the intensity of the M-16 signal is low it can be dubious as a proof of an *N*-oxide. A more reliable indication of an *N*-oxide will be peaks' characteristic for the degradation, which involves an initial loss of NO₂ followed by loss of diazoalkane (2002CHE1475).

The X-ray spectrum of several 2-substituted 1,2,3-triazole 1-oxides **326** has been reported (1993T5339, 2006MC259).

4.1.5. Preparation of 2-substituted 1,2,3-triazole 1-oxides

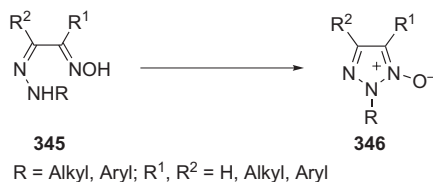
Despite many attempts it has not been possible to oxidize 2-substituted 1,2,3-triazoles **382** to the corresponding 1-oxides **326**. Peracetic acid, 3-chloroperbenzoic acid, dichloropermaleic acid, trifluoroperacetic acid, peroxydisulfuric acid, and *t*-pentyl hydrogen peroxide in the presence of molybdenum pentachloride all failed to oxidize **382** (1981JCS(P1)503). Alkylation of 1-hydroxytriazoles **443** invariably produced the isomeric 3-substituted 1,2,3-triazole 1-oxides **448** (see Scheme 132). However, the 2-substituted 1,2,3-triazole 1-oxides **326** can be prepared by oxidative cyclization of 2-hydroxyiminohydrazones (1,2-hydrazonooximes, α -hydrazonooximes) **345** or by cyclization of azoxyoximes **169**. Additional methods of more limited scope are reaction of nitroisoxazoles **353** with aryl-diazonium ion and base, and reaction of nitroimidazoles **355** with hydroxy-amine- or amine-induced rearrangement of nitro-substituted furoxanes **357**.

4.1.5.1. Oxidative cyclization of 2-hydroxyiminohydrazones

2-Hydroxyiminohydrazones (2-oximo hydrazones, 2-hydrazonooximes) **345** undergo oxidative cyclization upon treatment with even mild oxidants. Since several routes to 2-hydroxyiminohydrazones **345** exist they can bring in a great variety of substituents to the triazole *N*-oxide. The procedure allows the regioselective synthesis of 2-substituted 1,2,3-triazole 1-oxides **346** with both aliphatic and aromatic substituents and with no, one, or two substituents at the ring carbon atoms. Usually copper(II) salts, like copper(II) sulfate in aqueous pyridine solution, are the oxidants of choice (1979HCA779, 1981JCS(P1)503, 1982JCS(P1)2749, 1986ACSA(B)262). Oxidants like PbO₂, MnO₂, NiO₂, KMnO₄, HgO, FeCl₃, K₃Fe(CN)₆, H₂O₂, H₂S₂O₅, or *N*-iodosuccinimide (NIS) in CHCl₃ were less satisfactory (1973CHE120, 1982JCS(P1)2749, 1981JCS(P1)503, 1986ACSA(B)262, 1980AJC2447, 1977HCA2334, 1973IJC1077, 1997T1751, 1997JOC9177, 1980H1279) (Scheme 102).

The cyclization mechanism is unknown but a one-electron transfer mechanism has been suggested (1997JOC9177). Anodic oxidation of 2-hydroxyiminohydrazones **345** gives respectable yields of 1,2,3-triazole 1-oxides **346** (1982ZC25).

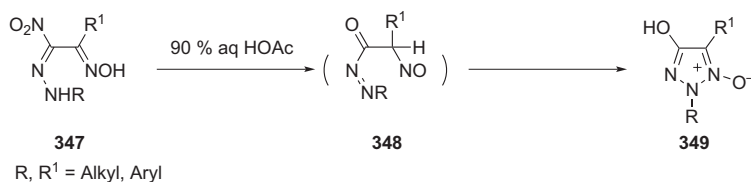
The 2-hydroxyiminohydrazones **345** are accessible from 1,2-dicarbonyl compounds *via* stepwise hydrazone and oxime formation, from carbonyl



Scheme 102

compounds by coupling with aryldiazonium ion followed by oxime formation, from carbonyl compounds or α -ketoesters by nitrosation, and subsequent reaction with a hydrazine (1981JCS(P1)503, 1986ACSA(B)262, 1986S704). Alternatively, the 2-hydroxyiminohydrazones **345** can be generated from 3,4-dinitrothiophene, which upon heating with diethylamine gives rise to 2,3-dinitro-1,3-butadienes. Subsequent reduction, selective hydrolysis, and reaction with a hydrazine produces the 2-hydroxyiminohydrazones **345** (1997T1751). In several cases, the generation of the 2-hydroxyiminohydrazones **345** and their cyclization can be run in one pot (1981JCS(P1)503, 1986ACSA(B)262, 1973CHE120).

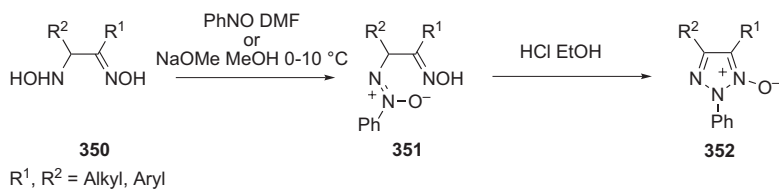
2-Nitro-2-phenylhydrazonooximes **347** when treated with acetic acid cyclize to give 4-hydroxy-1,2,3-triazole 1-oxides **349** presumably *via* a Nef type mechanism (1974S198) (Scheme 103).



Scheme 103

4.1.5.2. Cyclization of azoxyoximes

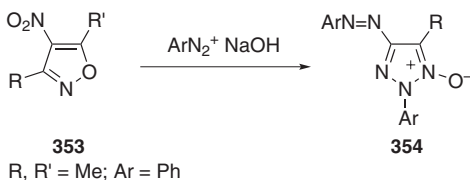
Treatment of 2-phenylazoxyoximes **351** with HCl in ethanol at room temperature gives rise to cyclization with elimination of water and formation of 2-phenyl-1,2,3-triazole 1-oxides **352** (1973CHE131, 1973CHE120). The azoxyoximes **351** are obtained from 2-hydroximinohydroxyamines **350** by reacting them with nitrosobenzene at room temperature in DMF solution. Two examples are presented in which R^1 and R^2 are aromatic or aliphatic groups. The method seems limited to give access to 2-aryl-substituted 1,2,3-triazole 1-oxides **352** (Scheme 104).



Scheme 104

4.1.5.3. Reaction of nitroisoxazoles with aryldiazonium ion

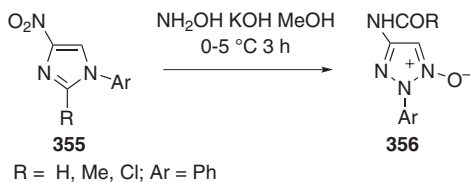
Treatment of 4-nitroisoxazole **353** with phenyldiazonium chloride and NaOH provides 2-phenyl-4-phenylazo-1,2,3-triazole 1-oxide **354**. A mechanism comprising base-induced ring opening followed by sequential addition of two equivalents of phenyldiazonium ion, terminated by cyclization has been proposed (1942G399) (Scheme 105).



Scheme 105

4.1.5.4. Reaction of nitroimidazoles with hydroxyamine

Treatment of 1-phenyl-2-methyl-4-nitroimidazole **355** at -5 to 20°C with hydroxyamine in the presence of KOH in methanol yields 2-phenyl-4-acetylamido-1,2,3-triazole 1-oxide **356** (1992TL7941, 1994H1511). A mechanism where initial addition of hydroxyamine is followed by ring opening and recyclization has been proposed. According to a series of experiments the reaction gives access to 2-aryl or heteroaryl-1,2,3-triazole 1-oxides **356** with an acylamido or chlorocarbonylamido group at position 4 (1993T5339) (Scheme 106).

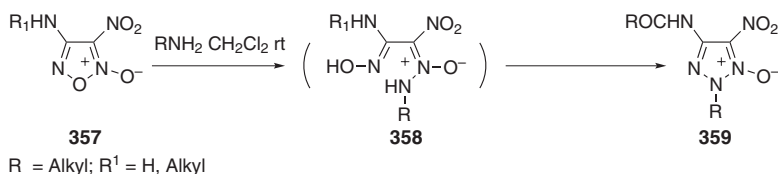


Scheme 106

4.1.5.5. Rearrangement of 5-nitro-substituted furoxanes

4-Amino or 4-alkylamino-1,2,5-oxadiazole 2-oxides (furoxanes) **357** with an electron-withdrawing group (a nitro group) at the 5-position react with primary amines with ring opening, which is followed by recyclization furnishing 4-alkylamino-5-nitro-2-substituted 1,2,3-triazole 1-oxides **359**. It was anticipated that **358** acts as an intermediate. It was demonstrated

in one case that the nitro group could be replaced with a phenyl group (1996CHE580, 1999CHE180, 2003MC272, 2006MC259) (Scheme 107).



Scheme 107

4.1.6. Reactions of 2-substituted 1,2,3-triazole 1-oxides

2-Substituted 1,2,3-triazole 1-oxides **326** undergo electrophilic and nucleophilic aromatic substitution and are subject to debromination, proton-metal exchange, and halogen-metal exchange followed by electrophilic addition, transmetallation, and cross-coupling. Reaction with aqueous HCl or HBr at 150°C causes bromination with simultaneous loss of the *N*-oxygen. In addition, 1,2,3-triazole 1-oxides **326** undergo *O*-alkylation, acylation, silylation, or phosphorylation, which can be followed by nucleophilic addition. Lateral positions are also activated. 2-Substituted 1,2,3-triazole 1-oxides **326** are stable toward oxidation, while reduction yields the parent 2-substituted 1,2,3-triazoles **382**.

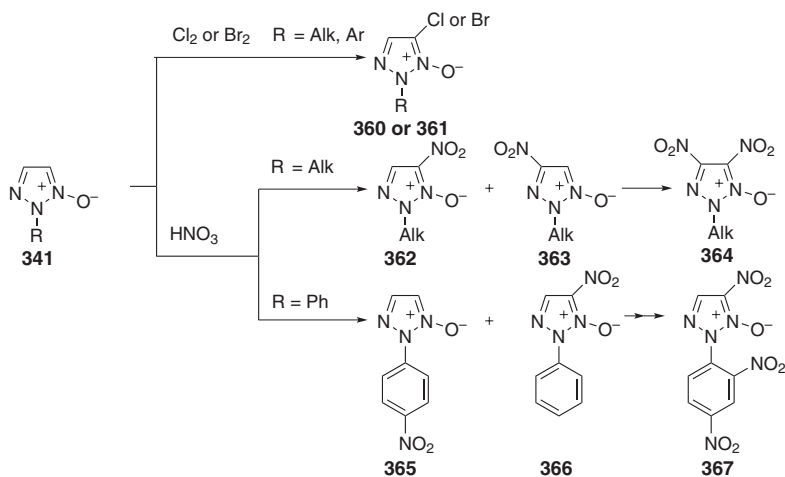
4.1.6.1. Electrophilic aromatic substitution

2-Methyl-1,2,3-triazole 1-oxide **341** (R=Me) reacts under mild conditions with chlorine and bromine in a mono and regioselective fashion affording the 5-chloro or bromo derivative **360** or **361** (R=Me). Further halogenation does not take place even under forcing conditions (1986ACSA(B)262). The halogenation of triazole 1-oxide **341** occurred with the predicted regioselectivity (see Section 1.4.1). As expected, the 1-oxide **341** is more reactive than the parent 2-methyl-1,2,3-triazole **382**, which provides no defined products upon chlorination while bromination requires elevated temperatures and a catalyst like Fe (1955A207). Under these conditions monoselectivity is lost and only 4,5-dibromotriazole could be isolated. The benzyl series follows the same trend. Thus 2-benzyl-1,2,3-triazole 1-oxide **341** (R=CH₂Ph) was brominated selectively at the 5-position. Likewise, 2-phenyl-1,2,3-triazole 1-oxide **341** (R=Ph) was chlorinated and brominated selectively at C5 activated by the *N*-oxide function. In contrast, the parent 2-phenyl-1,2,3-triazole **164** (R=Ph) does not react with bromine (1981JCS(P1)503). Attempts to introduce iodine by treatment of **341** (R=Ph) with iodochloride failed (2010UP2). The mono and regioselective halogenation of **341** is of great importance since the halogen at C5 can be subject to further transformations followed by deoxygenation as discussed below.

Nitration of 2-methyl-1,2,3-triazole **341** ($R=Me$) proceeded smoothly furnishing a mixture of 4- and 5-nitro derivatives **362** ($R=Me$) and **363** ($R=Me$). Both transformed to the 4,5-dinitro compound **364** ($R=Me$) at elevated temperature (1986ACSA(B)262).

The lost regioselectivity by the nitration indicates that the strong acids employed have protonated the *N*-oxygen atom of the starting material to neutralize and thereby outperform the negative charge at the oxygen atom, which conveys the activation of the 5-position observed under neutral conditions. This hypothesis is supported by the ready transformation of 1,2,3-triazole *N*-oxides into their hydrochlorides (1981JCS(P1)503).

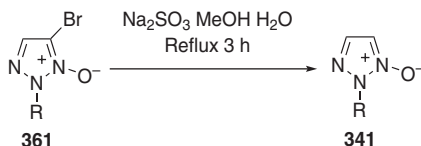
Protonation at the *N*-oxygen atom also accounts for absent activation of the triazole ring as testified by the unselective nitration of 2-phenyl-1,2,3-triazole 1-oxide **341** ($R=Ph$) using $HNO_3 + H_2SO_4$. Nitration preferentially takes place in the phenyl group and leads *via* mixtures of 4'-nitrophenyl- **365**, 5-nitro- **366**, and 4',5-dinitro-substituted derivatives to 2',4',5-trinitrophenyl-triazole 1-oxide **367** as the final product. A similar product distribution was observed upon nitration of the parent 2-phenyl-1,2,3-triazole **164** ($R=Ph$) (1899G283, 1981JCS(P1)503) (Scheme 108).



Scheme 108

4.1.6.2. Debromination

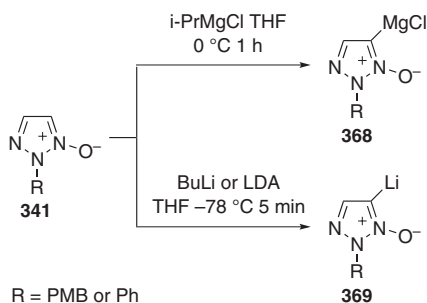
Bromine at C5 of 2-substituted 1,2,3-triazole 1-oxides **361** is readily removed without touching the *N*-oxygen by treatment with aqueous-methanolic Na_2SO_3 (2010UP2). Debromination has also been achieved by metallation followed by protonation as described in Section 4.1.6.4 (Scheme 109).



Scheme 109

4.1.6.3. Proton–metal exchange

Protons at position 5 of 1,2,3-triazole 1-oxides **341** are more acidic than corresponding protons in the parent triazoles since the negative charge at the corresponding anion is stabilized inductively by the adjacent positive nitrogen atoms (see [Section 1.4.3](#)). The activated proton at C5 of **341** could be abstracted by BuLi, LDA, or *i*-PrMgCl (2010UP2) ([Scheme 110](#)). Abstraction of the protons at the 4-position of 2-substituted 1,2,3-triazole 1-oxides **341** gives rise to an anion, which is not stabilized since a negative charge at C4 is distant from the positively charged nitrogen atoms. Accordingly, abstraction of the proton at C4 of *N*-oxides **341** was never observed.



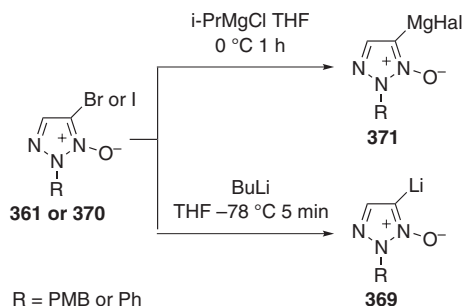
Scheme 110

4.1.6.4. Halogen–metal exchange

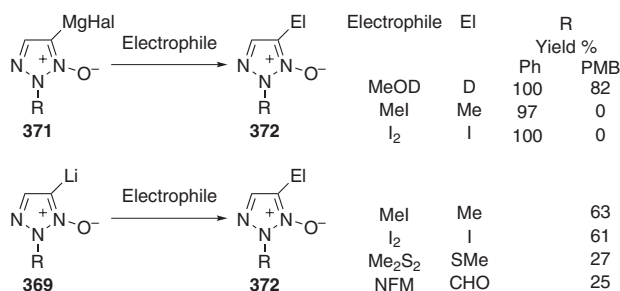
Bromine and iodine at the 5-position of 2-phenyl-1,2,3-triazole 1-oxides **361** and **370** could be replaced with lithium or magnesium using BuLi or *i*-PrMgCl (2010UP2) ([Scheme 111](#)).

4.1.6.5. Metallation followed by electrophilic addition

The anions generated by proton–metal or halogen–metal exchange ([Section 4.1.6.3–4](#)) reacted readily with electrophiles like MeOD, MeI, I_2 , and *N*-formylmorpholine (NFM) to give the 5-substituted 1,2,3-triazole 1-oxides **372** (2010UP2) ([Scheme 112](#)).



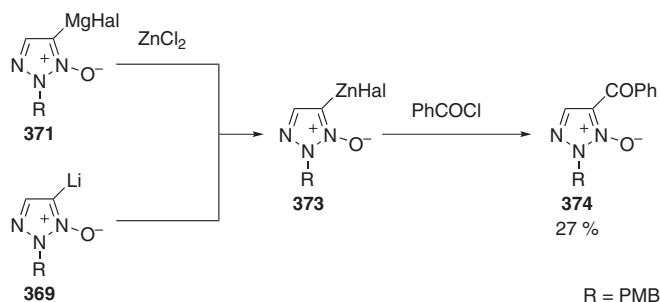
Scheme 111



Scheme 112

4.1.6.6. Transmetalation

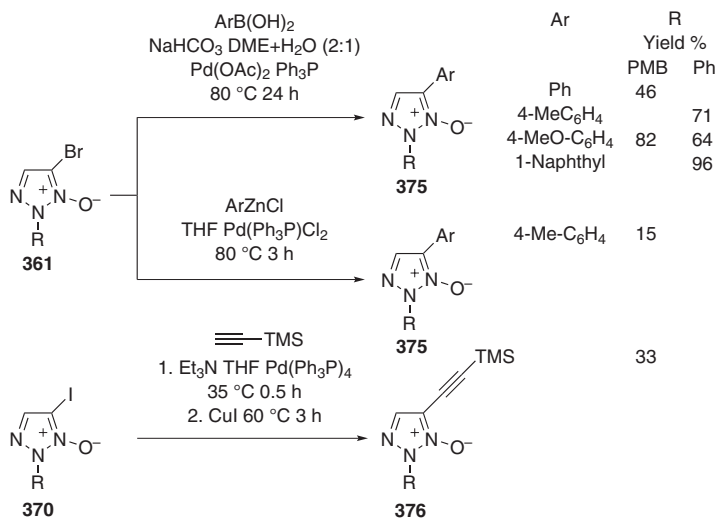
Lithium and magnesium of the metallated *N*-oxides **369** and **371** were readily replaced with zinc or boron. The boronic esters were very unstable undergoing deborylation. The zinc salts **373** were fairly stable and reacted with acyl chloride affording 1,2,3-triazolyketone **374** (2010UP2) (Scheme 113).



Scheme 113

4.1.6.7. Cross-coupling with 1,2,3-triazole donors

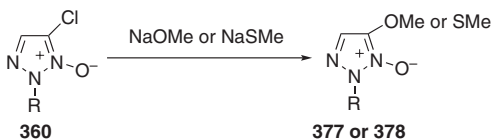
Palladium-catalyzed cross-coupling with 1,2,3-triazolyl boronic esters or zinc bromides as donors was of no avail. In contrast, cross-coupling between bromo-substituted 1,2,3-triazoles **361** and arylboronic acids proceeded smoothly giving rise to **375**. The reaction of **361** with arylzinc halogenide gave lower yields. Iodo-1,2,3-triazole **370** reacted under Sonogashira conditions with trimethylsilylacetylene to give ethynyl-1,2,3-triazole **376** (2010UP2) (Scheme 114).



Scheme 114

4.1.6.8. Nucleophilic substitution

Leaving groups at C5 of 2-substituted 1,2,3-triazoles are predicted to be the most reactive in nucleophilic aromatic substitution reactions following an AE mechanism (see Section 1.4.2). Accordingly, chlorine at C5 of **360** could be replaced by strong nucleophiles like methanethiolate or methoxide to give **377** or **378**. The unactivated 2-phenyl-4-chloro-1,2,3-triazole **380** (R=Ph) was inert toward these nucleophiles (1981JCS(P1)503) (Scheme 115).

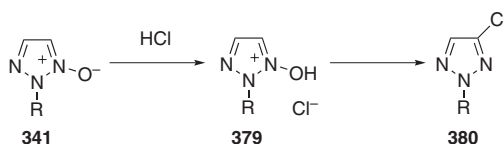


Scheme 115

Palladium activates halogen at the 5-position of 2-substituted 1,2,3-triazole 1-oxides and brings **361** and **370** to react as acceptors in cross-coupling reactions as described in [Section 4.1.6.7](#).

4.1.6.9. O-Protonation

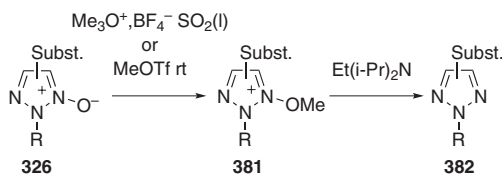
Strong acids like H_2SO_4 and nonaqueous HCl protonate the *N*-oxygen atom of 2-substituted 1,2,3-triazole 1-oxides **326** as reflected by a concomitant low-field shift of the ^{13}C NMR signal from C5. The shift is similar to that observed when the triazole 1-oxide **326** is alkylated (1981JCS(P1)705). Heating of the 1-hydroxy-1,2,3-triazolium halogenides **379** obtained from **341** procured halogen-substituted 1,2,3-triazoles **380** probably *via* mechanism (iii) or (iv) ([Section 1.5.1.3–4](#)) (1981JCS(P1)503) ([Scheme 116](#)).



Scheme 116

4.1.6.10. O-Alkylation

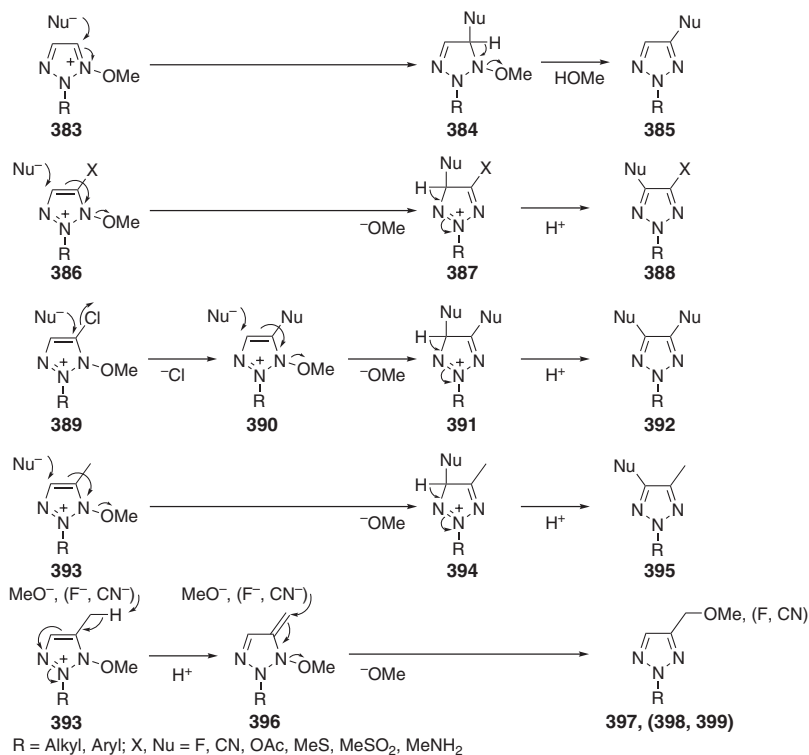
The 2-substituted 1,2,3-triazole 1-oxides **326** are alkylated at the oxygen by trimethyloxonium tetrafluoroborate in refluxing SO_2 or by methyl triflate generated in situ from iodomethane and silver triflate (1992JCS(P1)2555). The hygroscopic 2-substituted 1-methoxy-1,2,3-triazolium salt **381**, which can be isolated in high yield, readily undergoes further reactions with bases or nucleophiles (1981JCS(P1)503, 1982JCS(P1)2749, 1983ACSA97, 1986ACSA(B)262). Thus, non-nucleophilic bases like diisopropylethylamine abstract a proton from the OCH_3 group producing an anion that eliminates formaldehyde furnishing the deoxygenated 1,2,3-triazole **382**. The mechanism may be similar to that suggested for deformylation of 1-methoxypyrazolium salts (see [Section 2.1.8.9](#)). The mild conditions used make this sequence an interesting alternative to other deoxygenation procedures ([Scheme 117](#)).



Scheme 117

Weak nucleophiles add to the highly reactive immonium carbon atom at the 5-position to give adduct **384**, which then regains aromaticity by elimination of methanol. In this way fluoro, chloro, hydroxy, alkoxy, acyl, amino, substituted amino, azido, nitro, thio, alkylthio, acylthio, and cyano groups can be incorporated in the triazole nucleus. When HO^- was employed as the nucleophile, the initially formed 5-hydroxy compound itself acted as a nucleophile following the same schedule and giving rise to bistriazolyl ethers ([1983ACSA97](#)). The net reaction **383** \rightarrow **386**, **389** and **393** is a regioselective replacement of heteroaromatic hydrogen with a weak nucleophile at room temperature including traceless removal of the activating group, the whole sequence frequently being feasible in one pot.

Substituents at C4 and C5 influence the outcome of the reaction of the transient 1-methoxy-2-substituted 1,2,3-triazolium salts **383** according to the following trends extracted from the checker board investigation in ([1982JCS\(P1\)2749](#)) (Scheme 118):



Scheme 118

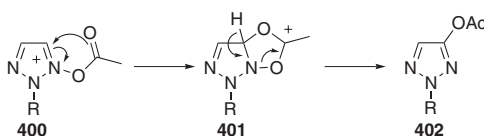
- C5 is the most reactive position.
- A methyl group at C4 does not influence the reaction pattern significantly, nucleophilic addition still taking place at C5.
- If a poor leaving group is present at C5 and no lateral protons are available at this position, the nucleophile adds at C4 and replaces methoxide in the allylic position by cleavage of the weak N–O bond. Subsequent proton abstraction provides the aromatic product **388**. This sequence gives access to 1,2,3-triazoles with two different substituents.
- If a good leaving group like chlorine resides at C5, nucleophilic displacement of the leaving group, most likely following a conventional AE mechanism, takes place prior to nucleophilic addition at C4 and elimination of methoxide from the allylic position followed by proton abstraction. This sequence gives access to 1,2,3-triazoles with two identical substituents **392**.
- If a methyl group is present at C5, fluoride, cyanide, acetoxy, azide, methylthio, methylsulfonyl anions, and methylamine predominantly attack at C4 replacing methoxide from the allylic position furnishing the corresponding 4-substituted 1,2,3-triazoles **395** in fair to good yields. Fluoride and cyanide to a minor extent, and methoxide ion predominantly so, also attack the lateral carbon atom with formation of fluoro-methyl, cyanomethyl, or methoxymethyl-1,2,3-triazole **397**, **398**, or **399**. These products may arise if the intermediate methoxytriazolium salt **393** abstracts a lateral proton leaving a neutral species **396**, which is then subject to nucleophilic allylic displacement of the *N*-methoxy group.
- If poor leaving groups are present at C4 and C5 and no lateral protons are available at these positions, nucleophile addition at the *para* position of the 2-phenyl group is observed ([1997BSB717](#)).

Navigation between these possibilities offers a great potential for optimization aiming at a specific target.

4.1.6.11. *O*-Acylation

2-Phenyl-1,2,3-triazole 1-oxide **341** (R=Ph) and its 4-methyl derivative **346** (R=Ph, R¹=H, R²=Me) both reacted with Ac₂O at elevated temperatures to give 2-phenyl-4-acetoxy-1,2,3-triazole **405** or **406**, respectively ([1981JCS\(P1\)503](#)). It was suggested that *O*-acylation with formation of 1-acetoxy-2-phenyl-1,2,3-triazolium salt **400** or **403** is succeeded by nucleophilic addition of acetate ion at C5 and subsequent rearomatization by elimination of AcOH ([Scheme 120](#), line 1). Trifluoroacetic anhydride reacted similarly and was more reactive allowing for lower reaction temperatures. AcCl was even more reactive and the reaction was exothermic. Compound **341** (R=Me) afforded 2-methyl-4-acetoxy-1,2,3-triazole **405** (R=Me) as the sole product ([1986ACSA\(B\)262](#)), while the corresponding phenyl-triazole **341** (R=Ph) gave an easily separable 8:1 mixture of 4-acetoxy- and 4-chloro-1,2,3-triazoles **405** (R=Ph) and **380** (R=Ph). AcCl first

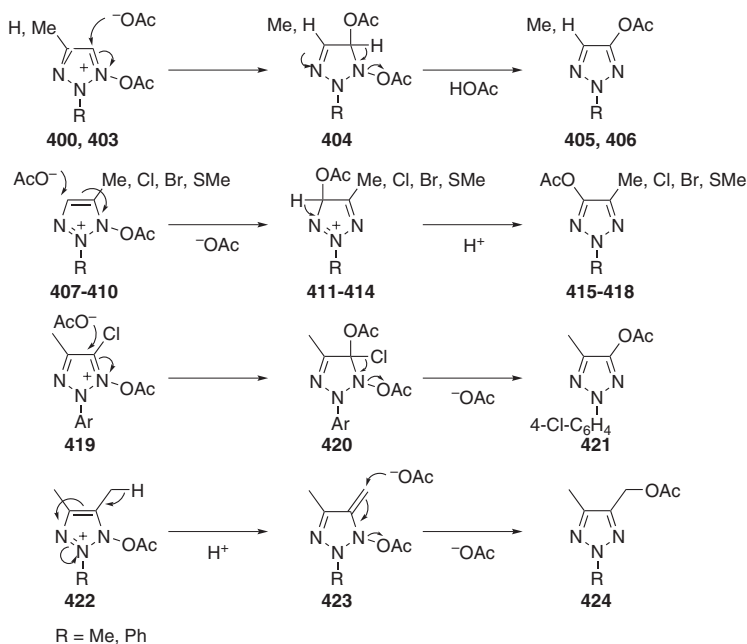
acylates the *N*-oxygen atom to give **400** ($R = \text{Ph}$) with simultaneous formation of chloride ions. It has been assumed that addition of the chloride anions at C5 of **400** ($R = \text{Ph}$) followed by rearomatization by elimination of HOAc renders the chloro-substituted product **380** ($R = \text{Ph}$). The eliminated HOAc competes with the chloride anion attacking at C5 of **400** producing the acetoxy-substituted product **405** by elimination of AcOH, which thus is regenerated. Later, accumulating evidence points to the intermediacy of an azadioxolenium ion **401** formed by cyclization of **400** (1997BSB717). Attack at C5 of **401** by chloride anion yields the chloro-substituted by-product **380** ($R = \text{Ph}$), while attack by AcOH or hydrolysis during workup affords the acetoxy-substituted main product **402** (Scheme 119).



Scheme 119

Substituents present in the starting material affected product composition according to a series of perceptions extracted from the outcome of the reaction of selected 2-phenyl-1,2,3-triazole 1-oxides with AcCl as illustrated in Scheme 120 (1981JCS(P1)503, 1997BSB717). The reasoning is based upon initial formation of an *O*-acetylated species shown in the left column, which then reacts with acetate ion in the product-determining step. The *O*-acetylated species may react in a similar fashion with other nucleophiles like the chloride ion.

- In C5 unsubstituted 2-methyl or 2-phenyl-1,2,3-triazole 1-oxides the intermediates **400** and **403** react at C5. A methyl group at C4 does not significantly influence product composition. The chloro analogue **380** is formed in minor amounts and is easy to remove. The reaction gives access to substituted acetoxy-1,2,3-triazoles **405** and **406**.
- If C5 possesses a substituent, intermediate **411–414** is formed. Acetate ion adds at C4 and replaces acetate from the allylic position by cleavage of the weak N–O bond. Then follows proton abstraction affording the aromatic products **415–418**. This behavior applies even when the 5-substituent is Cl, a potential leaving group, or a methyl group offering lateral protons. This sequence gives access to substituted acetoxy-1,2,3-triazoles **415–418**.
- If C4 carries a methyl group and C5 carries chlorine, the latter is replaced with acetate ion to give intermediate **420**. Intermediate **420** aromatizes by formal elimination of AcOCl, a chlorinating agent that attacks the



Scheme 120

phenyl group replacing its H4 with chlorine. If the phenyl 4-position is already occupied the chlorine adds at the phenyl 2-position. The sequence is terminated by proton abstraction yielding **421**. Additional experiments support this mechanism (1997BSB717). The sequence leads to acetoxymethyl-1,2,3-triazoles **421** though easier accessible by alternative methods.

- If a methyl group is situated both at C4 and at C5, O-acylation to give **422** is accompanied by abstraction of a lateral proton, most likely from the 5-methyl group. Then acetate ions attack replacing acetate from the allylic position. This sequence is an efficient route to 2-phenyl-4-acetoxymethyl-1,2,3-triazoles **424**.

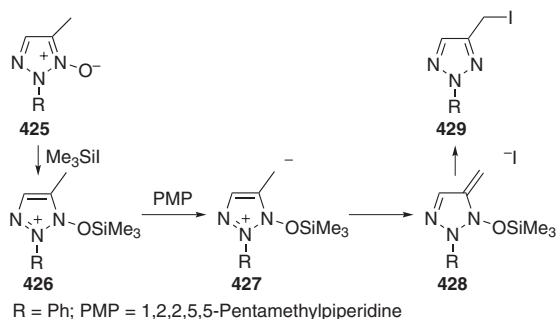
These observations lead to the conclusion that 2-substituted 1,2,3-triazole 1-oxides **326** react with AcCl with a regioselectivity that tends to drop in the order C5, C4 > 5-Me > C4' > C2' > 4-Me.

Other nucleophiles, like the chloride ion, react in the same fashion with the acyloxymethyl-1,2,3-triazolium salts in the left column of Scheme 120. More details are given in (1997BSB717).

4.1.6.12. O-Silylation

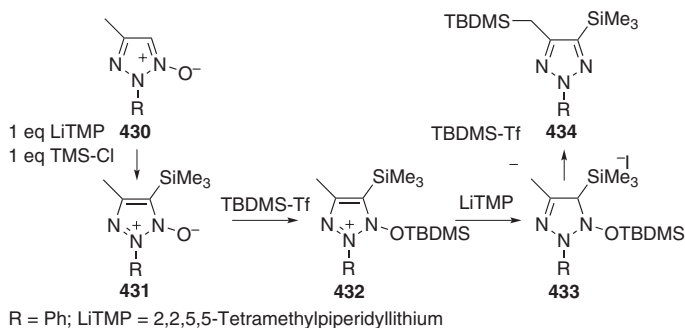
2-Substituted 1,2,3-triazole 1-oxides **326** are silylated at the oxygen atom to give moisture sensitive silyloxymethyl-1,2,3-triazolium salts, which have been characterized by their NMR spectra (1993JCS(P1)625, 1992JCS(P1)2555).

Both ring positions and lateral positions – both at C4 and C5 – are activated by the *O*-silylation. Substituents can be introduced at the lateral 5-position by *O*-silylation followed by abstraction of the activated lateral proton with a weak non-nucleophilic base. The neutral species **428** formed is subject to nucleophilic allylic displacement of the silyloxy anion rendering laterally substituted triazole **429** in one pot (Scheme 121).



Scheme 121

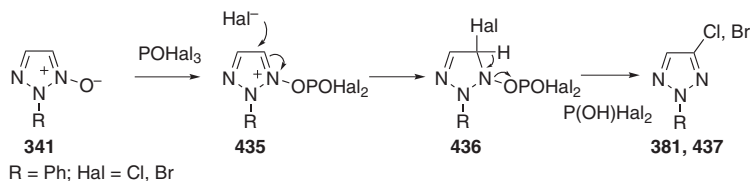
Substituents can be introduced even at the lateral 4-position (1993JCS(P1)625). In the example shown in Scheme 122, the reactive 5-position is first protected by silylation effected by abstraction of the proton at C5 using a strong non-nucleophilic base like LiTMP, followed by treatment with TMS chloride. With the 5-position thus protected subsequent *O*-silylation of **431** to give **432** activates the lateral proton at the 4-position, which is removed by a second equivalent of base. The lateral anion **433** is then quenched with an electrophile like *tert*-butyldimethylsilyl (TBDMS) triflate that produces **434**. The entire sequence **430** \rightarrow **434** can be preformed in one pot.



Scheme 122

4.1.6.13. O-Phosphorylation

2-Substituted 1,2,3-triazole 1-oxides **326** react with POCl_3 or POBr_3 in CHCl_3 solution producing 1-substituted 5-chloro or 5-bromo-1,2,3-triazoles **381** or **437** in high yields (1981JCS(P1)503). Most likely, initial O-phosphorylation is followed by nucleophilic addition of the halogenide ions liberated by the phosphorylation. Subsequent elimination of HOPHal_2 restores aromaticity affording halogen-substituted 1,2,3-triazoles **381** and **437** (Scheme 123).

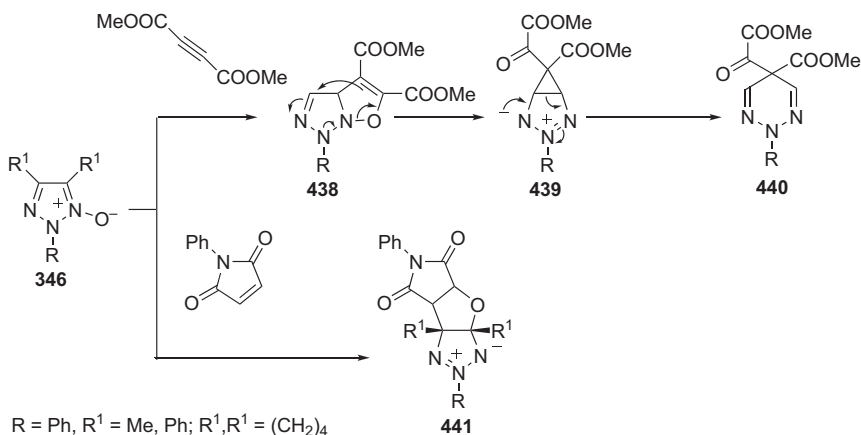


Scheme 123

4.1.6.14. 1,3-Dipolar cycloaddition

2-Substituted 1,2,3-triazole 1-oxides **346** act as 1,3-dipoles when heated with diethyl acetylene dicarboxylate yielding **440** (1987CC706, 1990JCS(P1)3321). A conceivable mechanism, slightly different from that presented in the original paper, is sketched in Scheme 124.

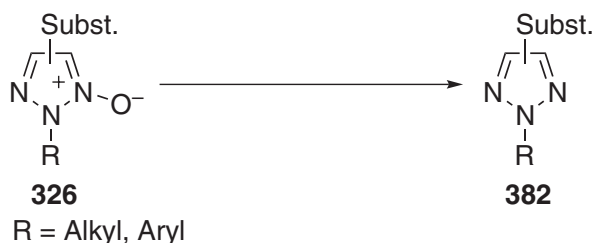
Also *N*-phenylmaleimide reacted as 1,3-dipolarophile with **346** producing the tetrahydrofuro[2,3-*d*]-1,2,3-triazole **441**. However, **326** failed to react with acrylonitrile, ethyl acrylate, methyl methacrylate, or fumaronitrile.



Scheme 124

4.1.6.15. Deoxygenation

2-Substituted 1,2,3-triazole 1-oxides **326** can be deoxygenated to give the corresponding 1,2,3-triazoles **382** by treatment with PCl_3 neat or in CH_2Cl_2 solution typically by heating to 60°C for 2–5 h (1992ACSA972, 2008SL2188, 2007PATWO71900). Heating with $\text{P}(\text{OEt})_3$ (1993T5339) and treatment with Zn and HOAc (1979HCA779, 1983ACSA97) also work well. Finally, the *N*-oxygen atom can be removed at low temperatures by sequential *O*-methylation, deprotonation with butyllithium at -78°C , and deformation by elevation of the temperature to about -20°C (1982JCS(P1)2749) (Scheme 125).



Scheme 125

4.1.6.16. Oxygenation

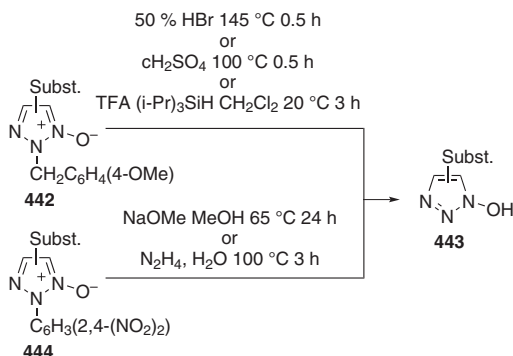
The *N*-oxide construct survived when 2-(2-hydroxypropyl)-4,5-dinitro-1,2,3-triazole 1-oxide was subject to destructive nitration under harsh conditions to provide 2-(trinitromethyl)-4,5-dinitro-1,2,3-triazole 1-oxide (2003CHE467).

4.1.6.17. *N*-Dealkylation

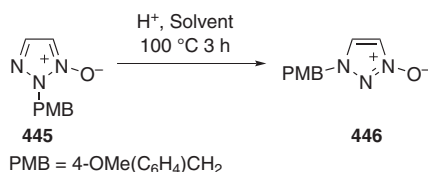
2-*t*-Butyl-1,2,3-triazole 1-oxides **326** ($\text{R} = t\text{-Bu}$) lose its *t*-butyl group when kept at room temperature with TFA + conc. H_2O_2 for 3 h. The product is the 1-hydroxy-1,2,3-triazole **443** (2003CHE608). 2-(4-Methoxybenzyl)-1,2,3-triazole 1-oxides **442** are dealkylated when heated to 70°C for 3 h with TFA affording **443** (2002JOC3904, 2001JOC8654). The dealkylation is facilitated by addition of triisopropylsilane. The *p*-methoxybenzyl (PMB) group can also be removed by heating to 100°C for 0.5 h with conc. H_2SO_4 . Many specifically functionalized 1-hydroxy-1,2,3-triazoles **443** have been obtained with regiocontrol by introducing the substituents in the activated 2-(4-methoxybenzyl)-substituted *N*-oxides **442**, followed by removal of the 4-methoxybenzyl group (Scheme 126).

4.1.6.18. Rearrangement

2-(4-Methoxybenzyl)-1,2,3-triazole 1-oxides like **445** when heated with strong acid rearranges to 3-(4-methoxybenzyl)-1,2,3-triazole 1-oxides **446** (2010UP3) (Scheme 127).



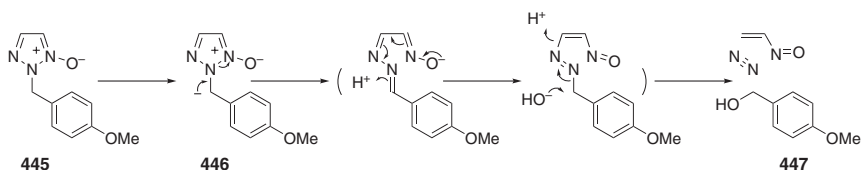
Scheme 126



Scheme 127

4.1.6.19. Ring opening

2-Benzyl-1,2,3-triazole 1-oxides are prone to undergo ring opening when treated with strong bases. Thus 2-(4-methoxybenzyl)-1,2,3-triazole 1-oxide **445** upon treatment with LDA at -78°C in the absence of electrophiles gives rise to 4-methoxybenzyl alcohol **447** as the solely isolable product. A putative mechanism for this transformation is shown in Scheme 128.



Scheme 128

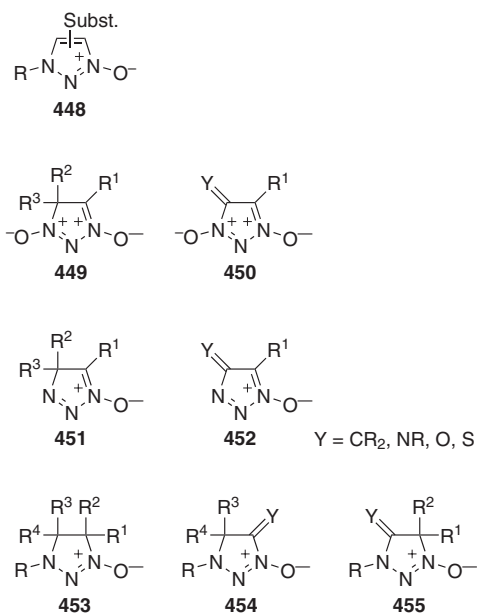
4.1.7. Applications of 2-substituted 1,2,3-triazole 1-oxides

The 2-substituted 1,2,3-triazole 1-oxides **326** have been used for synthesis of 2-substituted 1,2,3-triazoles **382** and regioselectively substituted 1-hydroxy-1,2,3-triazoles **443** manipulating the substituent in the *N*-oxide

series, where both ring and lateral positions are manageable. After introduction of the substituents and the *N*-oxygen, the 2-substituent or both can be removed. The 2-aryl-1,2,3-triazole 1-oxides themselves are of interest in industry and agriculture. Thus, 2-aryl-4-hydroxy-1,2,3-triazole 1-oxides and substituted 2-aryl-1,2,3-triazole 1-oxides containing a phosphorus atom hold promise as insecticides, fungicides, bactericides, nematocides, and acaricides (1975GEP(O)24422685, 1975GEP(O)2442843). The 2-aryl-1,2,3-triazole 1-oxides have been used as precursors for 2-aryl-1,2,3-triazoles with insecticidal activity, for example, against the house fly (1996PEST189). 2-(3-Phenyl-7-coumarinyl)-1,2,3-triazole 1-oxides with alkyl or aryl substituents at positions 4 and 5 have attracted interest as detergent and fluorescent whitening agents (1972USP3646054). Amino-nitro-triazole oxides hold great interest for the synthesis of new compounds in this class, mainly due to the possibility of replacing the nitro group with various nucleophiles. Furthermore, the 1,3-dipolar cycloaddition of olefins to the triazole oxide ring permits construction of other heterocyclic systems (1996CHE580). Additional uses are discussed in (1997MI1).

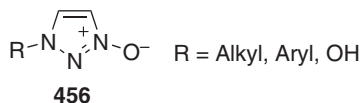
4.2. 3-Substituted 1,2,3-triazole 1-oxides

The aromatic 3-substituted 1,2,3-triazole 1-oxides **448** are derived from 1-substituted 1,2,3-triazoles **457** by appending an oxygen atom to the



Scheme 129

pyridine type ring nitrogen atom at position 3 of the triazole nucleus. The pyrrole type nitrogen atom of the triazole ring can be attached to an alkyl or aryl group or to a hydroxy or an amino group (Scheme 129). Except for **455** (Y=NR), nonaromatic N-oxides **451–454** and nonaromatic N,N'-dioxides **449–450** have not been reported (Scheme 130).



Scheme 130

The aromatic 3-substituted 1,2,3-triazole 1-oxides are represented by the formula **456** (Scheme 130). The parent compound **344** is one of the three tautomeric forms shown in Scheme 101.

4.2.1. Molecular structure

The resonance structures of the 3-substituted 1,2,3-triazole 1-oxides **456** are discussed in Section 1.1.1. 3-Substituted 1,2,3-triazole 1-oxides **456** are strictly according to IUPAC nomenclature 1-substituted 1*H*-1,2,3-triazole 3-oxides since when R=H the hydrogen position takes numbering precedence. The alternative, correct name 1-substituted 3-oxo-1*H*-1,2,3-triazoles has not been adopted in the literature. In the present review the most commonly used naming is adopted calling structure **456** a 3-substituted 1,2,3-triazole 1-oxide. This naming is accepted by IUPAC, *Chem. Abstr. Autonom.*

3-Substituted benzo-1,2,3-triazole 1-oxides were known when the first noncondensed 3-substituted 1,2,3-triazole 1-oxides **456** were reported in 1987 and it was shown that a compound believed to be the isomeric 1-benzyloxy-1,2,3-triazole was in fact the triazole 1-oxide **456** (R=CH₂Ph) (1987ACSA(B)724). Since then about 60 3-substituted 1,2,3-triazole 1-oxides with a variety of substituents at C3, C4, and C5 have been reported. No previous review on 3-substituted 1,2,3-triazole 1-oxides exists. Examples of the use of 3-substituted 1,2,3-triazole 1-oxides **448** by synthesis of substituted 1,2,3-triazoles are given in (1988BSB573).

4.2.2. Physical properties

The 3-alkyl- or aryl-substituted 1,2,3-triazole 1-oxides **448** are usually stable, crystalline, polar, and somewhat hygroscopic compounds. 3-Substituted 1,2,3-triazole 1-oxides **448** are weak bases being subject to protonation at the negatively charged oxygen atom. 3-Hydroxy-1,2,3-triazole 1-oxide **456** (R=OH) acts both as a base and as an acid. No pK_a values for 3-substituted 1,2,3-triazole 1-oxide have been reported.

4.2.3. Theoretical calculations

Theoretical calculations on the 3-*H* tautomer of 1-hydroxy-4-phenyl-5-carboxylic acid **443** ($R^4 = \text{Ph}$, $R^5 = \text{COOH}$) have been performed using the B3LYP/6-31G(*d*) (2005RJOC591) method.

4.2.4. Molecular spectroscopy

No UV data seem to have been published. IR and ¹H NMR data of a number of representative compounds have been reported (1987ACSA(B)724, 1993JCS(P1)625, 1993BAU711). MS data for a number of 3-substituted 1,2,3-triazole 1-oxides have been published. A M-16 peak seems to be characteristic but its intensity tends to be small to imperceptible. ¹³C NMR data for a series of 3-substituted 1,2,3-triazoles have been reported (1993JCS(P1)625). Comparison of the ¹³C NMR data of 3-benzyl 1,2,3-triazole 1-oxide **456** ($R = \text{CH}_2\text{Ph}$) (1993JCS(P1)625) with the corresponding signals of 1-benzyl-1,2,3-triazole **457** ($R = \text{CH}_2\text{Ph}$) (1988MRC134) reveals that introduction of the *N*-oxygen atom causes a 2.6ppm downfield shift of C4 and a 20.0ppm upfield shift of C5. The latter shift indicates that C4 has adopted negative charge from the oxygen to C5. Such delocalization cannot be due to mesomeric delocalization as discussed in Section 1.1.1. The increased negative charge at C5 is reflected by the observed activation of the 5-position toward electrophilic substitution discussed in Section 4.2.7.1. *N*-Oxidation leads to a 7.0 and a 2.6Hz increase in the one-bond C–H couplings at C4 and C5, while the two-bond C4–H5 coupling decreases to 2.9Hz and the C5–H4 coupling increases to 5.2Hz. ¹⁴N and ¹⁵N NMR data have been published (1993BAU711) and three structures have been studied by X-ray (1993BAU711). In addition, the X-ray data on the 3-*H* tautomer of 1-hydroxy-4-phenyl-5-carboxylic acid **443** ($R^4 = \text{Ph}$, $R^5 = \text{COOH}$) are available (2005RJOC591).

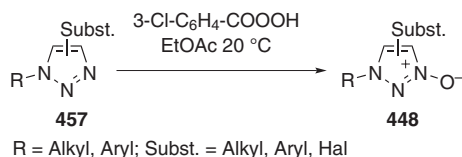
4.2.5. Preparation of 3-substituted 1,2,3-triazole 1-oxides

3-Substituted 1,2,3-triazole 1-oxide **448** can be prepared by *N*-oxidation of 1-substituted 1,2,3-triazoles **457**, by *N*-alkylation of 1-hydroxy-1,2,3-triazoles **443**, by cyclization of triazene 1-oxides **460**, or by rearrangement of 2-substituted 1,2,3-triazole 1-oxides **445** ($R = \text{PMB}$). Finally, base-mediated ring opening of pyrimidinediones **463** offers a route to **464**.

4.2.5.1. *N*-Oxidation of 1-substituted 1,2,3-triazoles

1-Substituted 1,2,3-triazoles **457** ($R = \text{Alk}$, Ar , or OH) are oxidized by 3-chloroperbenzoic acid in ethyl acetate solution to corresponding 3-substituted 1,2,3-triazole 1-oxides **448** (1987ACSA(B)724, 1995JCS(P1)243). The yields decrease when electron-attracting substituents are present, particularly if situated adjacent to the nitrogen atom to be oxidized. Phenyl groups at

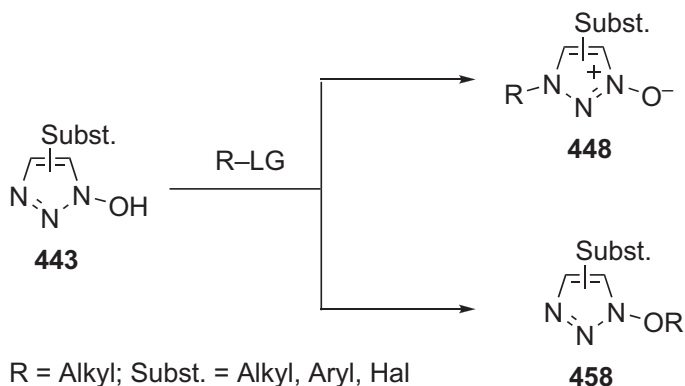
this position also lead to decreased yields. However, low yields are compensated for by easy recovery of the starting material (Scheme 131).



Scheme 131

4.2.5.2. *N*-Alkylation of 1-hydroxy-1,2,3-triazoles

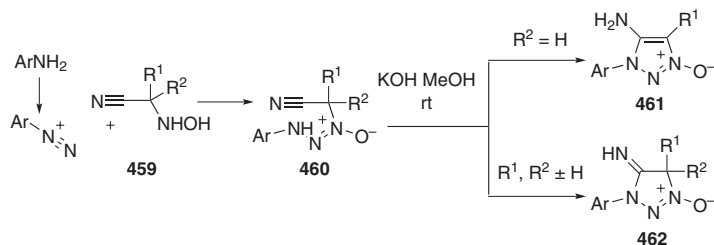
N-Alkylation of 1-hydroxy-1,2,3-triazoles **443** produces 3-substituted 1,2,3-triazole 1-oxides **448** (R=Alk). Competing *O*-alkylation of the 1-hydroxy-1,2,3-triazoles **443** to give 1-alkoxy-1,2,3-triazole **458** is suppressed by omitting addition of base during the alkylation (1996ACSA549, 2001S1053, 2002JOC3904) (Scheme 132).



Scheme 132

4.2.5.3. Cyclization of triazene 1-oxides

3-Aryl-1-(α -cyanoethyl)-triazene 1-oxides **460** upon treatment at room temperature for 0.5h with catalytic or equimolar amounts of KOH in methanol solution cyclize to give 3-aryl-4-amino-5-methyl-1,2,3-triazole 1-oxides **461**. The triazenes are synthesized by reaction of 4-nitrobenzenediazonium tetrafluoroborate with *N*-cyanomethylhydroxylamine **459** (1992BAU1895) (Scheme 133).



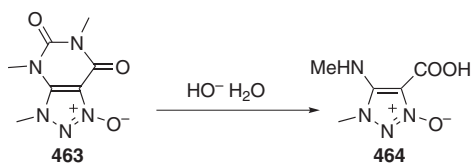
Scheme 133

4.2.5.4. Rearrangement of 2-substituted 1,2,3-triazole 1-oxides

The 4-methoxybenzyl group of 2-(4-methoxybenzyl)-1,2,3-triazole 1-oxides **445** is labile under strong acidic conditions and migrates to the 3-position as shown in [Scheme 127](#).

4.2.5.5. Ring opening of triazolopyrimidinediones

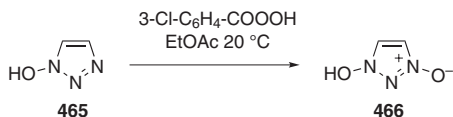
Hydrolysis of 2-phenyl-[1.2.3]triazolo[4,5-*d*]pyrimidine-5,7-dione *N*-oxides **463** in basic solution gives rise to 4-amino- and 4-ureido-2-phenyl-1,2,3-triazole-5-carboxylic acid 1-oxides **464**, as well as their hydrazides and methylamide ([2005JGU636](#)) ([Scheme 134](#)).



Scheme 134

4.2.6. Preparation of 3-hydroxytriazole 1-oxides

When 1,2,3-triazole was oxidized with 3-chloro perbenzoic acid in order to synthesize 1-hydroxy-1,2,3-triazole **465**, further oxidation of **465** took place affording 3-hydroxy-1,2,3-triazole 1-oxide **466** in 7% isolated yield. No attempts to optimize the yield of **466** or to explore its reactivity were reported ([1995JCS\(P1\)243](#)) ([Scheme 135](#)).



Scheme 135

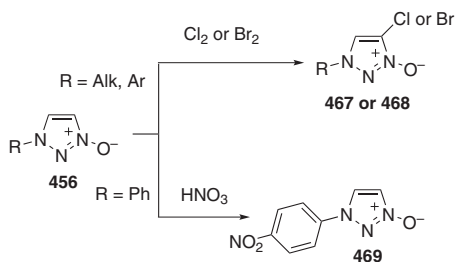
4.2.7. Reactions of 3-substituted 1,2,3-triazole 1-oxides

3-Substituted 1,2,3-triazole 1-oxides **448** have been reported to undergo electrophilic and nucleophilic aromatic substitution and are subject to debromination, proton–metal exchange, and halogen–metal exchange followed by electrophilic addition. Transmetallation and cross-coupling have not been described. 3-Substituted 1,2,3-triazole 1-oxides **448** can be protonated or alkylated at the O-atom and they can be deoxygenated and dealkylated. The individual reactions are described in [Section 4.2.7.1–4.2.7.14](#).

4.2.7.1. Electrophilic aromatic substitution

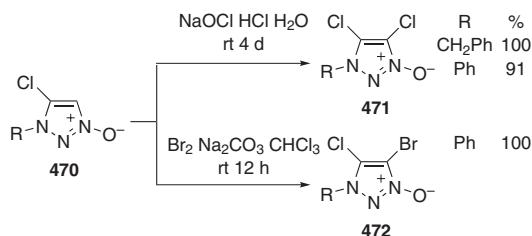
3-Substituted 1,2,3-triazole 1-oxides **456** are halogenated regioselectively at the 5-position to give **467** or **468** when treated with Cl_2 in $\text{CHCl}_3\text{--H}_2\text{O}$ or with Br_2 in CCl_4 ([1987ACSA\(B\)724](#)). Under similar conditions the corresponding parent 1-substituted 1,2,3-triazoles **478** are first attacked at the 4-position. The 1,2,3-triazole 1-oxides **456** are slightly activated as compared to the parent 1-substituted triazoles **478**, as testified by a competition experiment where an equimolar mixture of the triazole **478** ($\text{R}=\text{CH}_2\text{Ph}$) and its derived 1-oxide **456** ($\text{R}=\text{CH}_2\text{Ph}$) was treated with one equivalent of bromine to react exclusively with the 1-oxide **456**. 3-Phenyl-1,2,3-triazole 1-oxide **456** ($\text{R}=\text{Ph}$) was brominated to give the 5-bromo derivative **468** ($\text{R}=\text{Ph}$) in a clean reaction. Under identical conditions 1-phenyl-triazole **456** ($\text{R}=\text{Ph}$) was attacked at the phenyl group only. This confirms the *N*-oxide activation of the 1,2,3-triazole 1-oxide nucleus to be combined with deactivation of the phenyl group, which in the *N*-oxide is situated at an electron deficient N-atom. The observed regioselectivity cannot be explained by simple comparison of resonance structures. After introduction of halogen, *N*-deoxygenation furnishes otherwise difficult accessible 1-phenyl-4-halogeno-1,2,3-triazoles.

3-Phenyl-1,2,3-triazole 1-oxide **456** ($\text{R}=\text{Ph}$) is nitrated by $\text{HNO}_3 + \text{H}_2\text{SO}_4$ at the phenyl *para* position ([1987ACSA\(B\)724](#)). It was assumed that the strong acid protonates the *N*-oxygen atom, the triazole ring becomes positively charged and thus *deactivated* toward electrophiles. By protonation of the 1,2,3-triazole 1-oxide **456** ($\text{R}=\text{Ph}$), the phenyl group just *loses activation* and takes over as the most reactive entity ([Scheme 136](#)).



Scheme 136

The 4-chloro-substituted triazole 1-oxide **470** could be chlorinated and brominated at the 5-position affording **471** or **472** in excellent yield (1987ACSA(B)724). Even the 3-phenyl compound **470** ($R=Ph$) reacted regioselectively in the triazole ring confirming the activation conveyed by the N -oxide functionality (Scheme 137).

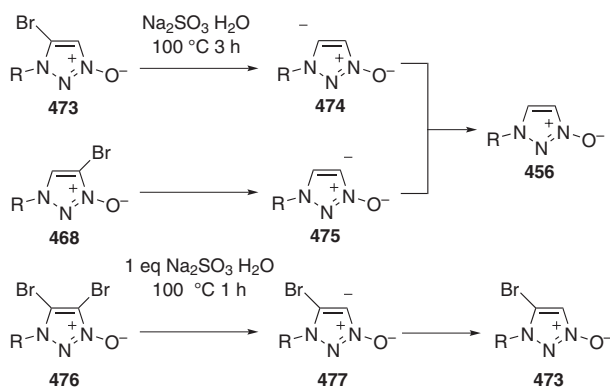


Scheme 137

4.2.7.2. Debromination, dechlorination, demethylthiolation, and demethylsulfonylation

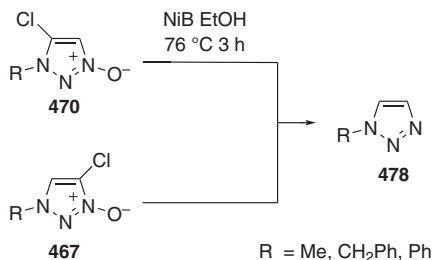
Dechlorination, debromination, demethylthiolation, and demethylsulfonylation of triazole 1-oxides **448** are all formally related to halogen-metal exchange and can also be regarded as reduction processes favored by the formation of a stabilized anion.

Debromination of **473** and **468** was achieved by heating with sodium sulfite in aqueous solution to give **456** (1987ACSA(B)724). The 4,5-dibromo compound **476** was debrominated regioselectively furnishing the 4-bromo compound **473** (1987ACSA(B)724). The regioselectivity reflects that the 5-anion **475** according to H/D exchange rates is formed faster than the 4-anion **474** (Scheme 138).



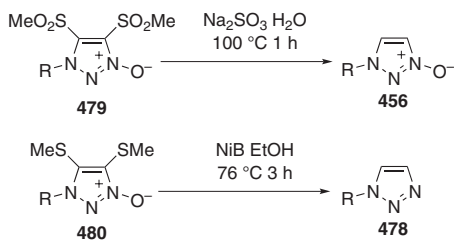
Scheme 138

Dechlorination of the 4-chloro or 5-chloro-1,2,3-triazole 1-oxide **470** or **467** required treatment with nickel boride, which caused loss of the *N*-oxygen and furnished **478** (Scheme 139).



Scheme 139

4,5-Dimethylsulfonyl- and 4,5-dimethylthio-1,2,3-triazole 1-oxide **479** and **480** were reduced unselectively with sodium sulfite and nickel boride, respectively. The latter reagent also removed the *N*-oxygen (Scheme 140).



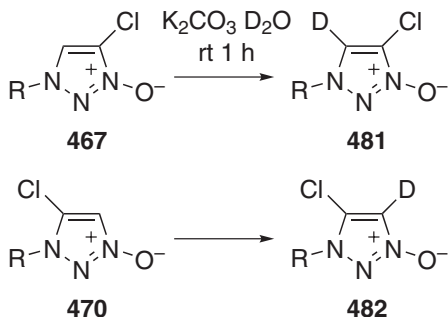
Scheme 140

4.2.7.3. Proton-metal exchange

Protons at positions 4 and 5 of 3-substituted 1,2,3-triazole 1-oxides **456** are more acidic than corresponding protons in the parent 1,2,3-triazoles **478** and are replaced quantitatively with deuterium within 1 h in deuterium oxide solution containing catalytic amounts of potassium carbonate (1987ACSA(B)724). In contrast, abstraction of H5 in 1-phenyl-1,2,3-triazole **478** (R=Ph) requires treatment with bases like *n*-butyllithium and the anion formed undergoes ring cleavage (1971CJC1792).

The observed enhanced acidity of H4 and H5 of the 1,2,3-triazole 1-oxides **456** may be explained by inductive stabilization of the anion negative charge by the adjacent positive nitrogen atoms as discussed in Section 1.4.3. The relative acidity of H4 and H5 conforms to that predicted in Section 1.4.3.1 as reflected by the relative H/D exchange rate of H4 and

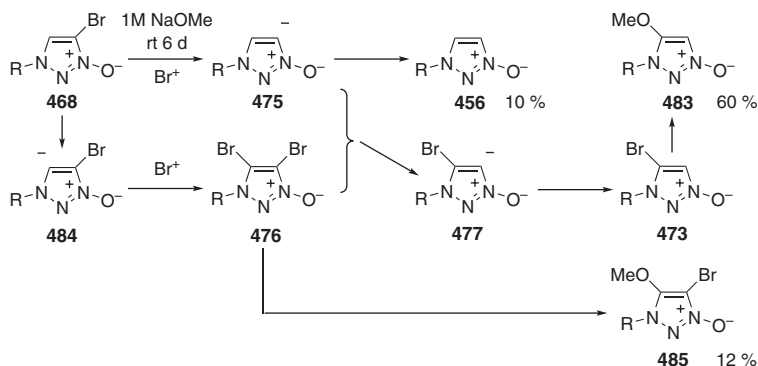
H5, which was found to be 1.8:1 in **456** (R=Me), 2.4:1 in **456** (R=CH₂Ph), and 6.1:1 in **456** (R=Ph) (1987ACSA(B)724). Substituents such as a halogen or a methoxy group enhance the acidity of adjacent protons significantly. Expectedly, the electron-attracting substituents stabilize the adjacent anion inductively. The generation and application of 1,2,3-triazole anions in synthesis are discussed in Section 4.1.6.2–5 (Scheme 141).



Scheme 141

4.2.7.4. Halogen–metal exchange

While 5-chloro-1,2,3-triazole 1-oxide **467** reacted with sodium methoxide with replacement of the chlorine (see Section 4.1.6.8), the corresponding bromo compound **468** under similar conditions afforded the *cine*-substitution product **483** as the main product (1987ACSA(B)724). A mechanism involving halogen dance and supported by control experiments is sketched in Scheme 142. The bromine in **468** is located at the less activated position with respect to nucleophilic displacement. On the other

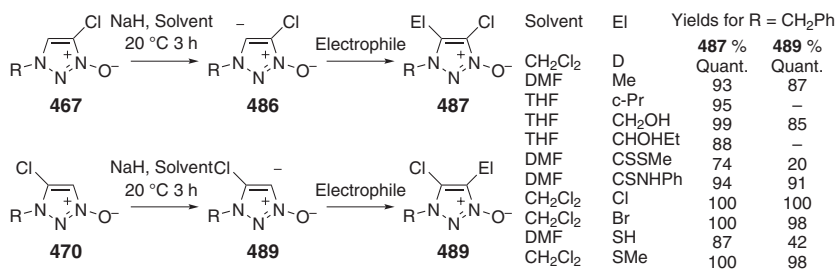


Scheme 142

hand, abstraction of a bromonium ion creates a stabilized anion **484**. The bromonium ion thus formed adds to the stabilized anion **484** derived from unchanged starting material producing the dibromo compound **476** with enhanced capability to abstract a bromonium ion due to the enhanced stability of the produced anions **477** and **484**. Protonation of the anion **484** leads to the starting material **468**, which reenters the reaction cycle, while protonation of the second anion **477** provides **473** with the bromine situated at the position reactive toward nucleophilic displacement, which leads to the methoxy compound **483**.

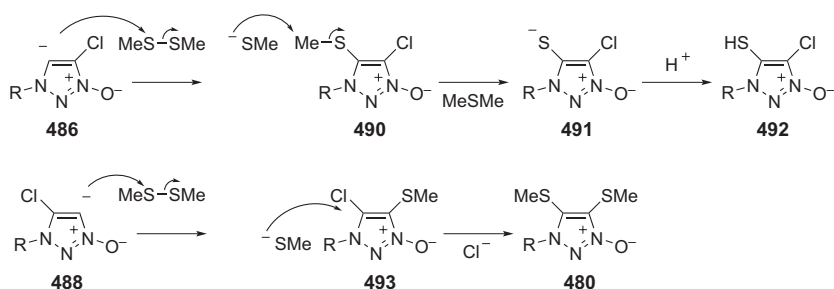
4.2.7.5. Metallation followed by electrophilic addition

Both the 4- and 5-position of 3-substituted 1,2,3-triazole 1-oxides **456** can be metallated by proton-metal or hydrogen-metal exchange. Several base and solvent combinations were tested for proton-metal exchange. Usually sodium hydride in dimethylformamide or CH_2Cl_2 is superior but potassium *t*-butoxide or *n*-butyllithium in THF are also applicable (1987ACSA(B)724, 2009UP1). Thus, 3-substituted 5-chloro-1,2,3-triazole 1-oxide **467** was deprotonated with sodium hydride in *N,N*-dimethylformamide or CH_2Cl_2 . The anion **486** formed was trapped with a series of electrophiles like MeOD, MeI, $\text{Cl}(\text{CH}_2)_3\text{Br}$, $(\text{CH}_2\text{O})_n$, EtCHO, cyclohexanone, CS_2 , PhNCS, CCl_6 , CBr_4 , S_8 , Me_2S_2 , and R_3SiCl to give **487** in high yields. The highly polar SH-substituted 1,2,3-triazole 1-oxides were difficult to isolate but *S*-methylation with MeI furnished easy manipulable methylthio derivatives **487** (E1=SMe) (1987ACSA(B)724, 2009UP1) (Scheme 143).



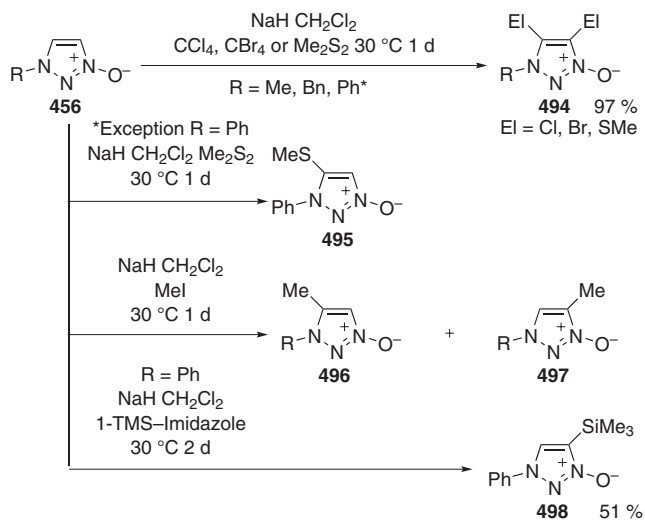
Scheme 143

The isomeric 3-substituted 4-chloro-1,2,3-triazole 1-oxides **470** reacted in a similar fashion. The chlorine in **470** is situated in the position most reactive toward nucleophilic displacement and is substituted with sulfide when sulfur or Me_2S_2 is used as an electrophile (1987ACSA(B)724, 2009UP1). A mechanism is suggested in Scheme 144.



Scheme 144

Deprotonation of 3-substituted 1,2,3-triazole 1-oxides devoid of substituents at C4 and C5 **456** may give rise to two isomeric anions **474** and **475**, both of which can react with electrophiles producing, e.g., **467** and **470**. If the substituent thus introduced is electron attracting, the derived anions, e.g., **486** and **488** are more stable than **474** and **475** derived from the starting material favoring disubstitution. Concordantly, disubstitution was the only or predominant reaction when Cl, Br or MeS were introduced in **456** by deprotonation followed by reaction with an electrophile. When an electron donating methyl group was introduced in **456**, monoselectivity and regioselectivity were observed (1987ACSA(B)724, 2009UP1). Steric factors may explain why the phenyl compound **456** (R=Ph) is monoselectively silylated at the less acidic but also less congested 5-position yielding **498** (Scheme 145).



Scheme 145

When Me_2S_2 is employed as an electrophile the reaction with the triazole anion gives rise to formation of methylthiolate anion which then can take part in nucleophilic displacement of existing leaving groups like chlorine or demethylate methylthio functionalities producing thiol and Me_2S . In order to facilitate workup and purification of products, iodomethane was added prior to workup converting all thiol groups to methylthio groups.

Deprotonation followed by addition of an electrophile, if needed combined with application of protecting groups, makes a great number of regioselectively substituted 1,2,3-triazole 1-oxides **448** accessible (Scheme 146).

4.2.7.6. Transmetallation

No examples of transmetallation in 3-substituted 1,2,3-triazole 1-oxides have been published.

4.2.7.7. Cross-coupling with 1,2,3-triazole donors

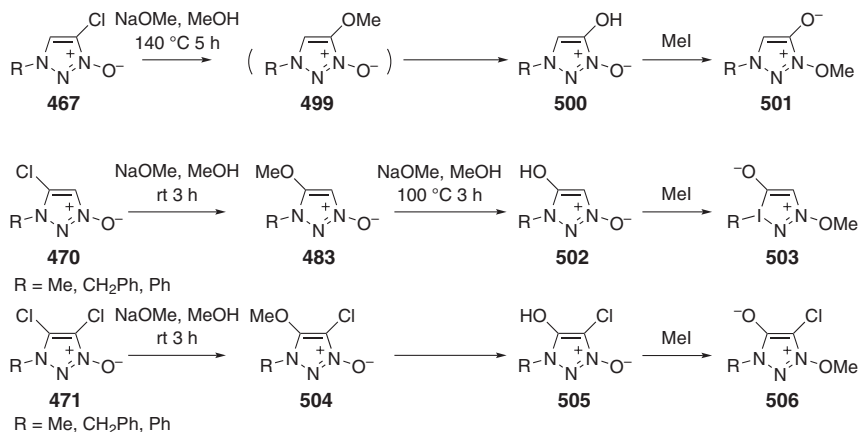
Cross-coupling of 3-substituted 1,2,3-triazole 1-oxides has not been reported.

4.2.7.8. Nucleophilic substitution

Halogen at the 4- and 5-position of 3-substituted 1,2,3-triazole 1-oxides **448** is activated toward nucleophilic substitution. While 1-benzyl 4-chloro-1,2,3-triazole **457** ($\text{R}=\text{CH}_2\text{Ph}$, Subst.=4-Cl) was recovered unchanged after heating to 140°C for 5h with 1-M sodium methoxide in methanol solution, the corresponding 1-oxide **467** under these conditions afforded the hydroxy compound **500** in quantitative yield as the result of nucleophilic displacement of the chlorine to give the methoxy compound **499**, which subsequently is demethylated by excess of methoxide producing **500** (1987ACSA(B)724). 1-Benzyl-5-chloro-1,2,3-triazole **457** ($\text{R}=\text{CH}_2\text{Ph}$, Subst.=5-Cl) does react with 1-M sodium methoxide to give the methoxy compound **457**($\text{R}=\text{CH}_2\text{Ph}$, Subst.=5-OMe) but complete conversion requires heating to 120°C for 16h. In contrast, chlorine in the derived *N*-oxide **470** is readily replaced at room temperature producing the methoxy compound **483** (1987ACSA(B)724). Heating of the latter compound with 1-M methoxide solution causes demethylation with formation of the hydroxy-substituted 1,2,3-triazole 1-oxide **502**. The same activation of halogen was found in the corresponding 3-methyl- and 3-phenyl-substituted *N*-oxides. The difference in reactivity of the 4- and 5-position makes regioselective nucleophilic displacement possible. Thus only the halogen at C4 of the 4,5-dichloro-1,2,3-triazole 1-oxide **471** was replaced with methoxy at room temperature to give product **505** (2009UP1).

The activation of halogen in 4- and 5-halogeno-substituted 1,2,3-triazole 1-oxides is in keeping with the prediction discussed in Section 1.4.2.

The difference in activation of halogen at the 4- and 5-position is much larger than in 1,3-disubstituted 1,2,3-triazolium salts (1988BSB573) and is useful for the regioselective introduction of nucleophiles in 1,2,3-triazoles.



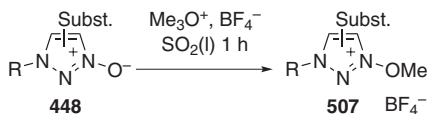
Scheme 146

4.2.7.9. O-Protonation

3-Substituted 1,2,3-triazole 1-oxides **448** are protonated at the oxygen atom. The site of the protonation is evident from ¹H and ¹³C NMR spectra, which are similar to those of the 1-methoxy-1,2,3-triazolium tetrafluoroborates **507** described in Section 4.2.7.10. The hydrochlorides are manipulable and separate from solutions in dry methanol upon addition of diethyl ether (1987ACSA(B)724).

4.2.7.10. O-Alkylation

The 3-substituted 1,2,3-triazole 1-oxides **448** were alkylated at the oxygen by trimethyloxonium tetrafluoroborate using liquid sulfur dioxide as the solvent affording hygroscopic 3-substituted 1-methoxy-1,2,3-triazolium tetrafluoroborate **507** in high yield (1987ACSA(B)724). The reactivity of these salts has not been reported (Scheme 147).



Scheme 147

The hydroxytriazole 1-oxides **500** and **502** when treated with methyl iodide were methylated predominantly at the *N*-oxygen affording mesoionic anhydro 1-methoxy-3-methyl-4-hydroxy- or 5-hydroxy-1,2,3-triazolium hydroxide **501** or **503** (Scheme 146) (1987ACSA(B)724). In both cases methylation at the C-hydroxy group took place to a minor extent giving rise to methoxy-substituted triazole 1-oxides **499** or **503**, respectively. Under similar conditions 3-methyl 4-hydroxy-5-chloro-1,2,3-triazole 1-oxide **505** produced a 2:1 mixture of the C-methoxy and the *N*-methoxy derivatives **504** and **506**. The mesoionic triazoles **501**, **503**, and **506** were dealkylated upon heating with 1-M sodium methoxide, reforming the hydroxy-substituted *N*-oxides **500**, **502**, and **505**, respectively.

4.2.7.11. *O*-Acylation

O-Acylation, *O*-silylation, or *O*-phosphorylation, expected to follow the trends observed for 3-substituted imidazole 1-oxides, have not been reported.

4.2.7.12. 1,3-Dipolar cycloaddition

No reports on 3-substituted 1,2,3-triazole 1-oxides **448** acting as 1,3-dipoles exist.

4.2.7.13. Deoxygenation

N-Deoxygenation of 3-substituted 1,2,3-triazole 1-oxides **448** was effected by PCl_3 under mild conditions (1987ACSA(B)724). Hydrogenolysis at room temperature in EtOH solution for 4–6h using hydrogen at 1atm and Raney nickel as catalyst is also efficient (2009UP1). NiB serves well too but it also reduces functionalities like chloro and methylthio groups (Section 4.2.7.2) (2009UP1). The facile deoxygenation makes 3-substituted triazole 1-oxides **448** with their palette of reaction possibilities excellent intermediates for the regioselective synthesis of 1,2,3-triazoles **457** with an otherwise inaccessible substituent pattern (Scheme 148).



Scheme 148

4.2.7.14. *N*-Dealkylation

3-PMB-substituted 1,2,3-triazole 1-oxides **448** (R=PMB) can be dealkylated to give *N*-hydroxy-1,2,3-triazoles **458** by heating to reflux with TFA. The dealkylation is facilitated by addition of triisopropylsilane. Also heating with conc. H_2SO_4 mediates dealkylation (2010UP3) (Scheme 149).

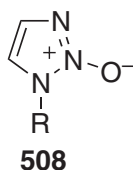


Scheme 149

4.2.8. Applications of 3-substituted 1,2,3-triazole 1-oxides

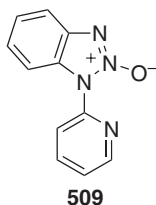
3-Substituted 1,2,3-triazole 1-oxides **448** have been used for and have a great potential for the synthesis of regioselectively substituted 1,2,3-triazoles **457** which possess their own virtues as mentioned in [Section 4.1.7](#). However, no reports on the biological activity or on the application of 3-substituted 1,2,3-triazole 1-oxides **448** are available. The missing data may be due to the, until recently, lack of a simple synthesis of the 1-oxides **448** based on a direct cyclization.

4.3. 1-Substituted 1,2,3-triazole 2-oxides



Scheme 150

1-Substituted 1,2,3-triazole 2-oxides **508** ([Scheme 150](#)) are only known as benzocondensed constructs **509**, which are beyond the scope of the present review [1973JHC495] ([Scheme 151](#)).

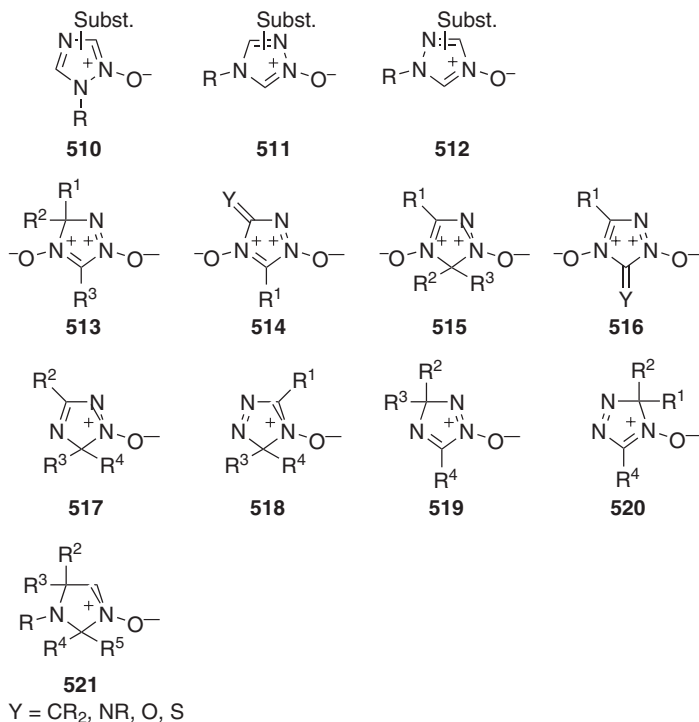


Scheme 151

5. 1,2,4-TRIAZOLE *N*-OXIDES

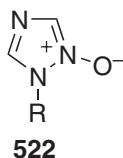
The three possible isomeric aromatic 1,2,4-triazole *N*-oxide constructs **510–512** are described individually in [Section 5.1](#), [5.2](#) and [5.3](#). Nonaromatic

1,2,4-triazoline *N,N'*-dioxides **513–516**, 1,2,4-triazoline *N*-oxides **517–520**, or 1,2,4-triazolidine *N*-oxides like **521** are imaginable but seem not to have been reported (Scheme 152).



Scheme 152

5.1. 2-Substituted 1,2,4-triazole 1-oxides

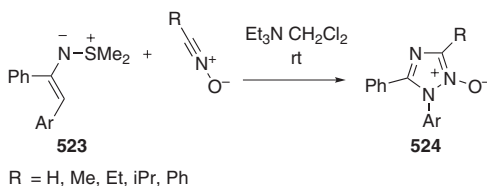


Scheme 153

13 Monocyclic 2-substituted 1,2,4-triazole 1-oxides derived from **522** have been reported (Scheme 153). The structure of the *N*-oxide fragment was proved by X-ray crystallography (2010LOCEC377). IR, H NMR, C NMR, and MS data have been published (1976JCS(P1)2166). 2-Substituted

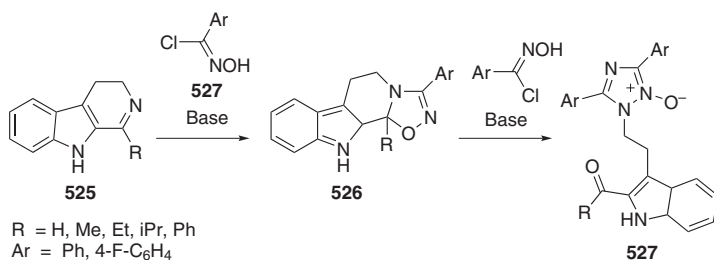
1,2,4-triazole 1-oxides **522** are crystalline polar substances, which are stable in solution up to 130°C.

2-Substituted 1,2,4-triazole 1-oxides **524** were first obtained by 1,3-dipolar cycloaddition of a nitrile oxide to *S,S*-dimethyl-sulfimides **523** (Scheme 154) (1974JSC(CC)486, 1976JCS(P1)2166, 1982JCR(M)3048).



Scheme 154

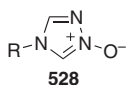
An electron-rich enamine double bond can also serve as the dipolar-enophile (2010LOCEC377) (Scheme 155). The initial cycloaddition product **526** then reacts with a second equivalent of nitriloxide with formation of the triazole *N*-oxide **527** in modest yield.



Scheme 155

The 2-substituted 1,2,4-triazole 1-oxides **524** could be *N*-deoxygenated by treatment with PCl_3 (2010LOCEC377). The oxygen was also lost by prolonged heating with boiling toluene (1976JCS(P1)2166, 2010LOCEC377).

5.2. 4-Substituted 1,2,4-triazole 1-oxides

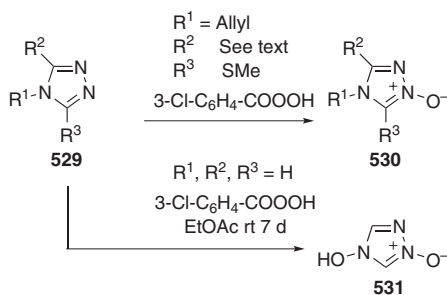


Scheme 156

Two 4-substituted 1,2,4-triazole 1-oxides, namely 2-(1-hydroxymethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline-1-yl)-4-allyl-5-methylthio 1,2,4-triazole 1-oxide **530** (1984H695) and 4-hydroxy-1,2,4-triazole 1-oxide **531** (1995JCS(P1)243), (Scheme 157) derived from the parent species **528** (Scheme 156), have been described. The compounds were characterized by their ¹H NMR and ¹³C NMR spectra.

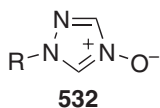
N-Oxide **530** was obtained by *N*-oxidation of the corresponding triazole **529** with 3-chloroperbenzoic acid providing the 1,2,4-triazole *N*-oxide in modest yield (Scheme 157).

The hydroxy-*N*-oxide **531** was prepared similarly in low yield by repeated *N*-oxidation with 3-chloroperbenzoic acid (Scheme 157).



Scheme 157

5.3. 1-Substituted 1,2,4-triazole 4-oxides



Scheme 158

Seven 1-substituted 1,2,4-triazole 4-oxides derived from **532** with R = Me, CH₂Ph, or Ph have been described (1972JPR101) (Scheme 158). Five of the compounds are devoid of substituents at C2.

The 1-substituted 1,2,4-triazole 4-oxides with the basic structure **532** are hygroscopic. They form hydrates, which lose the water by heating to melting or by recrystallization from anhydrous solvents. 1,2,4-Triazole 4-oxides **534** are 4 pK_a units weaker as a base than their deoxygenated progenitor **533** (1972JPR101).

The 1-substituted 1,2,4-triazole 4-oxides exhibit a solvent-dependent UV absorption at 230–250nm, which displays a bathochromic shift typical

for negative solvatochromy. A second absorption at about 320–350 nm observed in solutions in aprotic solvents assigned to a $n \rightarrow \pi^*$ or a $\pi \rightarrow \pi^*$ transition is also characteristic of *N*-oxides (1972JPR101).

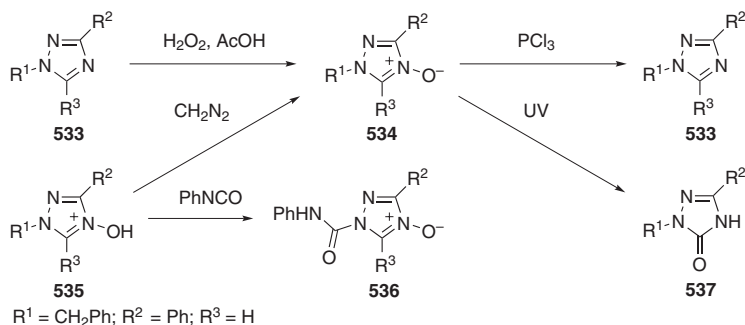
The IR spectra feature characteristic strong solvent- and substituent-dependent absorptions at 800–900, 1200–1300, and 3200–3500 cm^{-1} indicating strong association (1972JPR101).

The MS shows M-16 and M-17 signals typical of *N*-oxides (1972JPR101).

¹H NMR of the *N*-oxide **534** signaled anisotropy resulting from proximity of the two phenyl groups (1972JPR101).

The 1-substituted 1,2,4-triazole 4-oxides **534** have been prepared by heating the parent 1,2,4-triazole **533** with H_2O_2 in AcOH (1981CHE1145).

Attempts to alkylate the 4-hydroxy-1,2,4-triazoles **535** with MeI, Me_2SO_4 , or PhCH_2Br using different bases and solvents invariably gave difficult to separate mixtures. However, diazomethane methylated **535** to **534** together with the *O*-methylated isomer in a 1:2.2 ratio from which the pure *N*-oxide **534** could be isolated. Acylation of **535** with PhNCO gave the *N*-oxide **536** (1972JPR101) (Scheme 159).



Scheme 159

The 1,2,4-triazole 4-oxides **534** were deoxygenated smoothly upon treatment with PCl_3 (1972JPR101) furnishing **533**.

Irradiation of 1-benzyl-3-phenyl-1,2,4-triazole 4-oxide **534** dissolved in CH_2Cl_2 with UV light led to deoxygenation with formation of **533**. In methanol solution rearrangement to **537** was the predominant reaction. The product composition was only slightly dependent on the wavelength (1972JPR372). A mechanism involving a three-membered intermediate was presented.

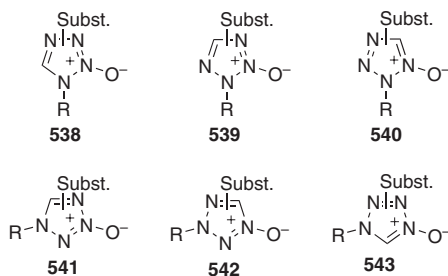
5.4. Applications of 1,2,4-triazole *N*-oxides

The 2-substituted 1,2,4-triazole 1-oxides **522** were regarded as potential inhibitors of mitogen-activated protein kinase (2010LOCEC377). Although

substituted 1,2,4-triazoles have many different uses (1987MI1), only few of these compounds have been synthesized *via* N-oxides, and the advantages by using N-oxides as intermediates for regiocontrolled introduction of substituents into the 1,2,4-triazole ring have only been explored to a limited extent.

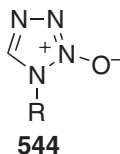
6. TETRAZOLE N-OXIDES

Six isomeric aromatic tetrazole N-oxide constructs **538**–**543** are conceivable (Scheme 160). They are discussed individually in Section 6.1–6.6.



Scheme 160

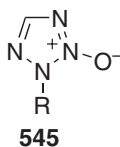
6.1. 1-Substituted tetrazole 2-oxides



Scheme 161

No 1-substituted tetrazole 2-oxides derived from structure **544** have been found in the literature (Scheme 161).

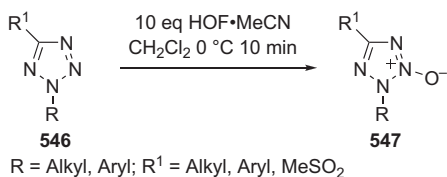
6.2. 3-Substituted tetrazole 2-oxides



Scheme 162

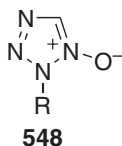
Four 3-substituted tetrazole 2-oxides **547** representing the parent structure **545** (Scheme 162) have been reported (2010JOC3141) (Scheme 163). The structure was proven by X-ray crystallography. UV and IR data have been recorded. ¹H NMR, ¹³C NMR, and ¹⁵N NMR spectra were assigned using heterocorrelated spectra. The oxidation of tetrazole **546** to tetrazole *N*-oxide **547** is reflected by a 32–51 ppm decrease in the shift of the ¹⁵N signals. MS obtained by using different ionization methods have been registered.

A series of 2,5-disubstituted tetrazoles **546**, which remained unchanged when treated with 3-chloroperbenzoic acid, dimethyldioxirane, or H₂O₂ in AcOH under microwave heating, could be oxidized at the 3-position by excess of HOF in MeCN at room temperature producing 1-substituted tetrazole 3-oxides **547** in excellent yields. The reaction was insensitive to electronic or steric effects imposed by the substituents. A methylthio substituent was oxidized completely to methylsulfone before oxidation of the tetrazole ring occurred (2010JOC3141) (Scheme 163).



Scheme 163

6.3. 2-Substituted tetrazole 1-oxides

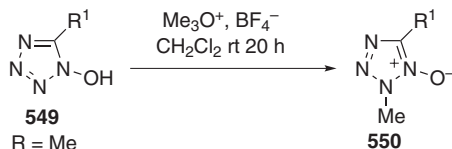


Scheme 164

Three 2-substituted tetrazole 1-oxides **550** representing the parent structure **548** (Scheme 163) have been reported (1913G71, 1983BAU181, 1984BAU142) (Scheme 165). These *N*-oxides are hygroscopic and crystallization with 0.5 mol of water has been observed. IR and ¹H NMR data have been reported (1984BAU142).

The 2-substituted tetrazole 1-oxides **550** were prepared from the corresponding hydroxytetrazoles **549** by methylation with trimethyloxonium tetrafluoroborate in CH₂Cl₂ at 20 °C (1984BAU142) or by benzylation of 1-hydroxytetrazole **549** (1913G71) (Scheme 165). Since *N*-alkylation and

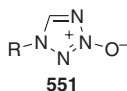
acylation of **549** is expected to take place at the most nucleophilic nitrogen atom, which is N-5, the structure of the products should not be taken for granted before unambiguous structural information has been acquired.



Scheme 165

The 2-substituted tetrazole 1-oxides **550** were readily deoxygenated by treatment with P + HI ([1984BAU142](#)).

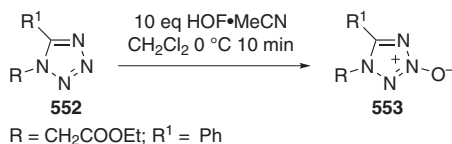
6.4. 1-Substituted tetrazole 3-oxides



Scheme 166

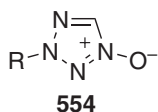
One 1-substituted tetrazole 3-oxide **553** representing **551** ([Scheme 166](#)) has been described ([2010JOC3141](#)) ([Scheme 167](#)). The structure was proven by X-ray crystallography. UV and IR data have been recorded. H NMR, C NMR and ^{15}N NMR spectra were assigned using heterocorrelated spectra. The oxidation of tetrazole **252** to tetrazole *N*-oxide **553** is reflected by decreased ^{15}N shift values, the signal from N-3 being displaced 40ppm as a consequence of the oxygenation. MS obtained by using different ionization methods have been registered.

2-Ethoxycarbonylmethyl-tetrazole **552** was oxidized at the 3-position by excess of HOF in MeCN at room temperature producing 2-ethoxycarbonyl-tetrazole 3-oxide **553** in excellent yield ([2010JOC3141](#)) ([Scheme 167](#)).



Scheme 167

6.5. 3-Substituted tetrazole 1-oxides

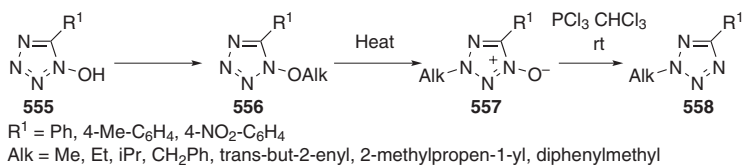


Scheme 168

14 Substances **557** derived from structure **554** (Scheme 168) have been described (Scheme 169). The structure of 3-methyl-5-phenyl-tetrazole 1-oxide monohydrate **557** (R=Ph, Alk=Me, H₂O) has been determined by X-ray crystallography (1993PJC1767). H NMR, C NMR, and MS data are also available (1993PJC1767).

3-Substituted tetrazole 1-oxides **557** were synthesized by thermal rearrangement of 1-alkoxy-5-substituted tetrazoles **556**, prepared by alkylation of the corresponding 1-hydroxy compounds **555**. Without a catalyst, migration of the alkyl group in **556** required heating to 200°C for 20min (1978TL399, 1993PJC1767) or to 120°C for 2h (1989BAU1488). Addition of TFA greatly facilitated the rearrangement causing migration of the 9-antracenylnmethyl group to occur at room temperature in 10min (2000AJC619) (Scheme 169).

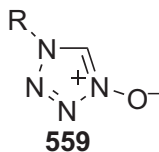
Upon heating to 129°C 3-substituted tetrazole 1-oxides **557** rearranged into 4-substituted tetrazole 1-oxides **559**, see Section 6.6.



Scheme 169

3-Substituted tetrazole 1-oxides **557** were deoxygenated upon treatment with PCl₃ in CHCl₃ solution at room temperature to give tetrazoles **558** (1978TL399, 1989BAU1488, 1993PJC1767) (Scheme 169).

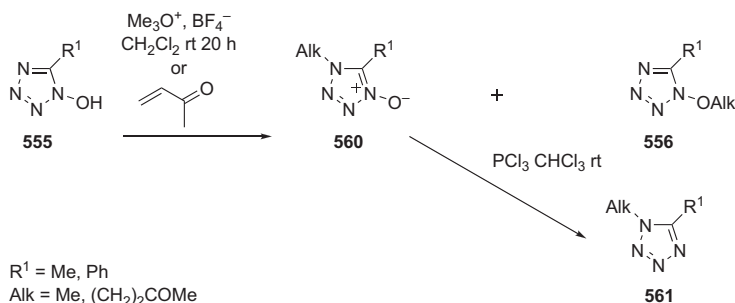
6.6. 4-Substituted tetrazole 1-oxides



Scheme 170

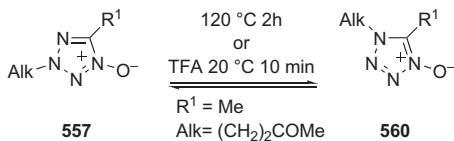
Three 4-substituted tetrazole 1-oxides **560** (Scheme 171) derived from the parent structure **559** (Scheme 170) have been described. H NMR, C NMR, ^{14}N NMR, and ^{15}N NMR data have been obtained (1989BAU1488). Line broadening of NMR signals provided information about the rate constant of the equilibrium between the *N*-oxides **554** and **559** observed at elevated temperatures.

4-Alkyl-substituted tetrazole 1-oxides **560** have been prepared by alkylation of the corresponding 1-hydroxytetrazole **555** with methylvinyl ketone to give a mixture of *N*-oxide **560** and the *O*-alkylated isomer **556** (1989BAU1488). Methylation of the *N*-hydroxytetrazole **555** with trimethyloxonium tetrafluoroborate afforded a mixture of *N*-oxide **560** (Alk=Me), an isomeric *N*-oxide of unknown structure, and the 1-methoxytetrazole **556** (Alk=Me) (1984BAU142) (Scheme 171).



Scheme 171

In another approach 3-substituted tetrazole 1-oxides **557** were isomerized to the 4-substituted analogues **560** by heating to 120°C for 2 h (1984BAU142) (Scheme 172).



Scheme 172

Heating 4-substituted tetrazole 1-oxides **560** gives rise to an equilibrium mixture of **560** with the corresponding 3-substituted isomer **557** (1989BAU1488).

4-Substituted tetrazole 1-oxides **560** were deoxygenated at 20°C by PCl_3 in chloroform solution or by heating with $\text{P} + \text{HI}$ to give their progenitors **552** (1984BAU142, 1989BAU1488).

4-Substituted tetrazole 1-oxides **557** were *N*-dealkylated by treatment with KOH + AgNO₃ in ethanol solution with formation of 1-alkoxytetrazoles **556** (1989BAU1488).

6.7. Application of tetrazole *N*-oxides

Tetrazole *N*-oxides and the tetrazoles formed by their deoxygenation are used as high energy containing compounds, explosives, and propellants. Several drug substances contain a tetrazole ring. In drug substances an *N*-unsubstituted tetrazole entity mimics a carboxylic acid group. By virtue of their high stability under metabolic conditions tetrazole entities have been made part of antibacterials, antivirals, and antifungals. Tetrazoles are also used as catalysts in acylations and in peptide and nucleotide synthesis. References to the applications are given in (2010JOC3141, 1997MI1).

LIST OF ABBREVIATIONS

AA	<i>Ann. Chem.</i>
AP	<i>Arch. Pharm.</i>
APMC	<i>Arch. Pharm. Pharm. Med. Chem.</i>
ARK	ARKIVOC
MRMC	<i>Mini Rev. Med. Chem.</i>
PEST	<i>Pesticides</i>

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CHAPTER 2

Heteroporphyrins: Synthesis and Structural Modifications

Kamaljit Singh, Amit Sharma and Shivali Sharma

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ABSTRACT

Structural variants of porphyrins obtained by heterocyclic core modification, macrocyclic ring expansion, alteration of structural topology, and incorporation of tailor-made substituents constitute an area of considerable interest. Potentially rich families of conjugated heteroporphyrins with well-defined structures provide an opportunity for implementation in applications in the field of chemistry, biology, and material science. This chapter reports on the synthesis and structural modifications of a number of heteroporphyrins.

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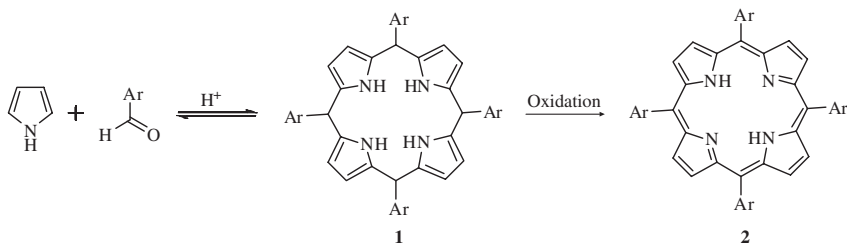
KEYWORDS

Heteroporphyrins; Core modification; Tetrathiaannulenes; Porphycenes; Porphyrinoids; Expanded porphyrinoids.

1. INTRODUCTION

The synthetic chemistry of porphyrin, the pigment of life (00MI), and its derivatives has been continually explored since the publication of the first report on the synthesis of unnatural porphyrins (1935JA2010, 1936JA625, 1941JA267). Porphyrin and its derivatives are among the most widely distributed and important cofactors found in nature and are crucial regulatory effectors in many biochemical processes. Additionally, efforts to understand the physico-chemical characteristics (1993ACR198), conformational flexibility (00JPC(A)4606), and aromaticity of porphyrin and its derivatives have led to the development of their applications in vast areas, such as photodynamic therapy (PDT) (09ACR1097, 09CR6047), redox catalysis (1992CR435, 1980JPC1822), metal coordination (1996ICA213, 1996JCS(CC)2133, 1995BCJ1989, 1997TL3821), sensors (05JA2944, 1996ACI2823), nonlinear optics (NLO) (1993AM341), and nanomaterials (09CR1630).

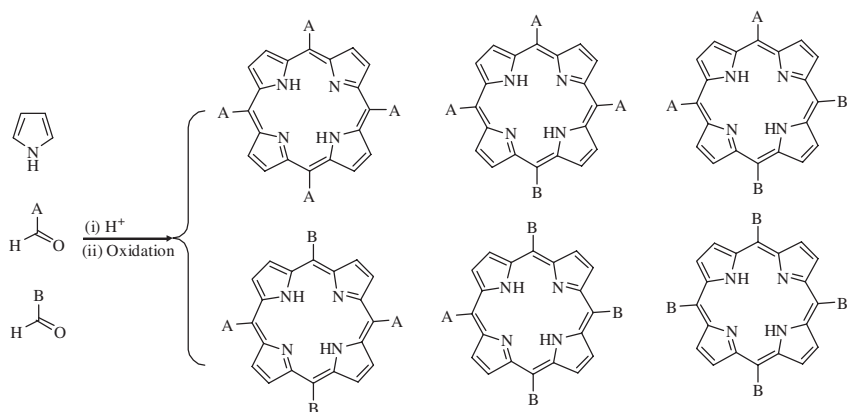
Initial synthetic investigations in this area were initiated by groups of Rothmund (1935JA2010, 1936JA625, 1941JA267), Adler (1964JA3145, 1967JOC476), Lindsey (1989JOC828), etc. The Adler methodology (Scheme 1), though low yielding, is prized for its simplicity and pliability for the large-scale preparation of *meso*-aryl porphyrins **2**. The in situ formed porphyrinogen intermediate **1** gets oxidized leading to the formation of **2**. The Lindsey group subsequently developed (1986TL4969, 1987JOC827, 1994JOC579) higher concentration conditions (up to 0.32 M) that were slightly lower yielding, but more practical for larger scale preparations. In 1997, it has also been found that the addition of salts, such as sodium chloride, during the condensation of pyrrole and aldehyde increases the yield (1997T12339).



Scheme 1 Condensation of pyrrole and aryl aldehydes to form *meso*-tetraarylporphyrins (1941JA267).

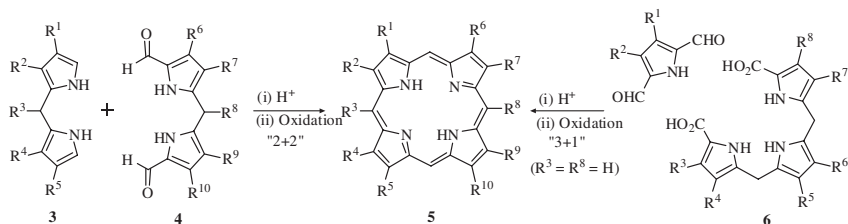
Variants of the Rothmund (1935JA2010, 1936JA625, 1941JA267) or Lindsey's (1997T12339) procedure employ hydroiodic acid, hydrochloric acid, *p*-toluenesulfonic acid (*p*-TsOH) (1960JA4384), perchloric acid (1990JA9310), trichloroacetic acid (1995JOC7177), trifluoroacetic acid (TFA) (00JOC7323), montmorillonite clay (1993TL2625), cation-exchange resins (03T2207), high-valent transition metals (1995JCS(P1)2611), and metal triflate (09T2043) as catalysts and/or oxidants and are synthetically useful. A solvent as well as catalyst-free preparation of *meso*-substituted porphyrins through pyrrole and aldehydes, together in the gas phase ($>200^{\circ}\text{C}$), using oxygen as an oxidant, has been reported (1997JCS(CC)2117) to furnish tetraphenylporphyrin **2** ($\text{Ar}=\text{C}_6\text{H}_5$) in 23% yield.

Earlier methodologies employing an aldehyde and pyrrole suffered, in that there was no provision of bringing variations of substituents at the four *meso*-positions, a limiting factor to form large covalently bonded arrays. Further, if a mixture of two or more different aldehydes is employed (Scheme 2), a statistical mixture of products is obtained and requires extensive chromatography for isolation of the desired porphyrin, generally formed in low yield by virtue of the statistical outcome (1994T8941, 1996JCS(P2)199, 1993JA4618).



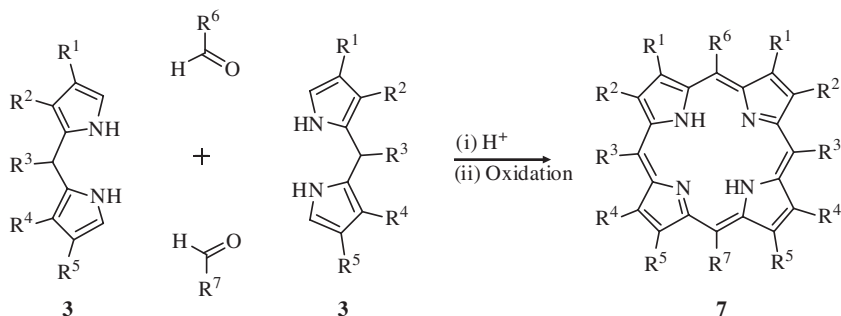
Scheme 2 Condensation of pyrrole with mixed aldehydes ($\text{ACHO}:\text{BCHO}/3:1$). Formation of a mixture of *meso*-tetraarylporphyrins ($\text{A}=\text{B}=\text{Ar}$).

Alternative approaches for substituted porphyrins have been devised in which pre-functionalized dipyrromethane derivatives **3** are condensed with similar diformyl dipyrromethanes **4** through a “2+2” condensation to form *meso*-tetraarylporphyrins **5** (Scheme 3). Such condensations are usually catalyzed by acids and the intermediate porphyrinogens are oxidized by air to obtain porphyrins. In a similar “3+1” synthetic approach, tripyrranes **6** are condensed with 2,5-diformylpyrroles to form etioporphyrin **5** (1996CEJ1197).



Scheme 3 "2+2" Condensation of dipyrromethanes by the MacDonald method and "3+1" synthesis of etioporphyrins.

An alternative "2+2" approach (Scheme 4) involves the acid-catalyzed condensation of α -free dipyrromethanes 3 (1994T11427, 05T6614, 05SC929) with aldehydes to form porphyrinogens, which are then oxidized to obtain porphyrins 7. This methodology is considerably more versatile for array formation, and is frequently higher yielding and produces more soluble products as well as allows better control over substitution at the *meso*-positions.



Scheme 4 "2+2" Condensation of α -free dipyrromethanes with aldehydes.

In view of the extensive literature on the development of synthetic methodologies in porphyrin chemistry as well as applications in a variety of areas, a number of comprehensive review articles have been published (10ACR300, 10CCR77, 01CR2751) and their discussion is beyond our scope. However, important aspects of structural modifications, reorganization, and expansion of a porphyrin scaffold (Figure 1), as outlined below (a–e), are discussed to highlight developments.

2. PORPHYRIN DERIVATIVES

(a) Contracted porphyrins (00MI1): the contracted porphyrin analogues, such as corroles, obtained by removing one of the *meso*-carbons.

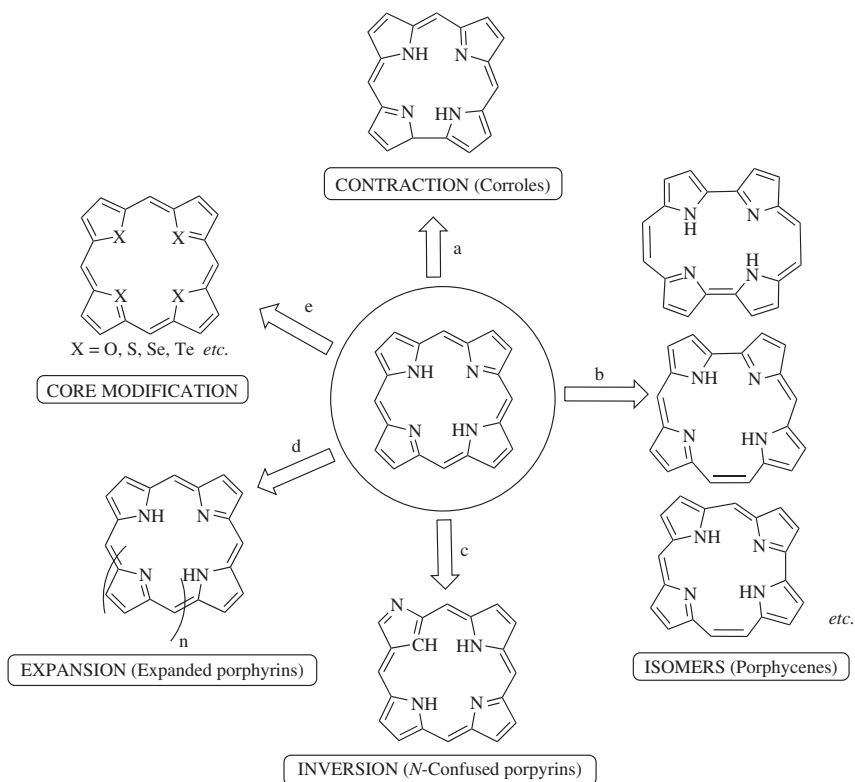


Figure 1. Structural modifications (a–e) of a porphyrin core.

- (b) **Isomeric porphyrins (00MI2)**: porphyrins obtained by scrambled pyrrolic subunits and the four bridging carbon atoms, and possessing the same molecular formula.
- (c) **Inverted porphyrins (00MI3)**: these are porphyrin isomers that have one or more of the core nitrogens pointing out of the ring and hence are called “N-confused porphyrin (NCP).”
- (d) **Expanded porphyrins (00MI4)**: these result from the expansion of the π -electron chromophores and are characterized by strong absorptions in the red region of the electromagnetic spectrum, compared to the normal 18π -porphyrins.
- (e) **Core-modified porphyrins (00MI3)**: these result from the replacement of the pyrrolic nitrogens by other heteroatoms (e.g., O, S, Se, Te, etc.).

2.1. Contracted porphyrins

Corroles **8** (Figure 2) are aromatic tetrapyrrole macrocycles bearing a direct pyrrole–pyrrole link. The lack of a *meso*-carbon atom leads to a smaller

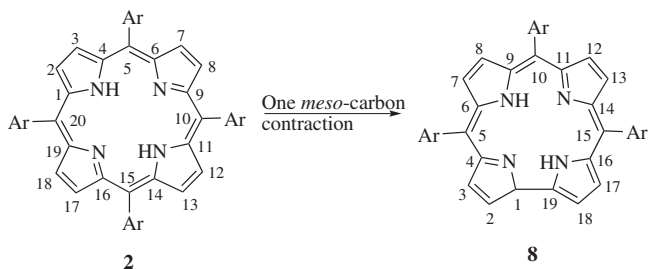
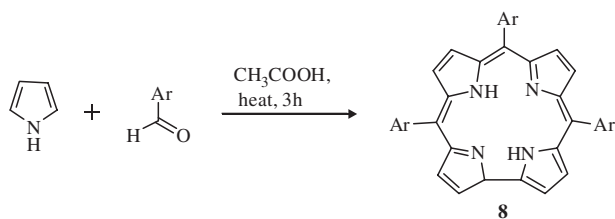


Figure 2. Transformation of porphyrin to corrole and the numbering schemes.

cavity than porphyrin **2** and also a reduction in symmetry from D_{4h} to C_{2v} (assuming that N–H tautomerism is fast).

Compared to the diprotonic porphyrins, corroles act as tetradentate trianionic ligands toward metal ions and stabilize higher oxidation states [e.g., Fe(IV), Co(IV), and Co(V)]. The first direct synthesis of corroles involved solvent-free condensation of equimolar quantities of pyrrole and aldehydes on a solid support using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant (1999ACI1427). Following a similar procedure, Paolesse *et al.* (1999JCS(CC)1307, 01JOC550) demonstrated that by modifying the molar ratio of pyrrole:aldehyde to 3:1 and replacing propionic acid of Adler–Longo porphyrin synthesis (1964JA3145, 1967JOC476) with glacial acetic acid (Scheme 5), corroles **8** can be obtained in an appreciable amount (1999JCS(CC)1307, 01JOC550).

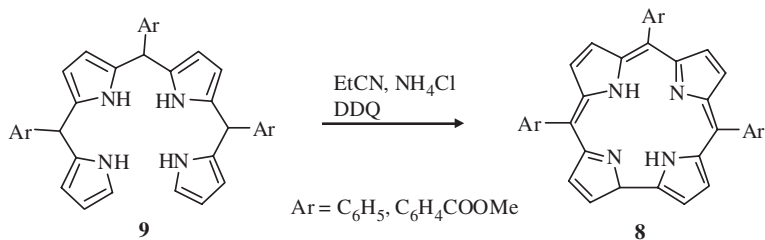


Ar = C₆H₅, C₆F₅, 2/3/4-NO₂-C₆H₄, 2-Cl/Br/4-Br/3-Br-C₆H₄, 4-MeO/4-Me-C₆H₄, 4-pyridyl, 2-furyl *etc.*

Scheme 5 One-pot synthesis of corroles under standard Adler–Longo-type protic acid-catalyzed conditions.

Another approach to **8** was developed by Lee *et al.* (00TL8121) through oxidation of bilanes **9** (products of pyrrole and aldehyde condensation) (Scheme 6) using DDQ to obtain **8** in a synthetically useful manner.

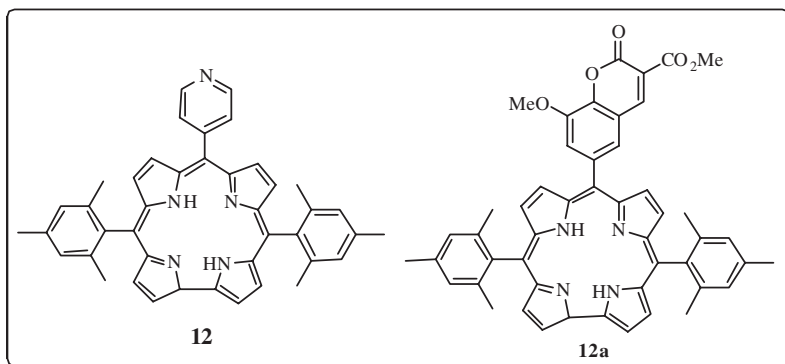
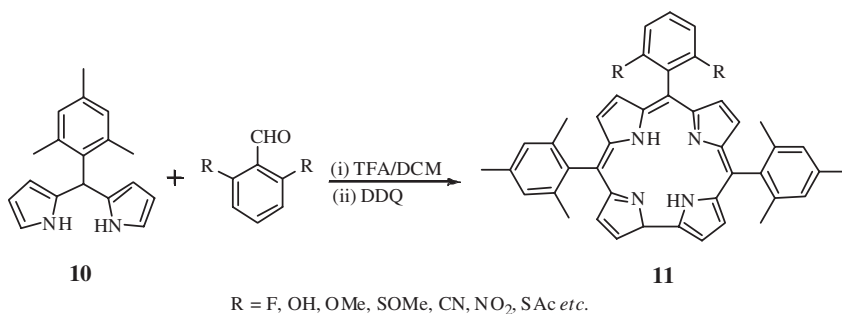
While the typical bands of porphyrins with general structure **2** appear at 419, 515, 548, and 591 nm in the UV–vis absorption spectrum, the



Scheme 6 Corrole synthesis through oxidation of bilanes.

absorption bands of corroles **8** appear at 421, 578, 614, and 649 nm and are considerably red-shifted (02JA8104).

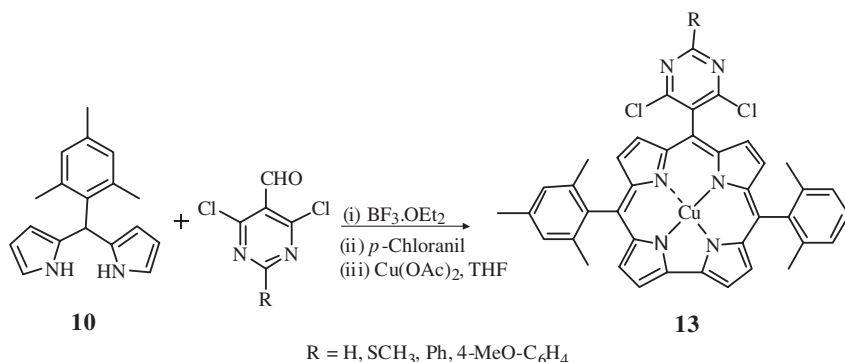
A simple and versatile one-pot synthesis of *meso*-substituted *trans*-A₂B-corroles (Scheme 7) was reported by Gryko and Jadach (01JOC4267). It affords regioisomerically pure *trans*-A₂B-corroles **11** through the TFA-catalyzed condensation of a dipyrromethane **10** and an aldehyde followed by oxidation with DDQ. The synthesis is compatible with diverse functionalities: ester, nitrile, ether, fluoro, hydroxy, etc. on the aryl group of the



Scheme 7 Acid-catalyzed synthesis of *meso*-substituted *trans*-A₂B-corroles.

carbonyl component. An extension of Gryko approach involves synthesis of *trans*-A₂B-type corroles bearing pyridyl **12** (02JPP81) and coumarin **12a** moieties (10CAJ130) at *meso*-position.

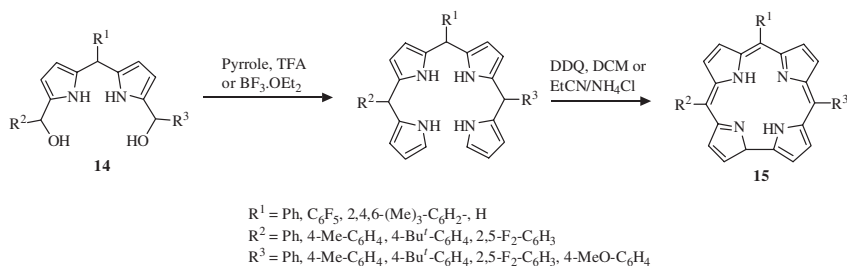
In 2010, *meso*-pyrimidinyl AB₂-corroles **13** are synthesized through acid-catalyzed condensation of 5-mesityldipyrromethane **10** and 2-substituted 4,6-di-chloropyrimidine-5-carboxaldehydes (Scheme 8) (10CEJ5691). The main advantage of pyrimidinylcorroles over other *meso*-triarylcorroles is their wide range of functionalization, which has been explored by nucleophilic and electrophilic aromatic substitution, and Pd-catalyzed cross-coupling reactions.



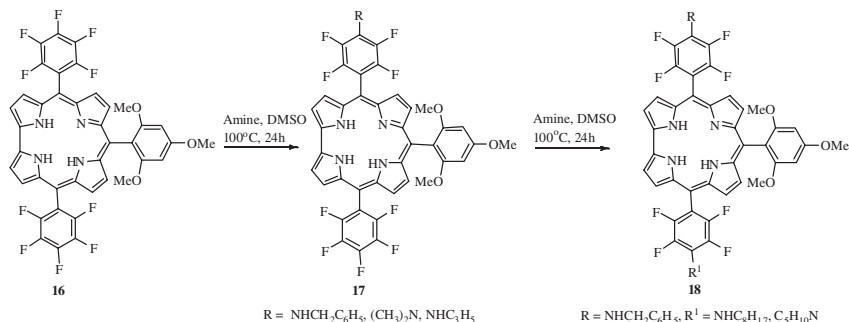
Scheme 8 Synthesis of *meso*-pyrimidinyl AB₂-corroles.

Synthesis of regioisomerically pure corroles **15** (Scheme 9), possessing up to three different substituents (ABC-type corroles) at the *meso*-positions, has been achieved (02OL4491) through acid-catalyzed condensation of a dipyrromethane-dicarbinol **14** with pyrrole followed by oxidation with DDQ.

Osuka and Hori (10EJOC2379) have reported the synthesis of ABC-type corroles **18** (Scheme 10) by nucleophilic substitution of *meso*-5,10,15-tris



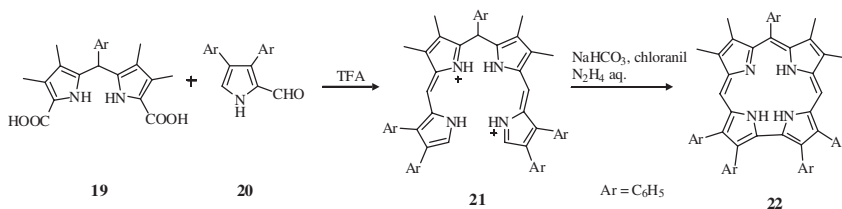
Scheme 9 Synthesis of ABC-type corroles bearing three different *meso*-substituents.



Scheme 10 Synthesis of ABC-type corroles by nucleophilic substitution reactions.

(pentafluorophenyl)corrole with amines. In these reactions, 5- and 15-pentafluorophenyl substituents were found to be more reactive than the substituent at the 10-position.

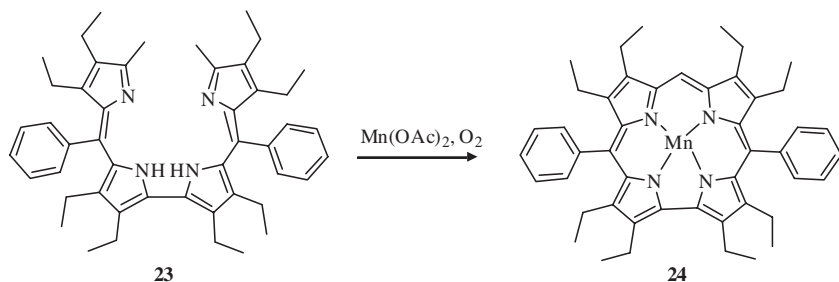
Since *meso*-substituted corroles with alkyl substituents at a β -position often exhibit reduced stability due to oxidative ring opening (01IC4845), attempt was made to obtain stable analogues by substituting aryl substituents at a β -position, which prevented corrole oxidation. Thus, condensation of dipyrromethane **19** (Scheme 11) and appropriately substituted aldehyde **20** under the influence of TFA furnished biladiene **21**, and subsequently cyclized to stable corrole **22** derivatives.



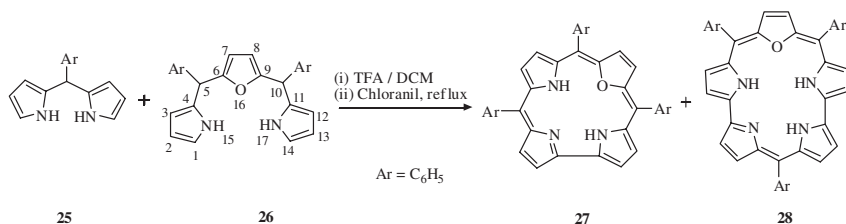
Scheme 11 Synthesis of β -aryl corrole from dipyrromethane and aldehyde.

In another approach, bis(dipyririn) **23** (Scheme 12) with Mn(II) acetate and molecular oxygen furnished corrole Mn(III) complex **24** (01JCS(CC)2336). Complex **24** with HBr in AcOH furnished the corresponding demetallated corrole.

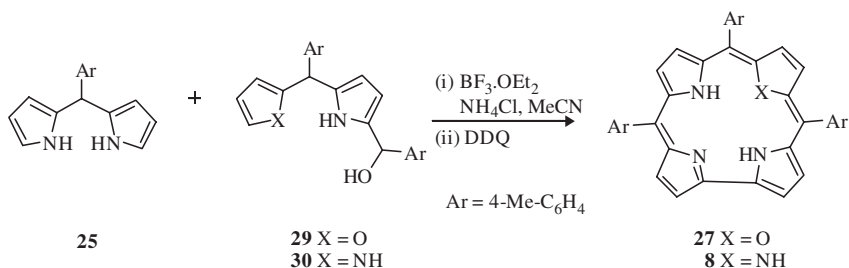
Core-modified corroles **27** (Scheme 13) have been obtained as a side product in addition to core-modified smaragdyrin **28** by Chandrashekar et al. (1999OL587, 00CEJ2554) in an acid-catalyzed “3+2” coupling of dipyrromethane **25** and 16-oxatripyrrane **26**.



Scheme 12 Synthesis of corrole Mn(III) complex.



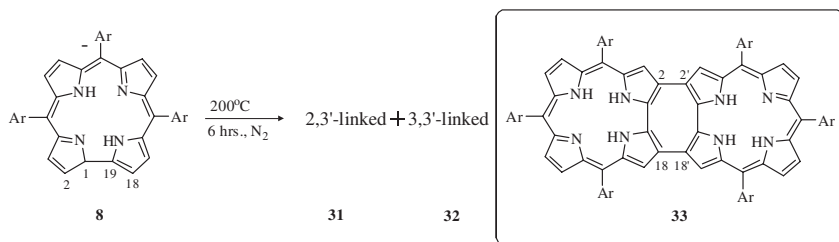
Scheme 13 Synthesis of core-modified smaragdyrin through "3+2" coupling.



Scheme 14 Core-modified corrole synthesis from *meso*-aryl dipyrromethane.

A different approach (00TL697, 00BKSC429) through the condensation of alcohols, such as **29** and **30** (Scheme 14), with *meso*-aryl dipyrromethane **25** furnished core-modified corrole **27** along with tetranitrogen corrole analogue **8**. Complexes of oxacorroles **27** with Cu(II), Ni(II), or Co(II) have also been prepared with the corresponding metal salts (1999OL587, 00CEJ2554).

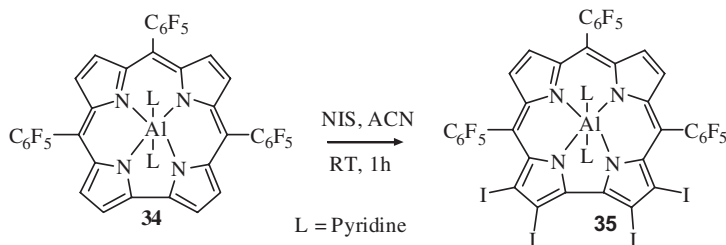
In 2006 (06TL8171), 2,3'-linked **31** and 3,3'-linked **32** β,β' -corrole dimers (Scheme 15) have been achieved by heating a 1,2,4-trichlorobenzene solution of 5,10,15-tris(pentafluorophenyl)corrole **8** (Ar=C₆F₅) at 200°C. In one



Scheme 15 Synthesis of β,β' -corrole dimers.

example, corrole units are linked through the 2,2',18,18'-carbons giving rise to an eight-membered ring containing dimer **33**. The doubly linked oxidized corrole dimers **33** show unusual biradical character as indicated by their UV-vis spectra (06JA12380).

In 2011, Gross et al. (11JA12899) have reported the synthesis of an aluminum complex of tetraiodinated corrole **35** (Scheme 16) by treating Al(III)-corrole **34** with *N*-iodosuccinimide (NIS) in acetonitrile (ACN). It exhibited red fluorescence and possessed a long-lived triplet excited state.

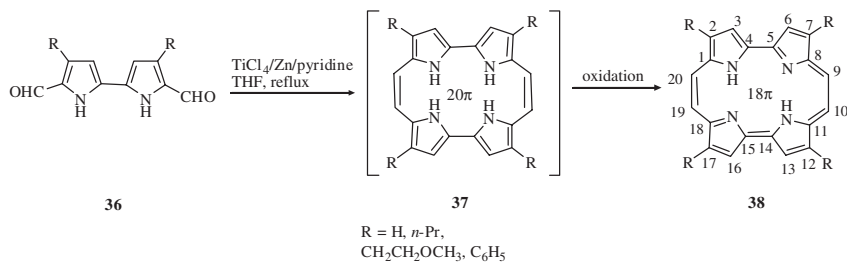


Scheme 16 Synthesis of aluminum complex of tetraiodinated corrole.

2.2. Isomeric porphyrins

One of the widely studied, stable constitutional porphyrin isomers encompassing 18π -electrons in a cyclic conjugated pathway is porphycene **38** (Scheme 17). Other isomers such as NCPs are much less stable and are not discussed here. Porphycenes consist of two 2,2'-bipyrrole subunits linked by two double bonds and are thus named as [18]porphyrin(2.0.2.0).*

*Following the standard system of nomenclature, the names of porphyrinoids consist of three parts: (i) a number in the square bracket corresponds to the number of π -electrons in the shortest conjugation pathway; (ii) a core name representing the number of pyrroles or other heterocycles in the overall system; and (iii) numbers in round brackets specify the number of bridging C-atoms between each pyrrole subunit, starting with the largest.



Scheme 17 Synthesis of β -substituted porphycenes and the numbering scheme.

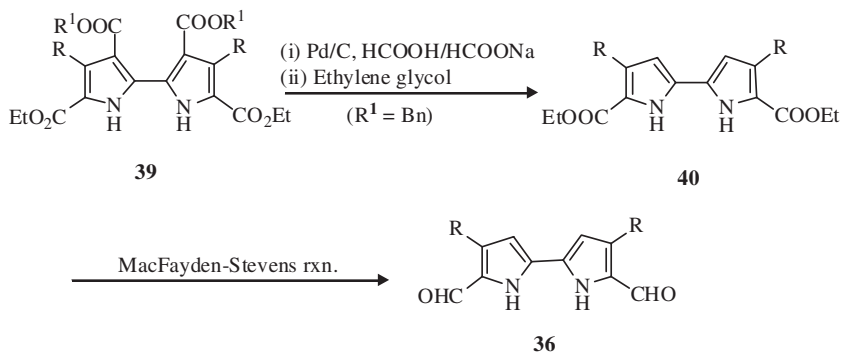
The first synthesis of a porphycene (2–3% yield) was achieved by Vogel and coworkers (1986ACI257) using McMurry-type coupling (1983ACR405, 1989CR1513, 1996ACI2442) of diformyl-2,2'-bipyrrole **36** (Scheme 17), followed by oxidation of the 20π -electron intermediate **37** with atmospheric oxygen. Subsequent investigations (1987ACI928) to enhance the yield, solubility, and crystallinity of porphycenes led to the synthesis of derivatives bearing methyl, ethyl, *tert*-butyl, *n*-propyl, and β -methoxyethyl-substituents at 2, 7, 12 and 17 positions.

Porphycenes are capable of forming metal complexes investigated for applications as catalysis (01O3074, 1997JCS(CC)1205), protein mimicry (06IC10530, 04JA16007, 06JCC1363, 06IB1265), and material chemistry (05MCH65, 1994JCS(CC)2757). Porphycenes possess lower symmetry as compared to porphyrins and show strong absorption bands in the far-red region (620–760 nm), a feature particularly attractive for PDT, and other biomedical applications such as photoinactivation of viruses and bacteria (02PPS468).

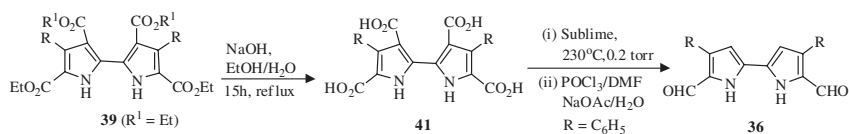
Following the general methodology developed by Vogel, porphycenes bearing aromatic groups at 2, 7, 12, and 17 positions of **38** ($\text{R} = \text{C}_6\text{H}_5$) were reported (1995TL3405), where Nonell avoided the sublimation step used by Vogel. A direct consequence of introducing phenyl groups at 2, 7, 12, and 17 positions of porphycene **38** ($\text{R} = \text{C}_6\text{H}_5$) is the modification of Q-bands as well as a dramatic bathochromic shift in its UV–vis absorption spectrum, compared with unsubstituted analogue **38** ($\text{R} = \text{H}$). Such features are considered advantageous for applications such as PDT (01JPP105, 1998T4151, 00ACDD143).

Nonell and coworkers (01JPP846) have also reported a non-decarboxylative procedure based on 2,2'-bipyrrole derivative **39** (Scheme 18), bearing two sets of orthogonal esters. The tetraester **39** could readily be transformed to dialdehyde **36** ($\text{R} = \text{C}_6\text{H}_5$) through the intermediacy of **40** by use of the MacFadyen–Stevens sequence (1962JA635) even as the direct conversion of **40** to **36** ($\text{R} = \text{C}_6\text{H}_5$) was not facile.

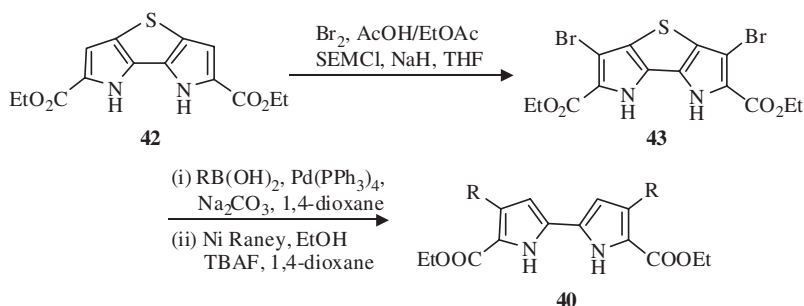
Alternatively, the conversion of tetraester **39** ($\text{R}^1 = \text{Et}$) to 2,2'-bipyrrole derivative **36** through **41** was achieved (1993JOC2340) by treating **39** with NaOH/ethylene glycol at reflux (Scheme 19).



Scheme 18 Synthesis of β -phenyl-substituted bipyrrrole porphycene precursors.



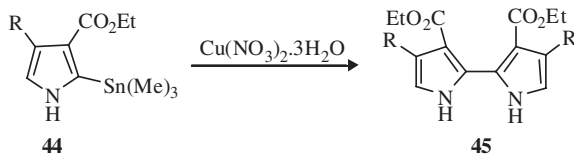
Scheme 19 Synthesis of β -alkyl-substituted bipyrrrole dialdehyde.



Scheme 20 Synthesis of β -substituted bipyrrrole diester.

Using thienobipyrrrole **42** as a masked bipyrrrole (with 3- and 3'-positions blocked), the synthesis of bipyrrrolic precursor **40** (Scheme 20) has been described (06OL847). Facile dihalogenation of **43**, followed by β -(trimethylsilyl)ethoxymethyl (SEM) protection and Suzuki coupling permits a higher level of functionalization on bipyrrrole **40** ($\text{R}=\text{C}_6\text{H}_5$, $\text{C}_5\text{H}_4\text{N}$, 4-MeO- C_6H_4), obtained by removing the sulfur atom with Raney Ni and SEM deprotection using tetra-*n*-butylammonium fluoride (TBAF).

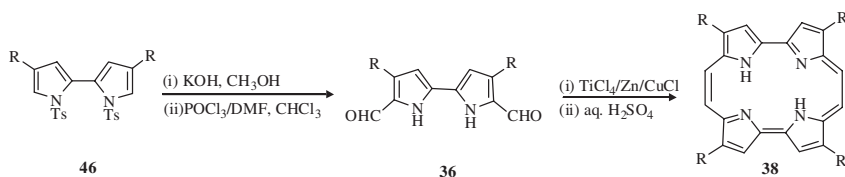
Sanchez-Garcia (09OL77) has reported a one-pot procedure (Scheme 21) for the synthesis of 4,4'-diaryl-4,4'-diheteroaryl-substituted-2,2'-bipyrrrole **45** based on the oxidative coupling of 2-trimethylstannylated pyrrole **44**.



R = C₆H₅, 4-Me/4-MeO/4-CF₃-C₆H₄, 4-CH₂OCH₃-C₆H₄, 3,5-(MeO)₂-C₆H₃, -C₅H₄N *etc.*

Scheme 21 One-pot synthesis of 2,2'-bipyrroles.

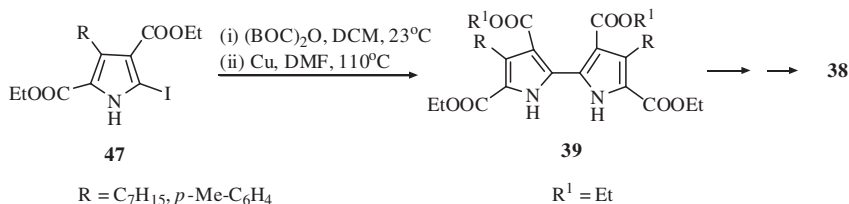
Another improved synthesis of unsubstituted porphycene **38** (R=H) using *tert*-butyl substituents as temporary stabilizing groups, as outlined in [Scheme 22](#), has been described ([07JPP596](#)). Thus, deprotection of the *N*-tosyl-protected bipyrrole **46**, followed by formylation yields diformyl intermediate **36**, which readily undergoes McMurry coupling to produce **38** (R=H, *t*-Bu).



Scheme 22 Improved synthesis of unsubstituted (R=H) porphycenes.

To further extend the usefulness, Sessler developed a simple procedure ([Scheme 23](#)) for procuring the key 2,2'-bipyrrole bearing substituents at 3,3'-positions using iodopyrroles **47**, obtained from simple intermediates ([06JPP854](#)). Ullman coupling of **47** (R=Et) furnished **39** (R=Et). Removal of ester functionalities from the 5,5'-positions, coupled with diformylation and McMurry coupling furnished porphycene **38**, bearing both alkylic (R=C₇H₁₅) and aromatic (R=*p*-Me-C₆H₄) substituents.

Porphycenes undergo selective reduction ([1987ACI931](#)) (H₂ or Na/ROH) and halogenations ([1990ACI1390](#), [02ACSC563](#)). Direct reaction



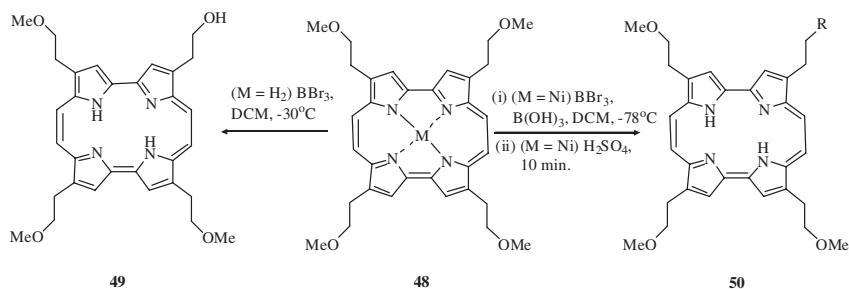
Scheme 23 Synthesis of porphycene bearing both alkylic and aromatic substituents.

with Br_2 or I_2 furnishes exclusively a 2-halogenated product and when this position is blocked, other β -pyrrolic positions get halogenated to furnish tri- and tetrahalogenated porphycenes. Monobromination, however, could be achieved using bromine on a polymeric support (1990ACI1390).

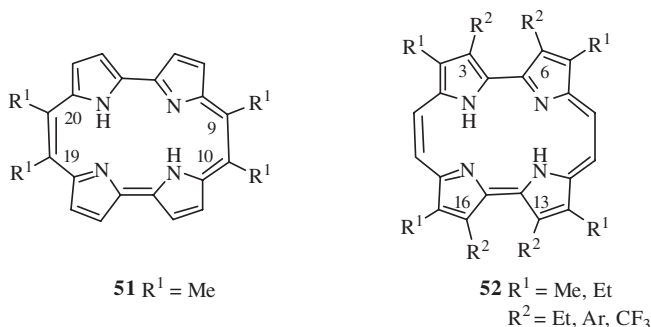
Sulfonation of porphycene furnishes mono-, di- and tri- β -sulfonated derivatives upon treatment with fuming sulfuric acid (04TL5973). Upon treatment with chlorosulfonic acid, the 3-sulfonyl chloride derivative is obtained, which can be transformed into sulfonamides (03JBS418). Nitration of porphycene using fuming HNO_3 (1997MI) or $\text{AgNO}_3/\text{CH}_3\text{COOH}$ in dichloromethane (DCM) yields the 9-nitro-substituted porphycene, which can be reduced (Zinin reduction (1973OR455) or Raney Ni and hydrazine), selectively, to the corresponding amine. 9-Acyloxy porphycene derivatives can be formed by treatment with a Pb(IV) salt in the presence of a carboxylic acid and can be converted to a free 9-hydroxyporphycene upon hydrolysis in basic (NaOMe/MeOH) media (1997MI).

Peripheral functionalization (2, 7, 12, and 17 positions) of porphycenes has relied on the use of β -methoxyethyl-substituted porphycenes. Synthetic sequences such as removal of a methyl ether group of β -methoxyethyl-substituted porphycene **48** ($\text{M}=\text{H}_2$) (Scheme 24) with a Lewis acid such as BBr_3 produces the alcohol **49** or other substituted products **50** ($\text{R}=\text{Br}$) (1994JMC2797). The hydroxyl-substituted porphycene **49** has further been converted to porphycene sugar derivatives (1973OR455). Further, both bromide **50** ($\text{R}=\text{Br}$) and mesylate **50** ($\text{R}=\text{OMs}$) produced from hydroxyl derivative **49** undergo substitution with NaCN to afford the cyano derivative **50** ($\text{R}=\text{CN}$), and then converted to a carboxylic ester **50** ($\text{R}=\text{COOEt}$) and its saponified product **50** ($\text{R}=\text{COOH}$) (1993MI).

The geometrical restrictions and its dependence on the peripheral substituents of porphycenes can be gauged from the fact that the metal cation coordination properties of this tetrapyrrolic ligand can be modified by changing the substituents at 9, 10, 19, and 20 positions (1989ACI1655, 1989IJC257) of **51** ($\text{R}^1=\text{Me}$) (Scheme 25), as well as β -pyrrolic 3, 6, 13, and



Scheme 24 Synthesis of functionalized porphycenes.

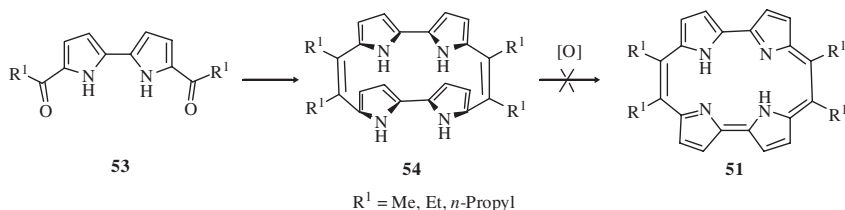


Scheme 25 Synthesis of *etio*-substituted porphycenes.

16 positions of **52** of the macrocycle. Species **52** are referred to as etioporphycenes (1993ACI1600, 1995S1480).

In contrast to the rectangular cavity of 2,7,12,17-tetra-substituted porphycenes **38**, which favors the formation of metal complexes with small cations, the larger cavity of etioporphycenes is able to accommodate even bigger cations favored by steric interactions of the alkyl chains at the β -positions.

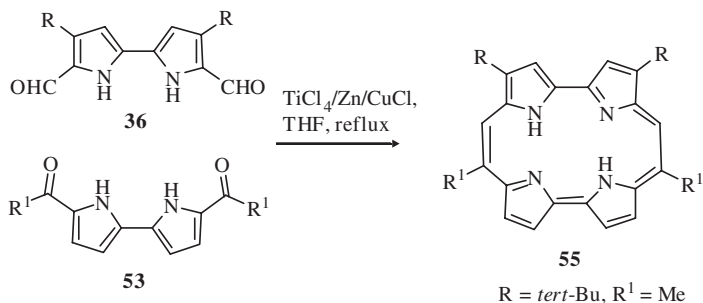
Porphycenes **51** bearing substituents at ethylenic carbons have been prepared from 5,5'-acyl bipyrroles **53** (05OL1887) (Scheme 26). However, oxidation of the intermediate annulene **54** is difficult, owing to the presence of the alkyl chains on the alkene bridges. These reduce conformational flexibility, resulting in a near-nonplanar geometry, which resists oxidation and/or aromatization (08CSR215).



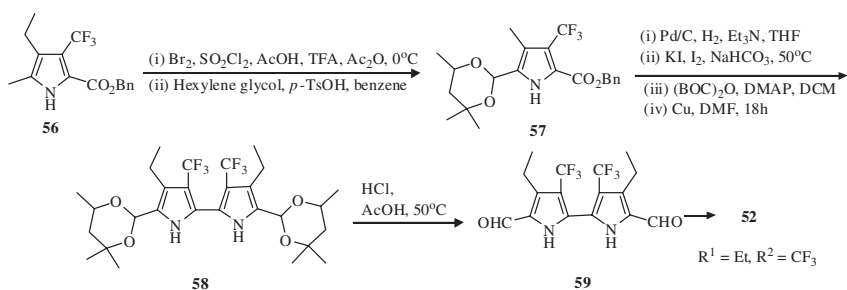
Scheme 26 Synthesis of an oxidation resistant substituted porphycene precursor.

An asymmetrical porphycene (07JPP596) bearing only two methyl groups at *meso*-positions was synthesized *via* the cross-coupling of diformyl **36** ($R=t\text{-Bu}$) and diacetyl bipyrroles **53** ($R=\text{Me}$), followed by facile oxidation to give **55** (Scheme 27).

In addition to Scheme 20, the synthesis of β, β' -substituted pyrroles has also been achieved through a Zard–Barton reaction (1985JCS(CC)1098, 1990T7587, 1991SL127). Likewise, Hayashi *et al.* (03OL2845, 03IC7345)



Scheme 27 Synthesis of asymmetrical *meso*-substituted porphycene.

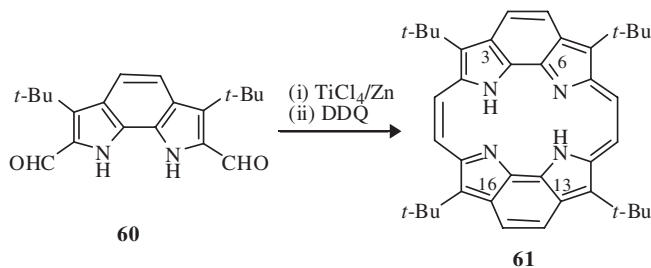


Scheme 28 Synthesis of a porphycene bearing a trifluoromethyl group.

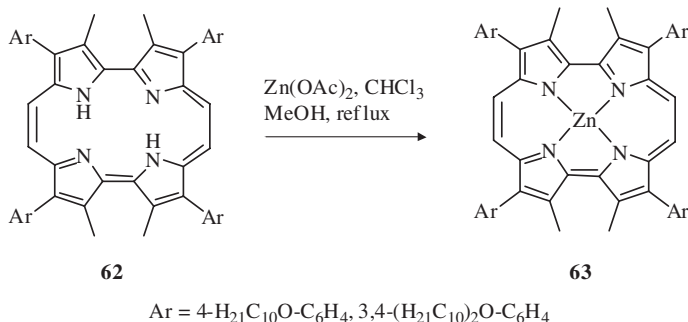
have reported trifluoromethyl bearing 2,2'-bipyrrrole **59** (Scheme 28) converted to porphycene **52**.

Porphycenes with fused aromatic rings between 3,6 and 13,16 positions of **61** (Scheme 29) have been prepared through McMurry coupling of aldehyde **60**, followed by DDQ oxidation of the nonaromatic *N,N'*-dihydroporphycene intermediate (05ACI4053, 1993PAC143).

In order to study the formation of liquid crystals, Sessler and coworkers (07CEJ6853) synthesized etioporphycenes **62** (Scheme 30),



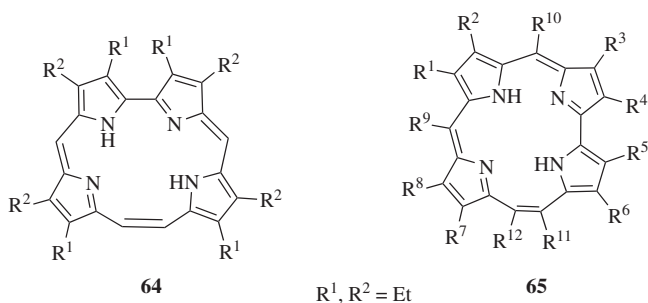
Scheme 29 Representative synthesis of *etio*-type benzoporphycene.



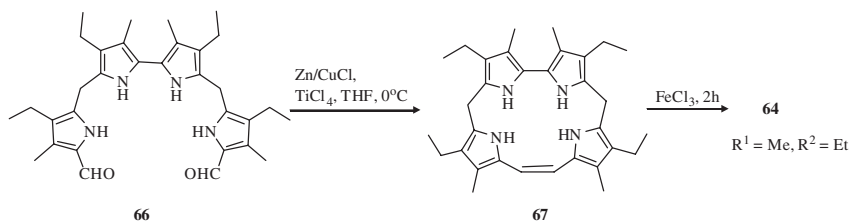
Scheme 30 Synthesis of aryl-substituted *etio*-type porphycenes and its zinc complex.

having aromatic groups bearing $\text{OC}_{10}\text{H}_{21}$ chains at 2, 7, 12 and 17 positions. Porphycenes **62** have been converted into zinc complex **63**.

Structural isomers of porphycenes, such as corrophycene ([1994ACI2308](#), [1994ACI1348](#)) **64** and hemiporphycene ([1995NJC155](#)) **65**, have also been synthesized through reductive coupling of the tetrapyrrolic α,ω -dialdehydes.

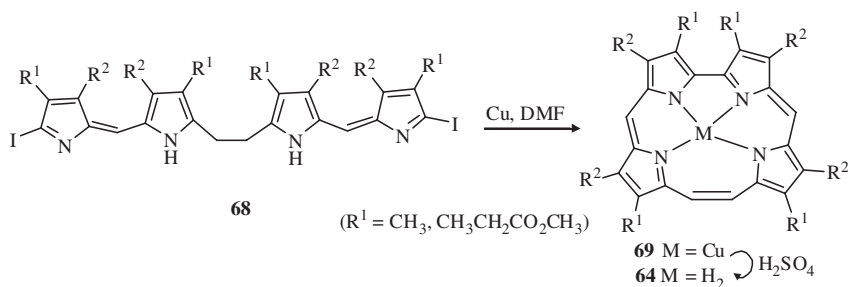


Unlike facile oxidation of *N,N'*-dihydroporphycenes, resulting in the formation of porphycenes, oxidation of coupled product **67** ([Scheme 31](#)) obtained from **66**, could only be allowed with FeCl_3 to obtain **64** ($\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{Me}$) ([Scheme 31](#)).



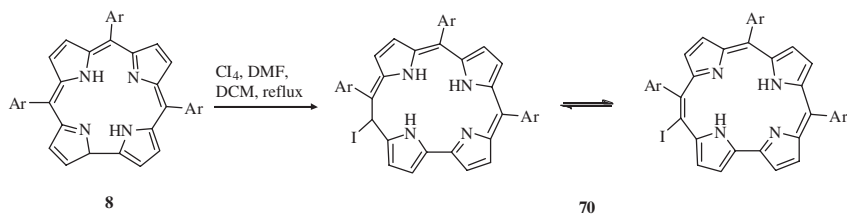
Scheme 31 Synthesis of corrophycene.

Yet another synthesis of corrphycene **64**, by means of copper-catalyzed intermolecular coupling of the easily accessible 1,2-bis-(1-iodo-dipyrryn-9-yl)-ethanes **68**, resulting in the formation of **69** (Scheme 32) and subsequent demetallation to corrphycenes **64** ($R^1 = \text{Me}$), has been reported (1996MC69).



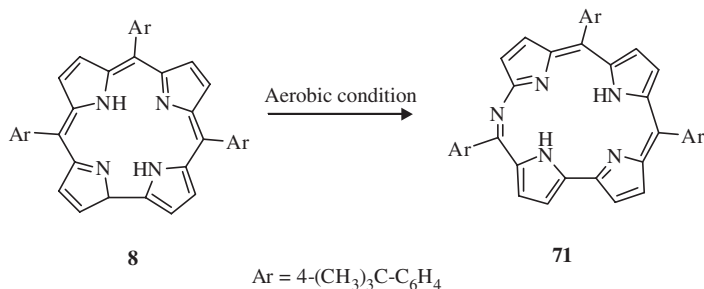
Scheme 32 Synthesis of corrphycene through copper-catalyzed intermolecular coupling.

Corrphycenes and their metal complexes undergo four distinct one-electron redox steps, two are reduction steps and two are oxidation steps. A comparison with porphyrins and porphycenes indicates that the first reduction potentials of the free base and of metallo-corrphycenes are between those of porphycene **38**, the easiest to reduce molecules, and those of porphyrins **2**. The oxidation potentials of corrphycenes and porphyrins, however, are quite similar (00IC2850). The synthesis of hemiporphycene **70** (Scheme 33) has been achieved (05ACI3047) from corrole **8** ($R = \text{C}_6\text{H}_5$).



Scheme 33 Synthesis of hemiporphycene.

Paolesse and coworkers (09JCS(CC)1580, 09IC10346) have reported the synthesis of new hemiporphycene, 6-azahemiporphycene **71** (Scheme 34), through metamorphosis of corrole **8**. Thus, corrole **8** undergoes ring expansion with 4-amino-4H-1,2,4-triazole under aerobic conditions.

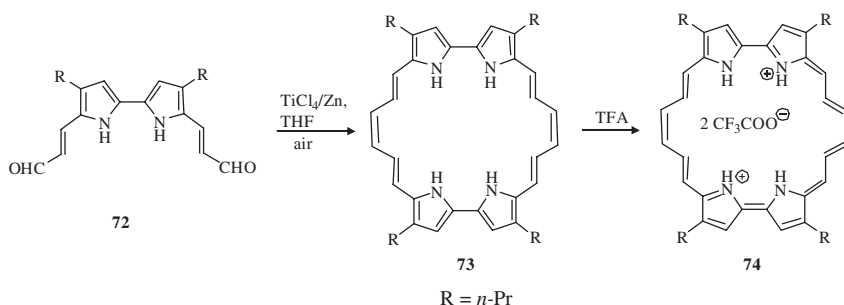


Scheme 34 Synthesis of 6-azahemiporphycene.

2.2.1. Expanded porphycenes

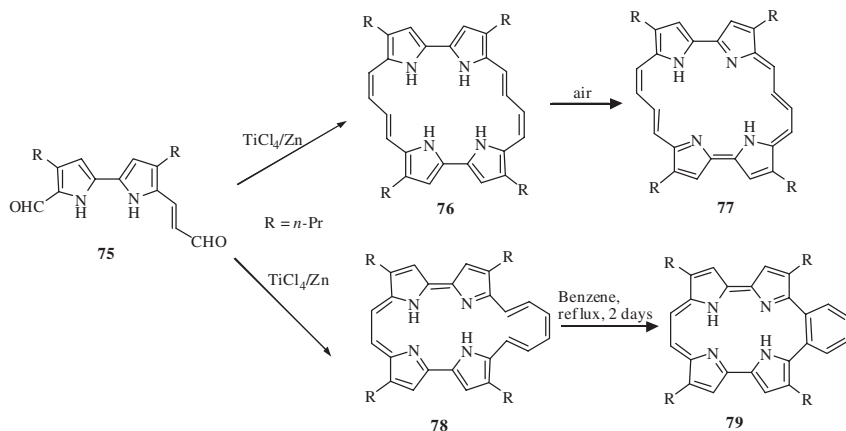
The advantage of inserting an even number of sp or sp² hybridized carbons into the linkers between the pyrrolic units of porphycenes to produce extended or expanded porphycenes arises from the lengthening of the [4*n*+2] π -electron conjugation pathway. The resultant chromophores absorb at longer wavelengths than regular porphycenes, a feature of immense practical utility to produce compounds in PDT-related applications (1992MIa, 1992MIb).

The general synthetic approaches for expanded porphycenes rely upon the insertion of alkylidene or alkylidyne moieties either as the *meso*-bridge or between the 2 and 2' positions of the bipyrrole subunits. Thus, the vinylogous dialdehyde **72** (Scheme 35) obtained from 4,4'-dipropyl-2,2'-bipyrrole with 3-(dimethyl-1-amino)acrolein has been converted to (**1993PAC143**) to **73** using a standard McMurry-type coupling. Expanded porphycene **73** with TFA precipitates as dication **74**.



Scheme 35 Synthesis of expanded porphycene using vinylogous dialdehyde.

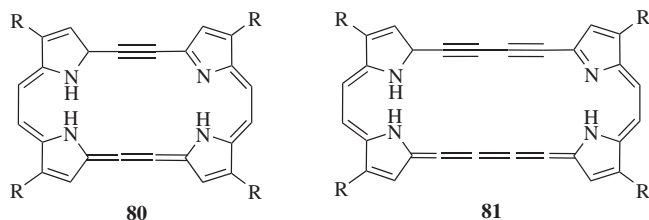
Similarly, the monovinylogous diformyl bipyrrole **75** (Scheme 36), under reductive McMurry conditions, followed by air oxidation, results in the formation of expanded porphycene **77** as the dominant product (7%)



Scheme 36 Synthesis of expanded porphycene using a monovinyllogous dialdehyde.

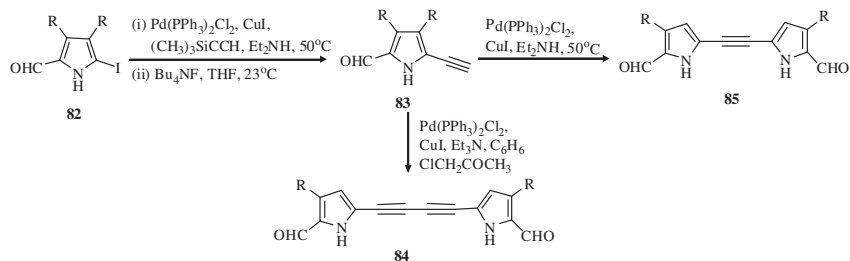
through the intermediacy of **76**, as well as the less symmetrical isomer **78** (1994MI) cyclizable to benzo derivative **79**.

Expanded porphycene **80** containing triple bonds inserted between the 2 and 2' positions of the 2,2'-biyrrole subunits (1990ACI1385, 1990ACI1387) is a 22π -electron aromatic macrocycle that displayed an acetylene-cumulene bonding motif, a feature in common with Sondheimer–Nakagawa $[4n+2]$ dehydroannulenes.

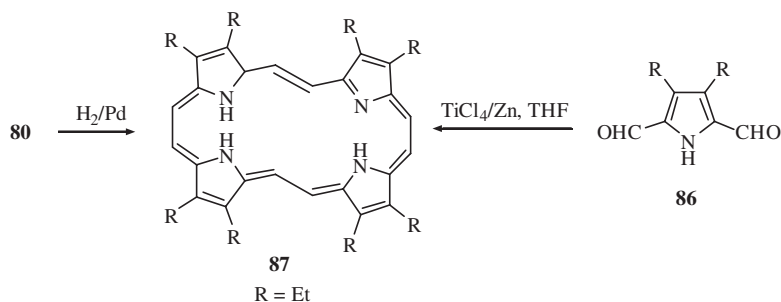


Synthesis of a 26π -electron homologue **81** (1992JA9969) (Scheme 37) has been achieved *via* the reductive dimerization of dialdehyde **84**, prepared from iodopyrrole **82** and an acetylene, employing Sonogashira coupling to obtain **83** after deprotection. For β -methyl-substituted derivatives, a refined procedure has been reported by Kim et al. (1999JOC8048). Similarly **85** obtained from intermediate **83** has been converted into **80**.

Another class of extended porphycene, containing an extra sp^2 hybridized link between 2 and 2' positions of the biyrrole subunit has been synthesized by hydrogenation of **80** resulting in the formation of 22π -electron conjugated porphycene homologue **87** (Scheme 38), also synthesized from pyrrole dialdehyde **86** by reductive coupling under McMurry conditions.



Scheme 37 Synthesis of precursors of expanded porphycenes.



Scheme 38 Synthesis of an extended porphycene containing an sp^2 hybridized linked bipyrrole.

2.3. Inverted porphyrins

Inverted porphyrin or 2-aza-21-carbaporphyrin **88** also known as an NCP ([Figure 3](#)) was first isolated as a by-product of normal acid-catalyzed condensation of pyrrole and benzaldehyde ([1994ACI779](#), [1994JA767](#)). Latos-Grazynski and coworkers employed a Rothmund reaction between tolualdehyde and pyrrole in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in DCM, followed by oxidation with 2,3,5,6-tetrachloro-*p*-benzoquinone (chloranil) to obtain NCP ([1994ACI779](#)). Simultaneously, Furuta and coworkers also reported

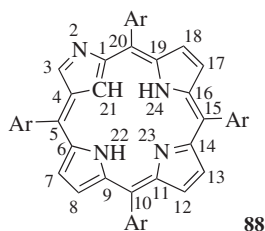
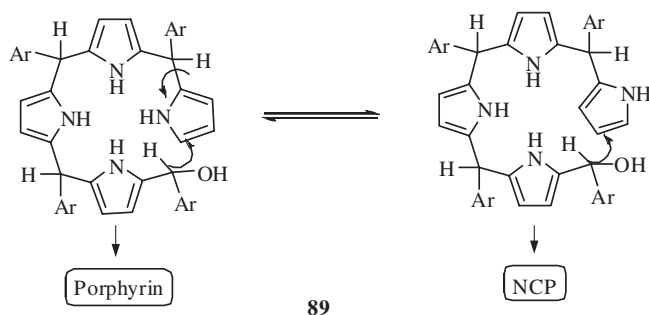


Figure 3. NCP and the numbering scheme.

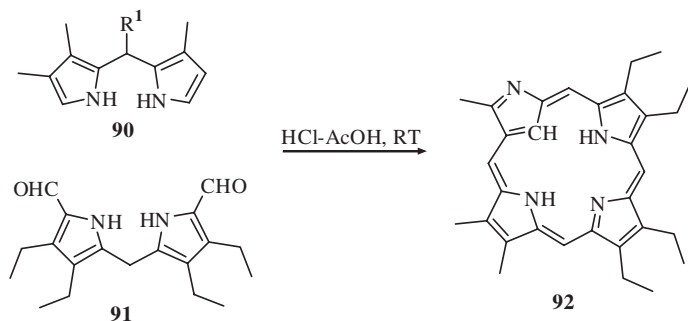
NCP from pyrrole and benzaldehyde in the presence of *t*-BuOH/DCM (1:1) and conc. HBr, followed by oxidation with chloranil (1994JA767).

The common feature between the mechanism of formation of a porphyrin and an NCP during the porphyrinogen **89** (Scheme 39) (1994ACI779) ring closure is the rotation of the terminal pyrrole with respect to the C α –C_{meso} bond in **88** that could furnish either product.



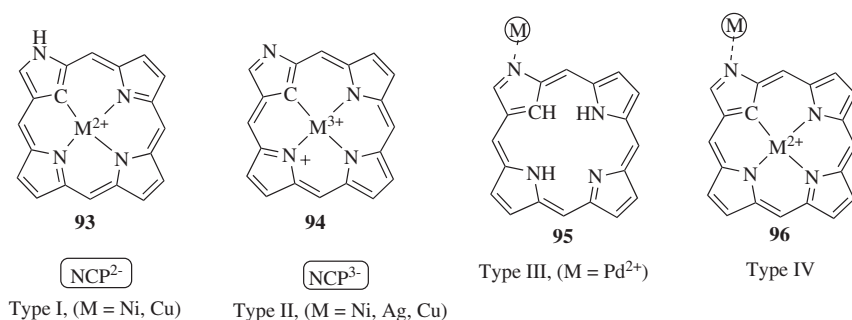
Scheme 39 Proposed mechanism for the formation of NCP.

Other syntheses of NCPs have also been reported (1996JCS(CC)2141, 1998TL7389, 1999JOC1596, 1999OL1455, 1999JOC7973). NCP **92** has been obtained by acid-catalyzed condensation of dipyrromethane **90** and dipyrromethanedialdehyde **91** (Scheme 40) (1996JCS(CC)2141). *meso*-Tetraaryl NCP **88** has been obtained through oxidative coupling of dipyrromethane **90** ($R^1 = C_6H_5$) and a catalytic amount of *p*-TsOH (1998TL7389) or as one of the products in an acid-catalyzed reaction of a pyrrole and an aldehyde (1999JOC1596, 1999OL1455) alkyl-substituted inverted porphyrins through a “3+1” condensation involving a tripyrrane dicarboxylic acid and a pyrrol-2,4-dicarboxaldehyde have also been reported (1999JOC7973).



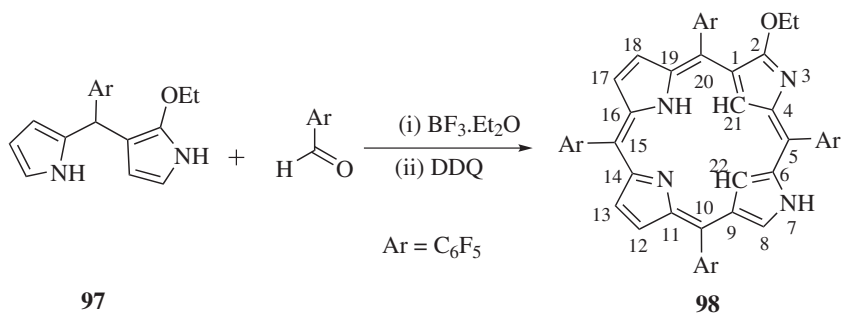
Scheme 40 Synthetic route to NCPs.

Owing to the modification of the core coordinating sites (inner core carbon and outward-pointing nitrogen), compared to porphyrins, the coordination chemistry of NCPs differs from porphyrins. NCPs, by virtue of forming a metal–carbon bond inside the cavity, act as a tetradentate ligand to make both simple and organometallic multivalent complexes **93–96** (Scheme 41) with Ni(II), Ni(III) (1994ACI779, 1997IC6287, 1996JA5690), Cu(II) (00IC5475), Ag(III) (1999IC2676), Pd(II) (00IC5424, 00JOC4222), and Pb(II) salts. The formation of these complexes involves both inner and outer *N*-coordination.

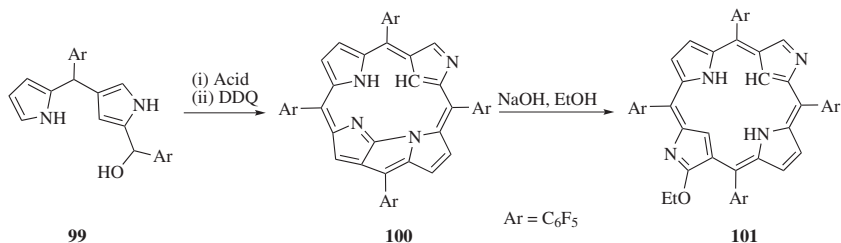


Scheme 41 Metal binding modes of NCPs.

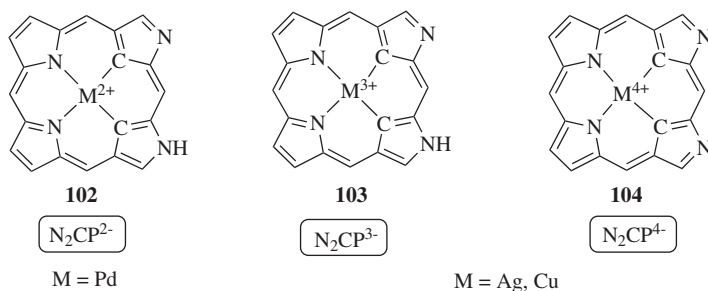
Doubly confused porphyrins [N_2 CP: 18porphyrin(1.1.1.1)-(C α , C β , N, N *)] (00JA803) are also known (00JA803, 03JA15690). Furata *et al.* through “2+2” acid-catalyzed condensation of *N*-confused dipyrromethane **97** and perfluorobenzaldehyde have isolated *cis*-regioisomeric N_2 CP **98** (Scheme 42) (00JA803). *trans*- N_2 CP **101** (Scheme 43) was synthesized (03JA15690) by “2+2” self-condensation of a monocarbinol derivative of *N*-confused dipyrromethane **99** through the intermediacy of *N*-fused derivative **100**.



Scheme 42 Synthesis of *cis*- N_2 CP and the numbering scheme.

Scheme 43 Synthesis of *trans*-N₂CP.

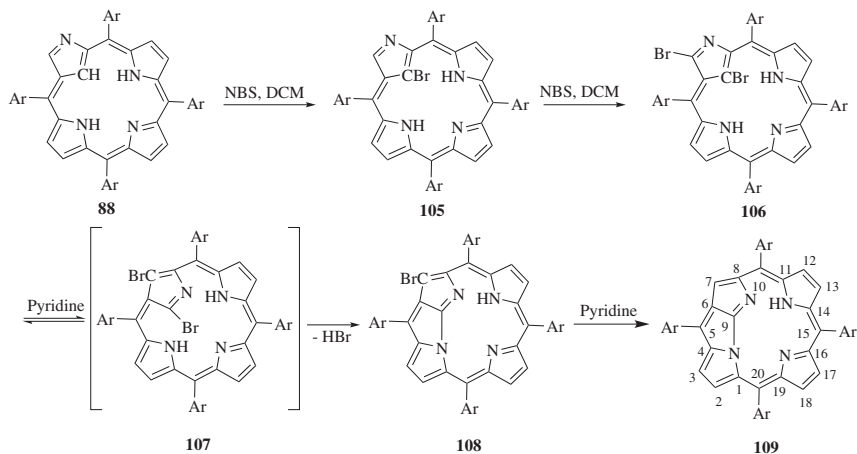
N₂CPs stabilize rare complexes containing Ag(III) and Cu(III) metal centers (00JA803). Similarly inner C-tolylated Pd(II) complexes have been prepared. N₂CPs exhibit divalent (N₂CP₂[−]) **102** (Scheme 44), trivalent (N₂CP₃[−]) **103**, or tetravalent **104** nature with Pd(II), Ag(III), and Cu(II), respectively (00JA803).

Scheme 44 Multivalency and metal binding modes of N₂CP.

N-Fused porphyrin (NFP) **109** (1999JA2945) (Scheme 45) was accidentally obtained from a pyridine solution of brominated NCP **106**. When **105** was treated with *N*-bromosuccinimide (NBS) for 5 min at room temperature, brominated NCP **106** was obtained. Using pyridine furnished NFP **109** (Scheme 45).

2.4. Expanded porphyrins

In Section 2.2.1–2.2.3, a brief discussion on the chemistry, properties and structure of contracted, isomeric, and inverted porphyrins has been presented. Here, a brief sketch of the structural diversity in expanded porphyrins is given. Expanded porphyrins represent those synthetic macrocycles in which pyrrole or heterocyclic rings possess connectivity through *meso*-carbon bridges. The conjugation of the porphyrin has been



Scheme 45 Mechanism for the formation of NFP and the numbering scheme.

expanded up to 64π -electrons (Figure 4a–f). Consequently, applications such as photosensitization for PDT (1994ACR43, 00BP733), anion sensing in certain protonation states, drug transport and delivery (01ACR989), magnetic resonance imaging (MRI), and NLO have benefited (1997MI1, 00MI4).

Recent reviews (1997MI1, 1997CR2267, 03ACI5134, 02PISC311) report on the chemistry and applications of expanded porphyrins. We highlight the most recent synthetic routes and chemical characteristics of *only pyrrolic* systems, presented in the order of increasing structural complexity. Expanded systems having heterocyclic species other than pyrrole have been avoided.

2.4.1. Expanded systems containing four pyrrolic subunits

The first synthesis of an aromatic and extremely stable [22]octaethylporphyrin(3.1.3.1) **111** (Scheme 46) was reported by Frank *et al.* It was obtained from biladiene **110** by heating with formaldehyde/MeOH, followed by in situ oxidation with DDQ (1990ACI1393). X-ray crystallographic analysis revealed that the conjugated perimeter of **111** is planar. The ^1H NMR spectrum indicated the presence of intense diamagnetic ring currents. The most interesting aspect of **111** was that the protons, inside and outside the aromatic systems, exhibited a large difference in reactivity. Whereas, the outer protons of the 22π -electron system readily undergo electrophilic substitution, the inner protons are relatively inert.

The synthesis of [22]porphyrin(3.1.3.1) **114**, also called [22]coproporphyrin II, through acid-catalyzed condensation of bis(carbonylvinyll)

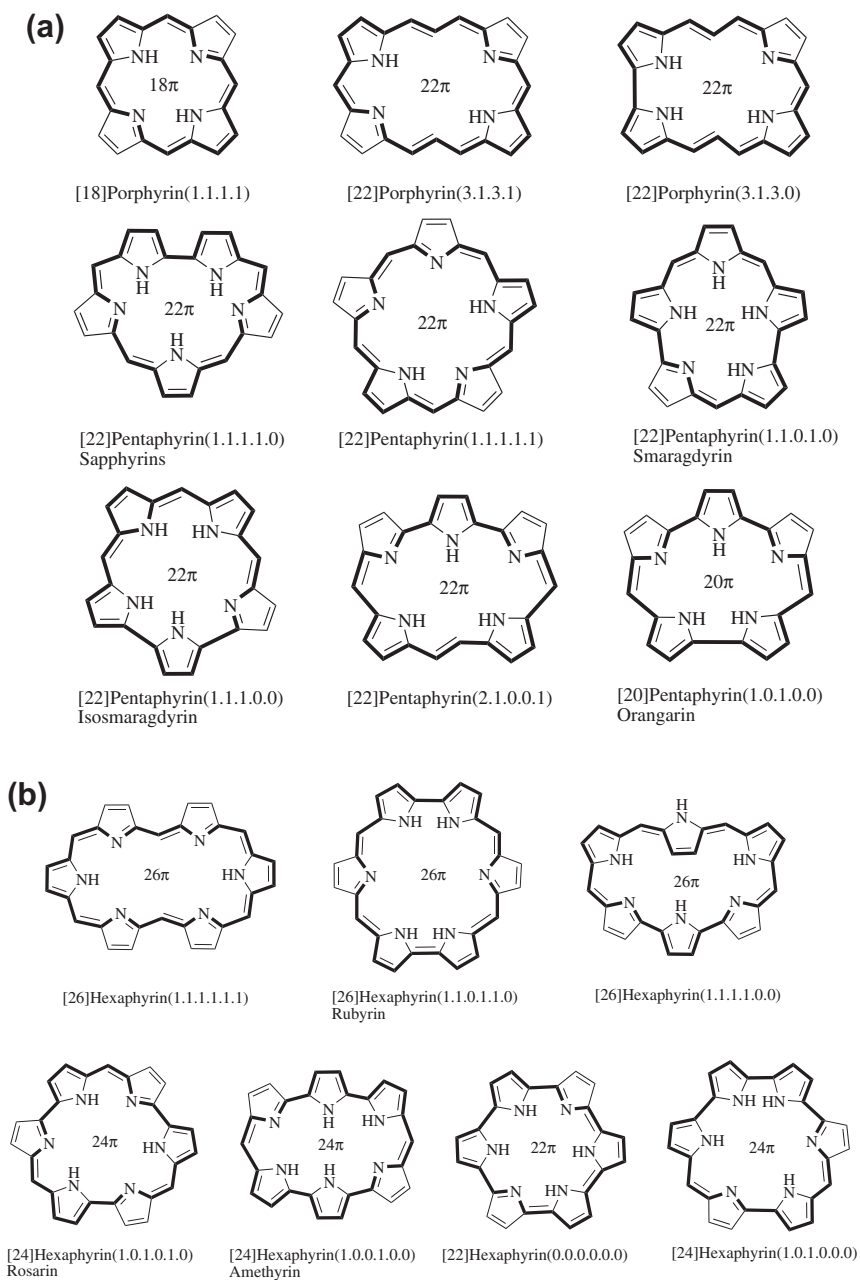


Figure 4. (a) Tetra- and pentapyrrolic expanded porphyrins. (b) Hexapyrrolic expanded porphyrins.

(Continued)

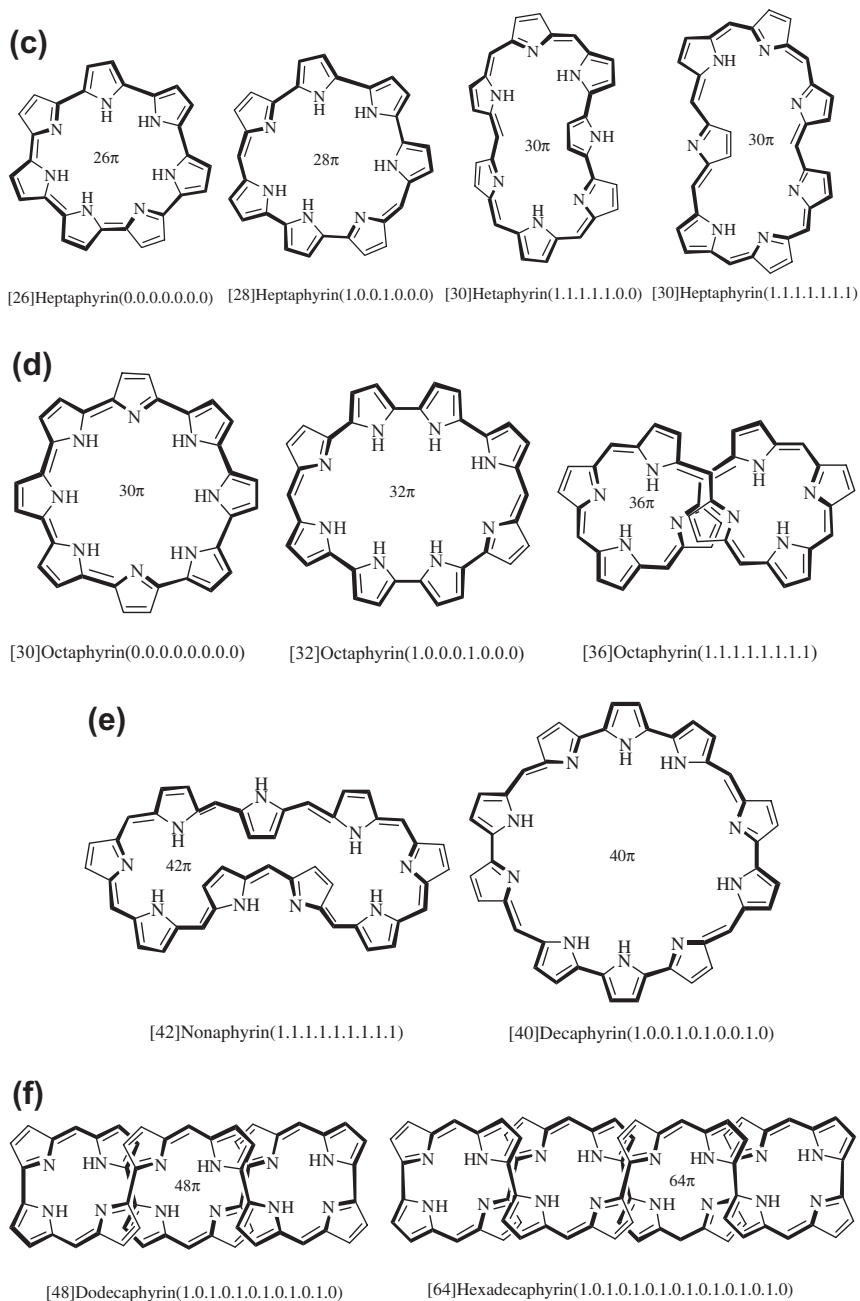
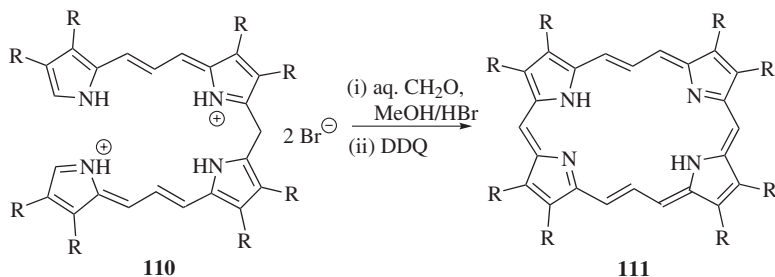
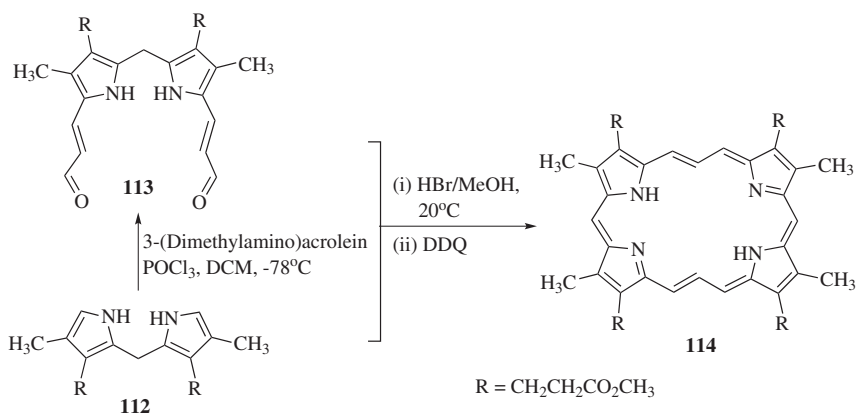


Figure 4. (Cont'd) (c) Heptapyrrolic expanded porphyrins. (d) Octapyrrolic expanded porphyrins. (e) Nona- and decapyrrolic expanded porphyrins. (f) Dodeca- and hexadecapyrrolic expanded porphyrins.



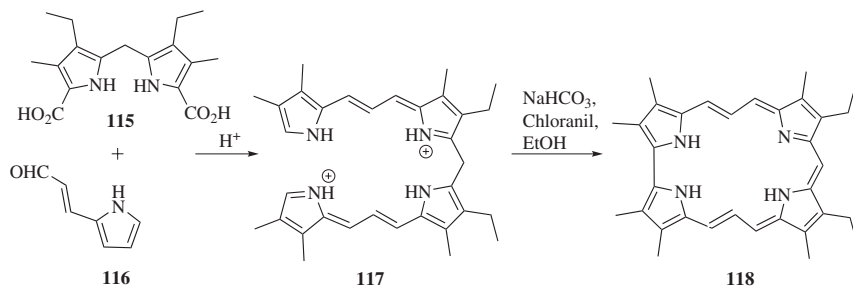
Scheme 46 First synthesis of aromatic [22]octaethylporphyrin(3.1.3.1) from biladiene.

dipyrrolmethane **113** (Scheme 47) with dipyrromethane **112** has also been reported. Subsequent, in situ dehydrogenation with DDQ leads to **114** in 35% yield (1990ACI1395).



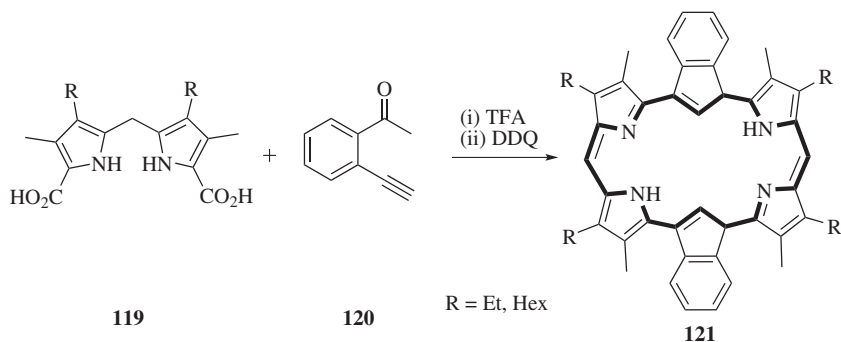
Scheme 47 Acid-catalyzed synthesis of [22]coproporphyrin.

Paolesse et al. have reported the synthesis of a [22]porphyrin(3.1.3.0) **118** (Scheme 48) (1999ACI2577) (an expanded corrole) in 54% yield through base-catalyzed, chloranil aided oxidative cyclization of tetrapyrrolic intermediate **117**, obtained from dipyrromethane **115** and pyrrole aldehyde **116**. The electronic absorption spectrum of **118** shows strong absorptions, significantly red-shifted relative to those of the corresponding porphyrin, indicating an expanded aromatic system. The protons in the ¹H NMR spectrum showed line broadening, attributed to aggregation that vanished when the NMR was recorded at high temperature (70°C).



Scheme 48 Base-catalyzed synthesis of [22]porphyrin.

Bampos and coworkers (10ACI3930) have reported the synthesis of a new indene expanded porphyrin also called [22]dibenzo-dicarba-hexaphyrin (1.0.0.1.0.0) **121** (Scheme 49) by “2+2” acid-catalyzed condensation of β -alkyl-substituted dipyrromethanes **119** with 2-ethynyl-benzaldehyde **120**.



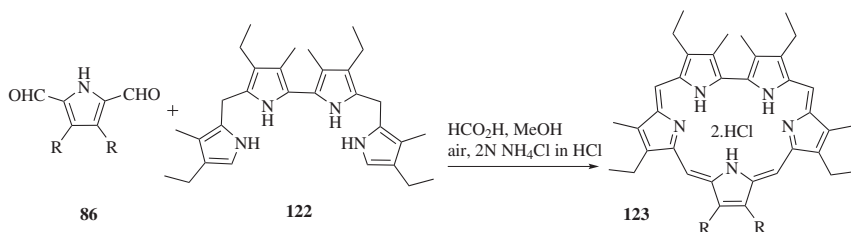
Scheme 49 “2+2” Condensation approach for the synthesis of [22]dibenzo-dicarba-hexaphyrin.

2.4.2. Pentapyrrolic expanded porphyrins

Here five pyrrolic units are connected by a different number of methine bridges. Representative systems shown in Figure 4 are [22]pentaphyrin(1.1.1.1.0), [22]pentaphyrin(1.1.1.1.1), [22]pentaphyrin(1.1.0.1.0), [22]pentaphyrin(1.1.1.0.0), [22]pentaphyrin(2.1.0.0.1), and [20]pentaphyrin(1.0.1.0.0).

2.4.2.1. [22]Pentaphyrin(1.1.1.1.0)

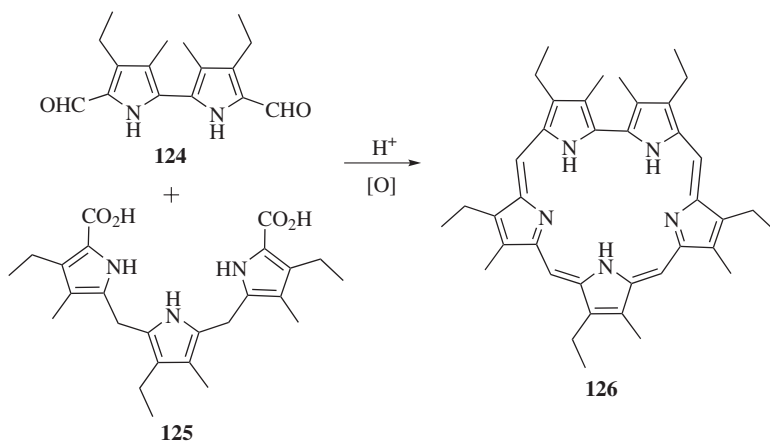
The [22]pentapyrrolic(1.1.1.1.0), sapphyrins (1966MI), are aromatic and show intense blue-green color in organic solvents. Serendipitous isolation of sapphyrins by Woodward (1966MI) led to the development of synthetic



Scheme 50 Synthesis of β -substituted sapphyrin.

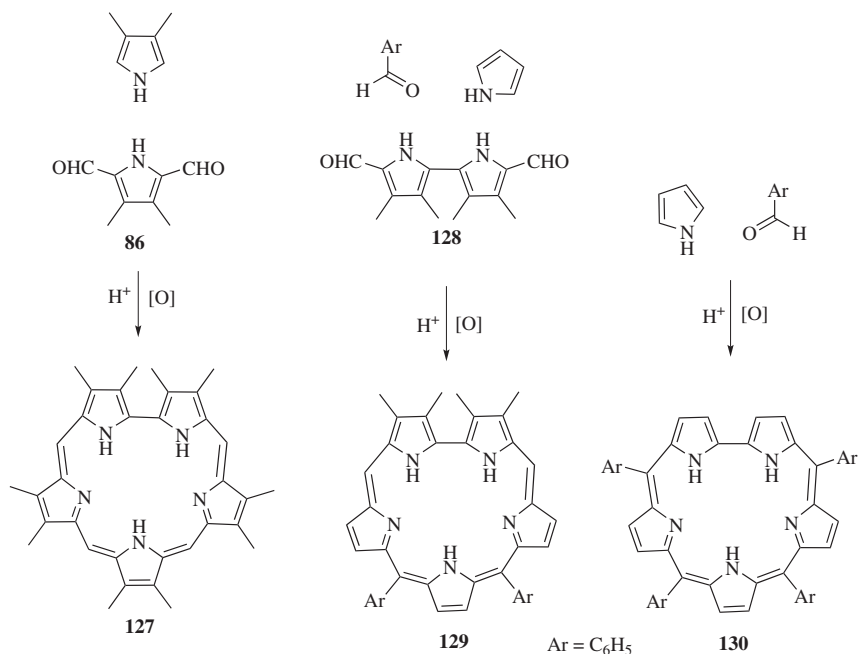
methods for sapphyrins. Sapphyrin **123** ($R=\text{Me}$) ([Scheme 50](#)) was obtained as a dihydrochloride salt in the “4+1” condensation between linear tetrapyrrolic precursor ([1983JA6429](#)) **122** and 2,5-diformyl-3,4-dimethylpyrrole **86** ($R=\text{Me}$) in acid.

Likewise, “3+2” condensation ([1987JOC4394](#), [1995CEJ68](#)) involving bipyrrole dialdehyde **124** and tripyrrane dicarboxylic acid **125** catalyzed by acid followed by air oxidation is another widely used methodology for sapphyrin **126** ([Scheme 51](#)).



Scheme 51 “3+2” Condensation approach for sapphyrin.

Other syntheses of sapphyrins include (i) a one-pot reaction of 3,4-dimethyl pyrrole with pyrrole dialdehyde **86** ([1983JA6429](#)); (ii) acid-catalyzed reaction of pyrrole, bipyrrole dialdehyde **128** ([Scheme 52](#)), and benzaldehyde ([1987JOC4394](#)); and (iii) reaction of benzaldehyde and pyrrole in 1:3 molar ratios under oxidative acid catalysis ([1995CEJ68](#)). These sequences furnish sapphyrins **127**, **129**, and **130**, respectively ([1983JA6429](#),

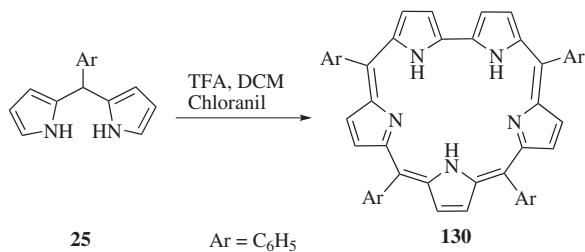


Scheme 52 Different routes to sapphyrins using pyrrole.

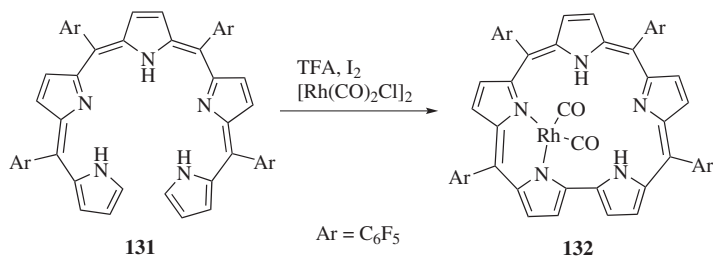
1987JOC4394, 1995CEJ68, 1997JCS(CC)1689). Smith and coworker (1997JOC5133) have also reported the formation of sapphyrin from biladiene **109** and formyl pyrrole.

Improved yields of sapphyrins have been reported by Lindsey and Geier (1999JOC1596) and Chandrashekar *et al.* (1998TL7389). The latter used a single precursor dipyrromethane **25** bearing a *meso*-phenyl group to obtain sapphyrin **130** ($\text{Ar} = \text{C}_6\text{H}_5$) (Scheme 53) (1998TL7389).

Gross and coworkers (01TL4929) have reported that pentapyrrole **131** (Scheme 54) can be converted into sapphyrin using a variety of oxidants



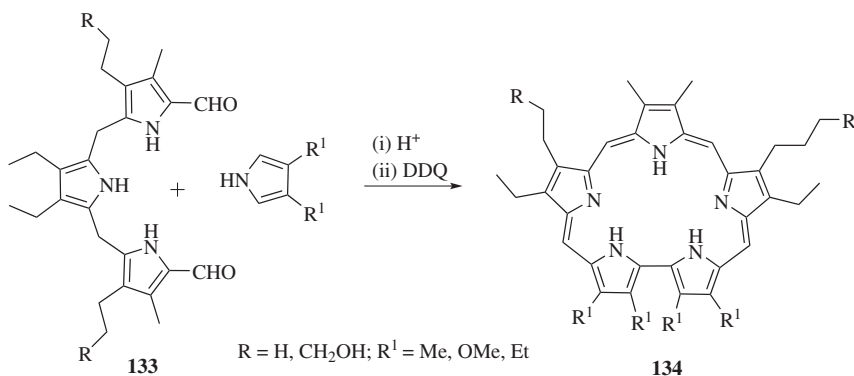
Scheme 53 Synthesis of *meso*-substituted sapphyrin.



Scheme 54 Synthesis of a rhodium-sapphyrin complex.

($\text{Na}_2\text{Cr}_2\text{O}_7/\text{TFA}$, DDQ, and I_2). The crude sapphyrin obtained in this way, being unstable, was treated with $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ to isolate stable complex **132**.

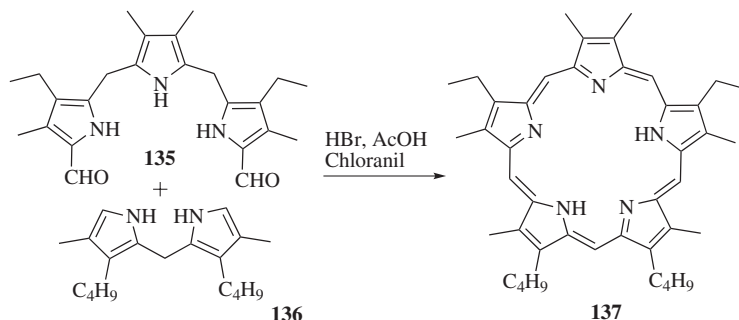
Sessler and coworkers reported a new “3+1+1” route for sapphyrins, without using a bipyrrrolic moiety (01TL2447). Tripyrrane dialdehyde **133** with two equivalents of a pyrrole under acidic conditions, followed by oxidation with DDQ furnished sapphyrins **134** bearing different substituents in yields lower than by the “3+2” approach (Scheme 51), but the need of a bipyrrrole synthesis could be obviated. This method (Scheme 55) allowed the synthesis of otherwise not known sapphyrins that contained various symmetric bipyrrrolic subunits.



Scheme 55 Synthesis of sapphyrin by the “3+1+1” approach.

2.4.2.2. [22]Pentaporphyrin(1.1.1.1)

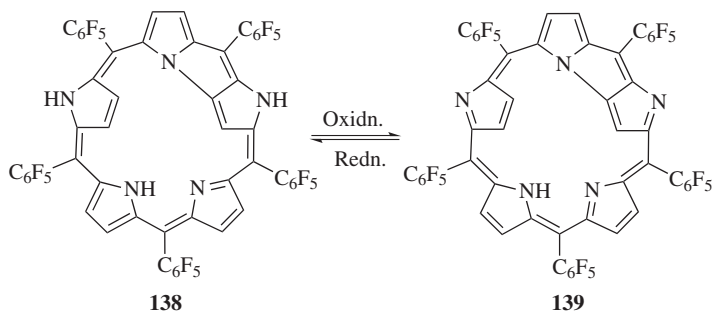
[22]Pentaporphyrin(1.1.1.1.1) **137** (Scheme 56) has been obtained (1983JCS(CC)275, 1983BSCB793) by an HBr-catalyzed oxidative condensation of diformyltripyrane **135** and dipyrromethane **136** in 31% yield.



Scheme 56 Synthesis of [22]pentaphyrin(1.1.1.1.1).

A *meso*-diphenyl pentaphyrin has also been reported by Dolphin, which involves a TFA-catalyzed “3+2” condensation (1997JCS(CC)1689).

Furuta *et al.* have reported the synthesis of an *N*-fused normal 22 π -electron pentaphyrin containing a fused tripentacyclic ring from the Rothmund reaction of an aldehyde and a pyrrole using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and DDQ (Scheme 57) (01ACI619).

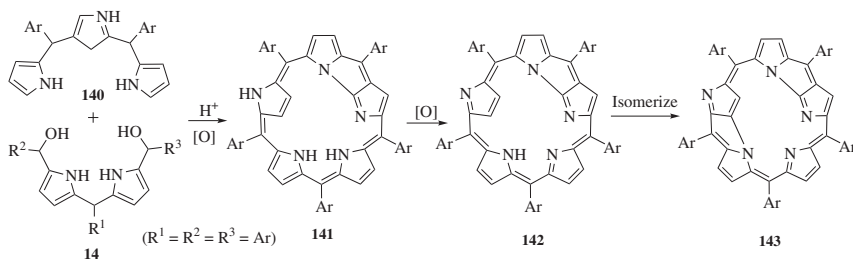


Scheme 57 Synthesis of an *N*-fused pentaphyrin containing a fused tripentacyclic ring.

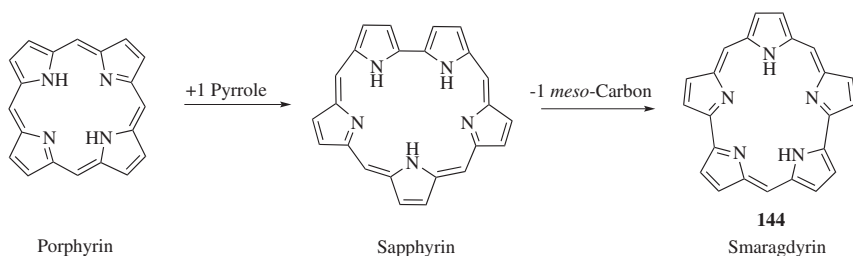
Likewise, in a “3+2” acid-catalyzed condensation of *N*-confused tripyrrene **140** and dipyrromethane-dicarbinol **14** ($\text{R}^1=\text{R}^2=\text{R}^3=\text{Ar}$), the *N*-fused pentaphyrin **141** with all nitrogens pointing inward was obtained. Subsequent oxidation of **141** (Scheme 58) gave **142**, which isomerized into doubly *N*-fused pentaphyrin **143**, devoid of aromaticity (04ACI876).

2.4.2.3. [22]Pentaphyrin(1.1.0.1.0)

Removal of one *meso*-carbon from the sapphyrin skeleton leads to relatively unstable non-sapphyrin 22 π smaragdyrin **144** (Scheme 59) (1983JA6429). These (1972JCS(1)2111) bear a structural relationship analogous to that between a porphyrin and a corrole. The earlier attempts to



Scheme 58 Synthesis of a doubly *N*-fused pentaphyrin.



Scheme 59 Pentaphyrins derived from porphyrin.

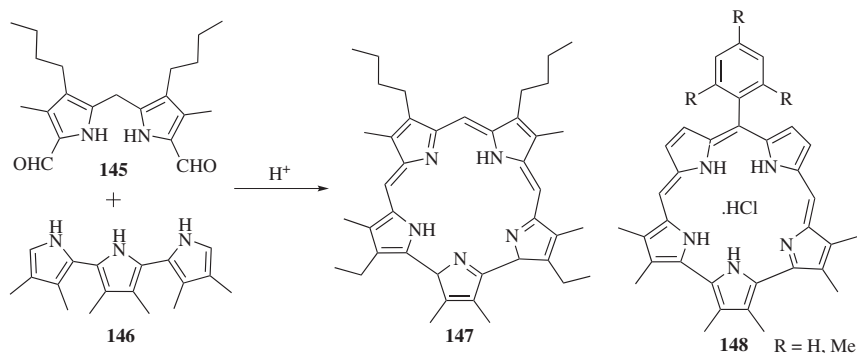
synthesize β -substituted smaragdyrins were only partially successful due to their inherent instability toward light and acid. Chandrashekar et al. (00IC3669) demonstrated the synthesis of modified smaragdyrin from a modified tripyrrane and a dipyrromethane using 0.1 equiv. of TFA followed by oxidation with chloranil. A number of reports on the synthesis of heterosmaragdyrin have appeared, a topic outside our scope.

2.4.2.4. [22]Pentaphyrin(1.1.1.0.0)

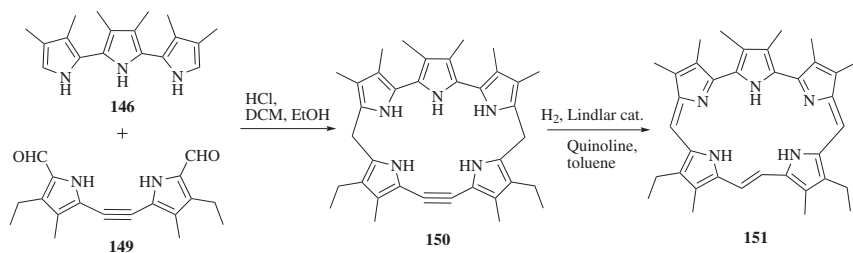
An isomeric contracted sapphyrin, namely, “is smaragdyrin” or [22]pentaphyrin(1.1.1.0.0) **147** (Scheme 60) has been obtained *via* the acid-catalyzed condensation of bisformyl dipyrromethane **145** with bis- α -free-terpyrrole **146** (1998JOC7062). Using the same terpyrrole **146** and a bisformyl *meso*-aryl-substituted dipyrromethane of *meso*-substituted is smaragdyrin **148** has also been reported (01T3743).

2.4.2.5. [22]Pentaphyrin(2.1.0.0.1)

Sessler and coworkers have synthesized [22]pentaphyrin(2.1.0.0.1) **151** (Scheme 61) by condensing terpyrrole **146** with an alkyne bridged bipyrrole **149** under MacDonald conditions giving rise to a 22 π aromatic macrocycle dehydropentaphyrin **150**, which upon treatment with a poisoned Lindlar catalyst (Pd/CaCO₃) gave **151** (1995TL4713).



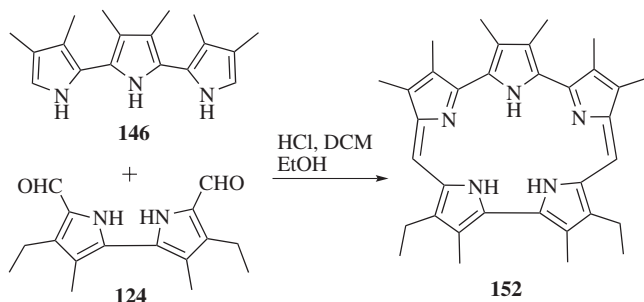
Scheme 60 Synthesis of isosmaragdyrin.



Scheme 61 Synthesis of [22]pentaphyrin(2.1.0.0.1).

2.4.2.6. [20]Pentaphyrin(1.0.1.0.0)

The smallest pentapyrrolic is [20]pentaphyrin(1.0.1.0.0) (orangarin) **152**. Acid-catalyzed condensation between hexamethyl terpyrrole **146** (Scheme 62) and diformyl bipyrrole **124** (1995CEJ56) furnishes **152**. Compared to Huckel (18π , 22π) aromatic species, **152** is 20π antiaromatic as attested by its extremely broad absorption spectrum. While the pentapyrrolic aromatic species displays appreciable fluorescence, no appreciable fluorescence is seen for the antiaromatic species.



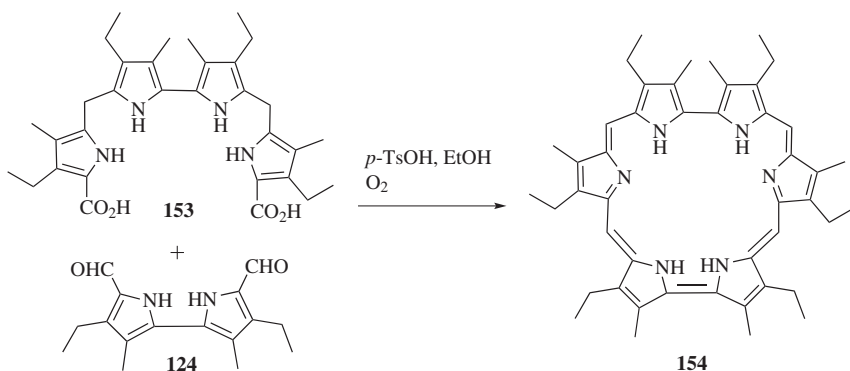
Scheme 62 Synthesis of orangarin.

2.4.3. Hexapyrrolic expanded porphyrins

As the number of pyrrole rings in a macrocycle increases, the number of possible combinations for a given set of pyrroles and *meso*-carbons also increase. As a consequence, at least six hexapyrrolic systems have been reported (03ACI5134, 02PISC311). However, only the latest information on the hexapyrrolic systems is summarized.

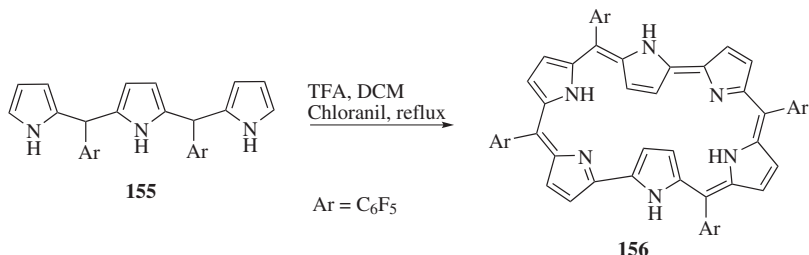
2.4.3.1. [26]Hexaphyrin(1.1.0.1.1.0)

The first [26]hexaphyrin(1.1.0.1.1.0) **154** (Scheme 63) was obtained by condensing tetrapyrrolic precursor **153** with the diformyl bipyrrole **124** under acid-catalyzed conditions, followed by air oxidation. The resulting macrocycle was assigned the trivial name “ruberin” due to its dark orange-red color in DCM (1991ACI977).



Scheme 63 Synthesis of β -substituted ruberin.

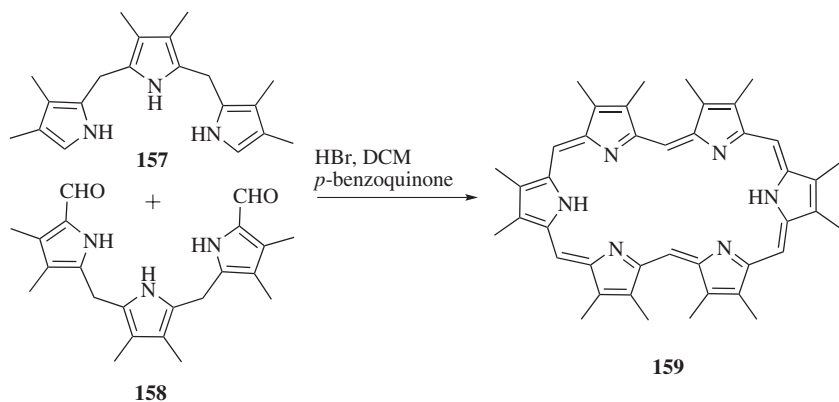
A *meso*-substituted ruberin **156** ($\text{Ar}=\text{C}_6\text{H}_5$) (Scheme 64) has been obtained by acid-catalyzed condensation of *meso*-substituted tripyrrane **155** ($\text{Ar}=\text{C}_6\text{F}_5$), followed by oxidation with chloranil (08CEJ2668).



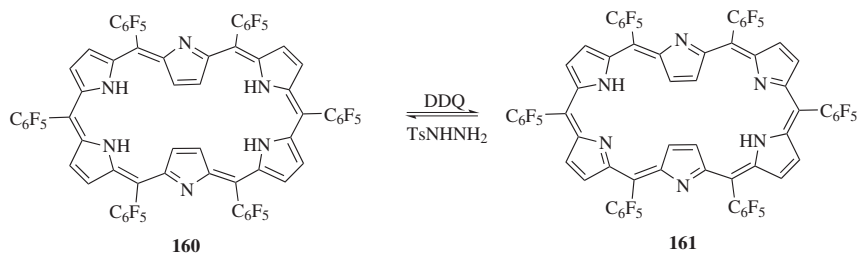
Scheme 64 Synthesis of *meso*-substituted ruberin.

2.4.3.2. [26]Hexaphyrin(1.1.1.1.1.1)

[26]Hexaphyrin(1.1.1.1.1.1) **159** (Scheme 65) represents a homologue of porphyrin in terms of a conjugated cyclic π -system with an alternate arrangement of heterocyclic rings and methine bridges. The presence of six *meso*-carbons allows this flexible molecule to adopt different conformations. Hexaphyrin **159** was first synthesized (02PISC311, 1983BSCB793) by the acid-catalyzed “3+3” condensation of α -free tripyrrane **157** and tripyrrane dialdehyde **158**, although the first *meso*-aryl hexaphyrin was obtained through condensation of 5,10-diphenyl tripyrrane and benzaldehyde, it was found to be unstable (1997JCS(CC)1689). However, using a Rothmund-type strategy, employing pentafluorobenzaldehyde and pyrrole as reactants, a stable mixture of a blue and a violet *meso*-aryl hexaphyrin was obtained (1999JCS(CC)385). Both compounds were identical, depicted parent ion peak at m/z 1462, and were found to interconvert by hydrogenation–dehydrogenation processes, i.e., by reacting the blue compound with DDQ in CHCl_3 , the violet **161** is obtained and reduction of the violet compound with tosylhydrazine (TSNHNH₂) furnished blue **160** (Scheme 66). The macrocycle displayed



Scheme 65 Synthesis of β -substituted hexaphyrin (1.1.1.1.1.1).



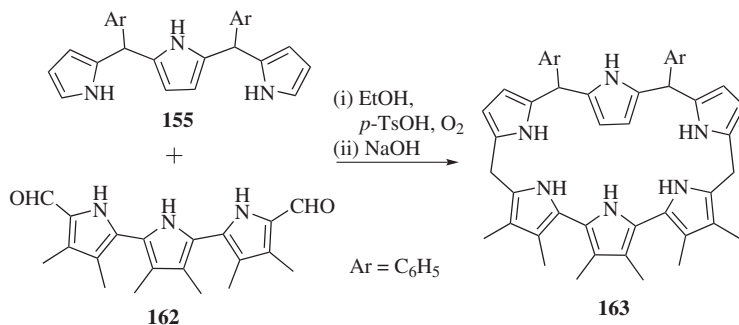
Scheme 66 Redox behavior of hexaphyrin.

behavior analogous to that of *N*-fused pentaphyrin, the ability to exist simultaneously in two different oxidation states with inverted pyrrole rings.

Furuta and coworkers reported a procedure that allowed improvement in the yield of product up to 20%. Anderson and coworkers have reported the synthesis of *meso*-trialkynyl-[28]hexaphyrin in 37% yield (01JA7190).

2.4.3.3. [26]Hexaphyrin(1.1.1.1.0.0)

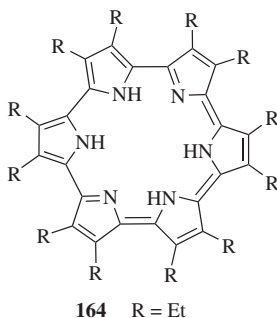
[26]Hexaphyrin(1.1.1.1.0.0) **163** (Scheme 67) represents an isomer of rubyrin, which was prepared (00JCS(CC)1473) in 46% yield by acid-catalyzed condensation of an equimolar mixture of *meso*-aryl-substituted tripyrrane **155** with the diformylhexamethylterpyrrole **162** in ethanol in the presence of air.



Scheme 67 Synthesis of hexaphyrin.

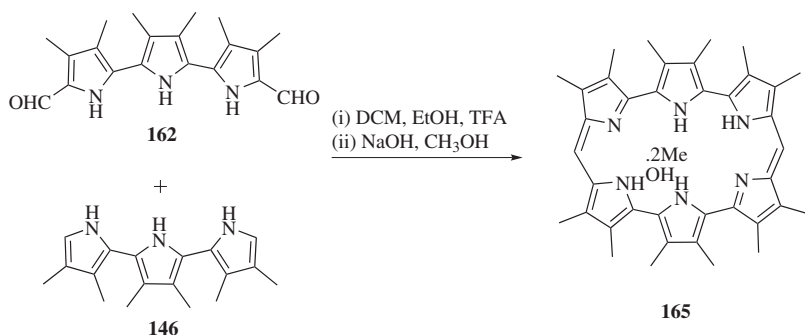
2.4.3.4. [22]Hexaphyrin(0.0.0.0.0.0)

[22]Hexaphyrin(0.0.0.0.0.0) **164** has been obtained as its HCl salt by Fe(III)-mediated cyclization of bipyrrole in 1 M HCl (03JA6872).



2.4.3.5. [24]Hexaphyrin(1.0.0.1.0.0)

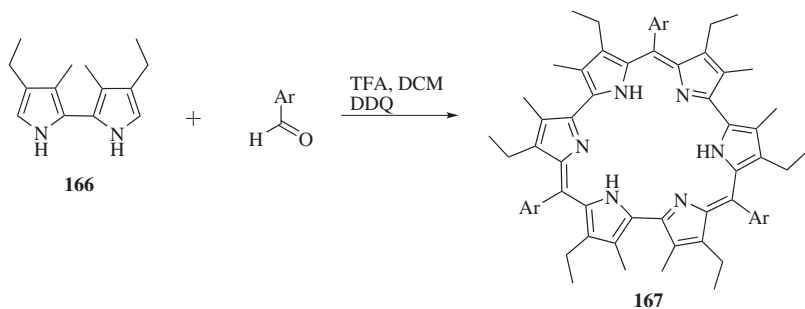
The smallest hexapyrrolic macrocyclic system, [24]hexaphyrin(1.0.0.1.0.0), “amethyrin” has been obtained through the condensation of diformyl-terpyrrole **162** and terpyrrole **146** (Scheme 68) in the presence of TFA. Treatment of the resulting amethyrin–TFA salt with NaOH, followed by crystallization from methanol, resulted in the formation of an amethyrin–bismethanol complex in 90% yield (01ICA211). The Ni(II) complex of amethyrin **165** has been prepared from Ni(II)–acetylacetonate in toluene. Metal complexation is accompanied by ligand oxidation such that the formally 24π antiaromatic **165** transforms to an aromatic 22π -electron system.



Scheme 68 Synthesis of amethyrin.

2.4.3.6. [24]Hexaphyrin(1.0.1.0.1.0)

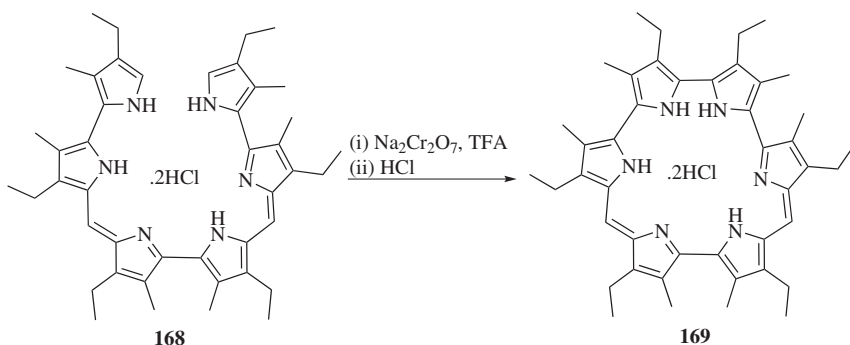
Another antiaromatic hexapyrrolic macrocycle, [24]hexaphyrin(1.0.1.0.1.0), rosarin **167** has been prepared by acid-catalyzed condensation of bipyrrole **166** and an aromatic aldehyde (Scheme 69) (1992JA8306).



Scheme 69 Synthesis of rosarin.

2.4.3.7. [24]Hexaphyrin(1.0.1.0.0.0)

[24]Hexaphyrin(1.0.1.0.0.0) **169** (Scheme 70), an isomer of amethyrin **165**, has been synthesized (01ACI591) by oxidizing the open-chain hexapyrrolic precursor **168** with $\text{Na}_2\text{Cr}_2\text{O}_7$ in TFA and is isolated as its salt after treatment with HCl. The antiaromatic nature of 24 π -electron **169** has been confirmed from the downfield shifts of the inner NH protons and upfield resonance of the *meso*-CH protons in its ^1H NMR spectrum. Treatment of **169** with actinide salts furnishes 22 π -electron uranyl U(VI) and Np(V) complexes as attested by a considerable downfield shift of the *meso*-CH protons, confirming reversal of the ring-current effects upon oxidation.



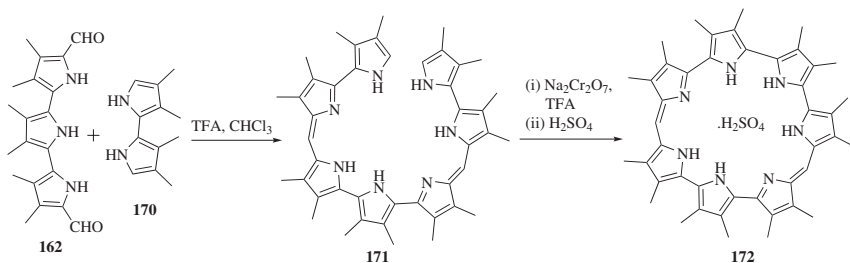
Scheme 70 Synthesis of [24]hexaphyrin(1.0.1.0.0.0.0).

2.4.4. Heptapyrrolic expanded porphyrins

There are only few reports on expanded porphyrins containing seven pyrrolic units till date. These have been summarized below.

2.4.4.1. [28]Heptaphyrin(1.0.0.1.0.0.0)

The first heptapyrrolic expanded porphyrin, [28]heptaphyrin(1.0.0.1.0.0.0), **172** (Scheme 71) was reported in 1999 through a two-step procedure

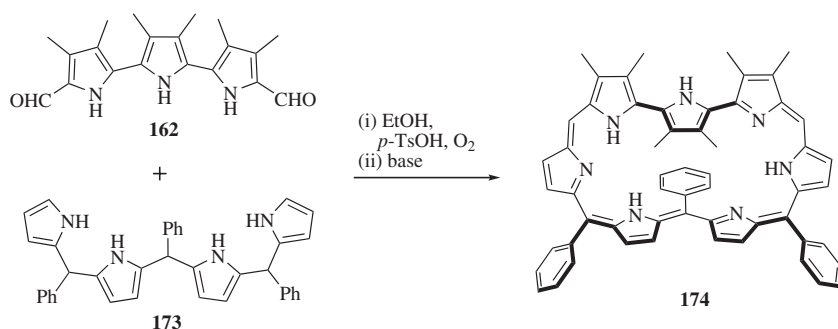


Scheme 71 Synthesis of quaterpyrrole-containing heptaphyrin.

involving condensation of tetramethylbipyrrole **170** with diformylhexamethylterpyrrole **162** giving rise to the open-chain heptapyrrolic species **171**, which upon subsequent treatment with $\text{Na}_2\text{Cr}_2\text{O}_7/\text{TFA}$ furnished (1999JA11257) [28]heptaphyrin(1.0.0.1.0.0.0) **172** as its dihydrogen sulfate salt. Being a 28π -electron system, it was found to be antiaromatic from the considerable downfield resonances of its NH protons. Similarly the signals of the *meso*-CH were found to be upfield.

2.4.4.2. [30]Heptaphyrin(1.1.1.1.1.0.0)

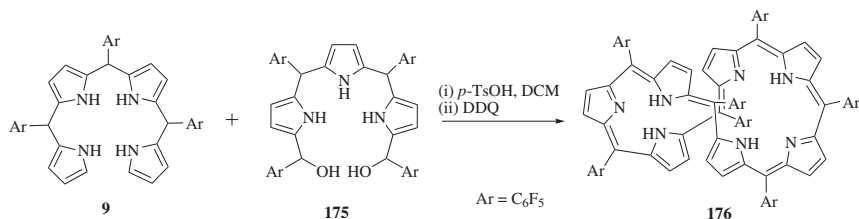
[30]Heptaphyrin(1.1.1.1.1.0.0) **174** (Scheme 72) has been reported by Sessler *et al.* through acid-catalyzed condensation of a 1:1 mixture of diformylhexamethylterpyrrole **162** with *meso*-phenyl-substituted tetrapyrane **173** (02JCS(CC)328).



Scheme 72 Synthesis of heptaphyrin.

2.4.4.3. [30]Heptaphyrin(1.1.1.1.1.1.1)

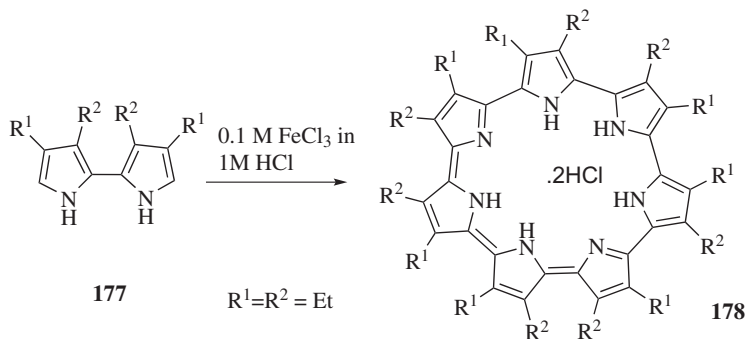
meso-Heptakis(pentafluorophenyl)heptaphyrin(1.1.1.1.1.1.1) derivative **176** (Scheme 73) has been made (06CEJ9095) by employing a unique *N*-fusion resulting in the formation of singly, doubly, and quarterly *N*-fused heptaphyrins. A solution of tripyrrane dicarbinol **175**, tetrapyrane **9**, and *p*-TsOH furnishes **176**, after oxidation of the resulting product with DDQ. ^1H NMR data confirmed it to be a nonaromatic 32π -electron system.



Scheme 73 Synthesis of *meso*-heptakis(pentafluorophenyl)heptaphyrin(1.1.1.1.1.1.1).

2.4.4.4. [26]Heptaphyrin(0.0.0.0.0.0.0)

Sessler and coworkers (03JA6872) have prepared [26]heptaphyrin(0.0.0.0.0.0.0) **178** (Scheme 74) in 5% yield through Fe(III)-mediated cyclization of bipyrrrole **177**.

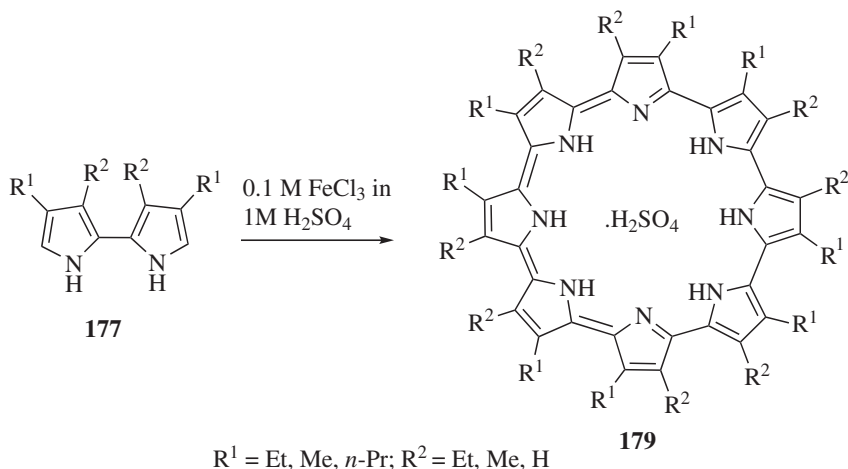


Scheme 74 Synthesis of [26]heptaphyrin(0.0.0.0.0.0.0).

2.4.5. Expanded systems containing eight or more pyrrolic subunits

2.4.5.1. [30]Octaphyrin(0.0.0.0.0.0.0.0)

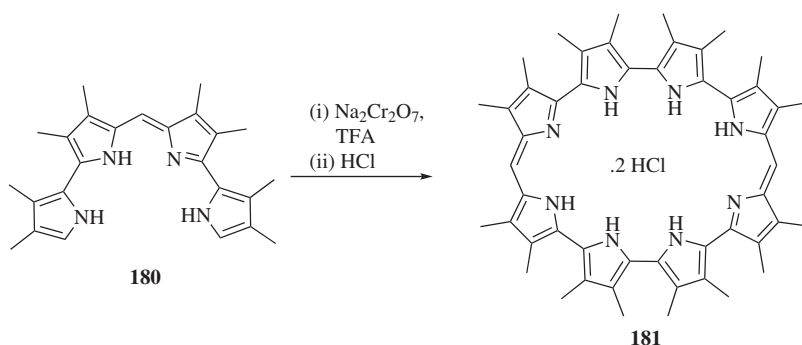
Cyclo[8]pyrroles, [30]octaphyrin(0.0.0.0.0.0.0.0) **179** (Scheme 75), have been reported (02ACI1422) in good yields through an Fe(III)-based oxidative coupling of bipyrrroles **177** using biphasic conditions (bipyrrrole in DCM/0.1 M FeCl₃ in 1 M H₂SO₄). The ¹H NMR spectrum confirmed the 30 π -electron aromatic system.



Scheme 75 Synthesis of [30]octaphyrin(0.0.0.0.0.0.0.0).

2.4.5.2. [32]Octaphyrin(1.0.0.0.1.0.0.0)

Sessler *et al.* (1999JA11257) have prepared [32]octaphyrin(1.0.0.0.1.0.0.0) **181** (Scheme 76) as its HCl salt through a Cr(VI)-based oxidative coupling of tetrapyrrole **180**.

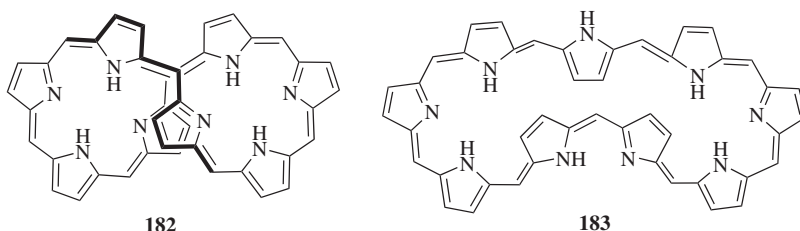


Scheme 76 Synthesis of [32]octaphyrin(1.0.0.0.1.0.0.0).

Despite containing a 32π -electron periphery, its ^1H NMR spectra did not show any sign of an antiaromatic ring-current effect, indicating strong deviation from planarity as also confirmed from its X-ray analysis and UV-vis spectra, which show a broad band at 586 nm.

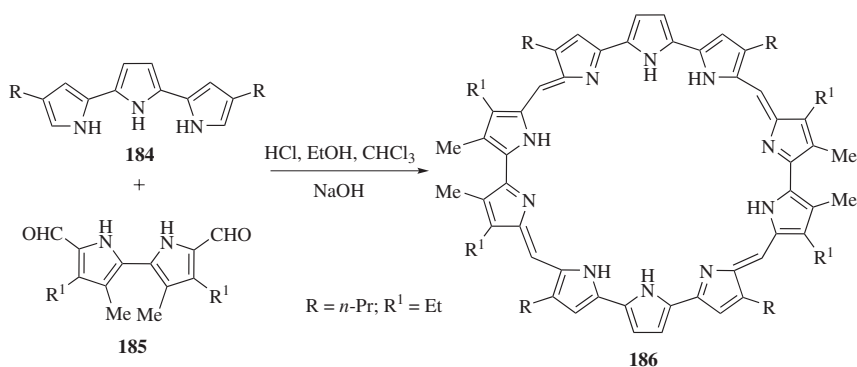
2.4.5.3. [36]Octaphyrin(1.1.1.1.1.1.1.1) and [42]nonaphyrin(1.1.1.1.1.1.1.1)

Utilizing a modified Rothmund condensation of pyrrole and pentafluorobenzaldehyde (01JA7190), Furuta and coworkers obtained octaphyrin **182** and nonaphyrin **183**, as well as several higher homologues in very low yields in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, followed by oxidation with DDQ.



2.4.5.4. [40]Decaphyrin(1.0.0.1.0.1.0.0.1.0)

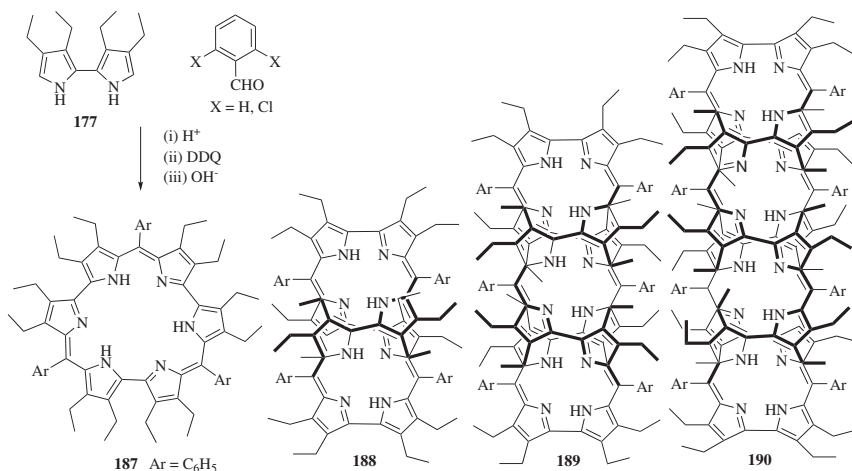
Sessler *et al.* (1994ACI1509) made decapyrrolic turcasarin **186** (Scheme 77) by acid-catalyzed condensation of dialkylterpyrrole **184** and hexamethylterpyrrole **185** ($\text{R}^1 = \text{Et}$), following “3+2+3+2” condensation.



Scheme 77 Synthesis of decapyrrolic turcasarin.

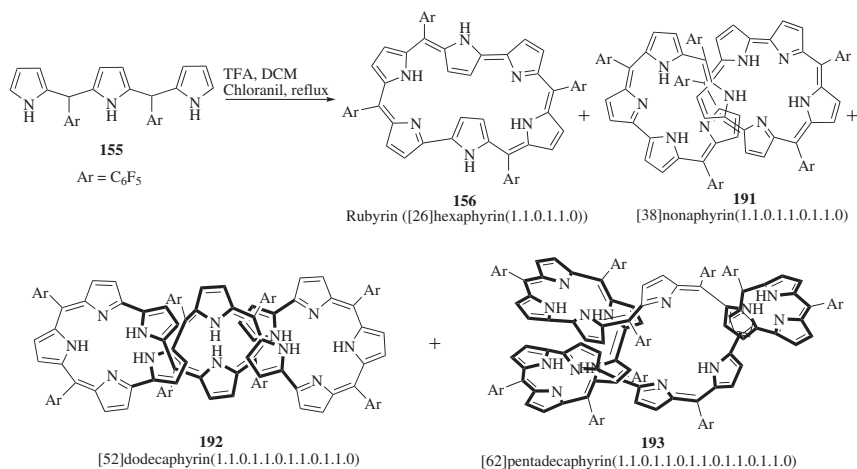
2.4.5.5. [48]Dodecaphyrin(1.0.1.0.1.0.1.0.1.0) and [64] hexadecaphyrin(1.0.1.0.1.0.1.0.1.0.1.0.1.0)

Tetraethylbipyrrole **177** (Scheme 78) and 2,6-dichlorobenzaldehyde under acid-catalyzed conditions with Zn^{2+} furnished (1999J A8957) a complex mixture that contained **187**, **188**, [48]dodecaphyrin(1.0.1.0.1.0.1.0.1.0.1.0) **189** and [64]hexadecaphyrin (1.0.1.0.1.0.1.0.1.0.1.0.1.0.1.0.1.0) **190** possessing a large cavity surrounded by a wall of “zigzag-tracked π -conjugation.”



Scheme 78 Synthesis of [48]dodecaphyrin(1.0.1.0.1.0.1.0.1.0.1.0) and [64]hexadecaphyrin (1.0.1.0.1.0.1.0.1.0.1.0.1.0.1.0.1.0).

Oxidative coupling involving tripyrrane **155** (Scheme 79) using TFA/DCM followed by treatment with chloranil furnished (08CEJ2668), in addition to rubyrin ([26]hexaphyrin(1.1.0.1.1.0)) **156** and [38]nonaphyrin(1.1.0.1.1.0.1.1.0) **191**, higher analogues such as [52]dodecaphyrin(1.1.0.1.1.0.1.1.0.1.1.0) **192** and [62]pentadecaphyrin(1.1.0.1.1.0.1.1.0.1.1.0.1.1.0) **193**.



Scheme 79 Synthesis of rubyrin and its higher analogues.

2.5. Core-modified porphyrinoids

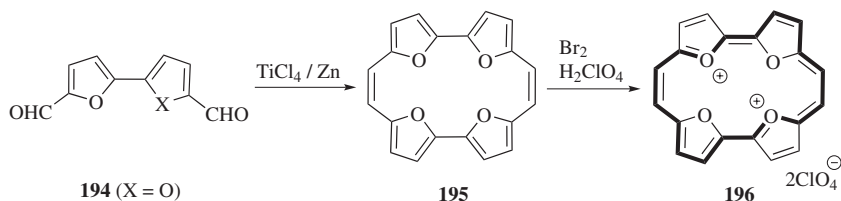
In the many examples above, as a consequence of π -conjugation extension and increase in cavity size, the electronic absorption of the expanded porphycene witnesses a significantly red shift relative to porphyrins. To understand a relationship between the photophysical properties and the electronic structure, core modification by replacing nitrogen atoms with other heteroatoms such as O, S, Se, etc. has also been undertaken. Such core perturbations result in significant impacts on the electro-chemical properties of the resulting heteroporphyrins or heteroporphyrinoids (00MI3).

We have compiled synthetic chemistry and properties of porphyrin analogues containing only furan, imidazole, or thiophene subunits in place of pyrrole subunit(s). Expanded porphyrinoids have been excluded. This write-up is not intended to give a comprehensive treatment, but is aimed to complement earlier reviews (06CCR468, 08CSR215). In the following two sections, the chemistry of core-modified porphycenes and porphyrins is presented.

2.5.1. Core-modified porphycenes

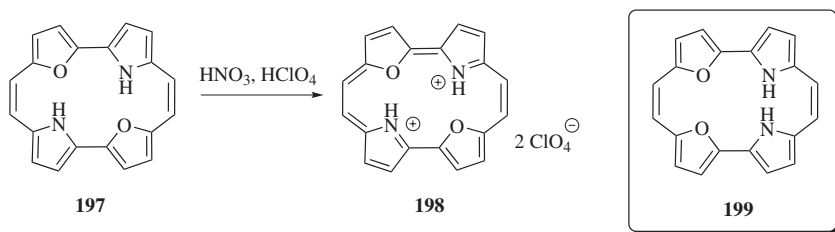
Structural variations of tetrapyrrolic porphycene **38** (Scheme 17) in such a way that an 18π -electron conjugation pathway is retained, have furnished a variety of neutral as well as charged porphycene analogues. These variations mainly include replacement of a pyrrole heterocycle with furan, thiophene, or imidazole.

Vogel et al. (1988ACI411) provided access to tetraoxaporphycene dication **196** (Scheme 80), the furan-based analogue of **38**. It was synthesized by subjecting 5,5'-bi-2,2-furfuraldehyde **194** ($X=O$) to reductive coupling to **195**, followed by two-electron coupling to produce **196**, isolated as a perchlorate salt that exhibits aromatic character and is comparatively stable than the corresponding pyrrole analogue **38**.



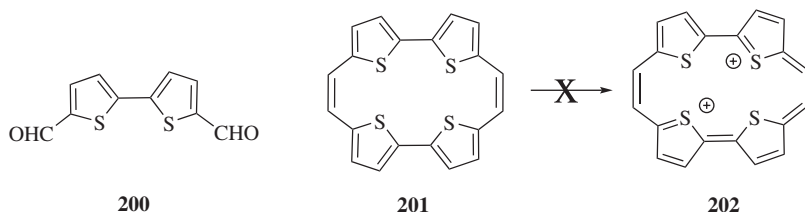
Scheme 80 Synthesis of tetraoxaporphycene dication.

Similarly, starting from furan-pyrrole dialdehyde **194** ($X=NH$), porphycene analogue **197** (Scheme 81) containing two nitrogens and two oxygens in the core was synthesized and oxidized to 18π -electron dioxaporphycene dication **198**. However, the formation of symmetrical analogue **199** was not observed (1991MI).



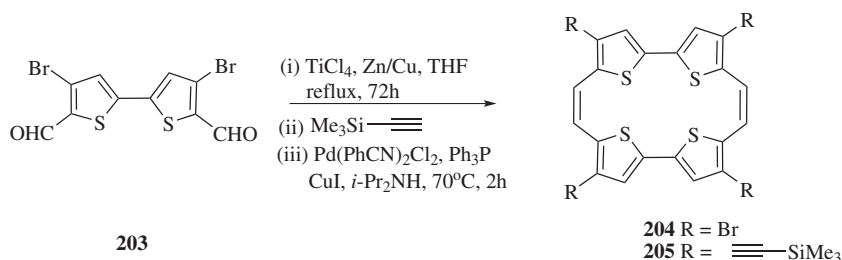
Scheme 81 Synthesis of dioxaporphycene dication.

The sulfur analogue of porphycene, **201** (Scheme 82), was synthesized from 2,2'-bithiophene-5,5-carboxaldehyde **200**. It is a distorted nonplanar 20π -electron annulene. However, conversion of **201** to **202** has not been evidenced (1993MC931, 1994JOC8071, 1994TL3493).



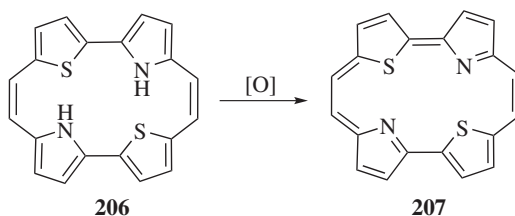
Scheme 82 Sulfur analogue of porphycene.

Employing Sonogashira coupling (1988JOC2489) of the tetrabrominated macrocycle **204** (Scheme 83), obtained from dibrominated bis-thiophene dialdehyde **203** using standard reductive coupling, the synthesis of alkynyl-substituted annulene **205** has been reported (1998EJOC525) without oxidation to the corresponding dicationic analogues.



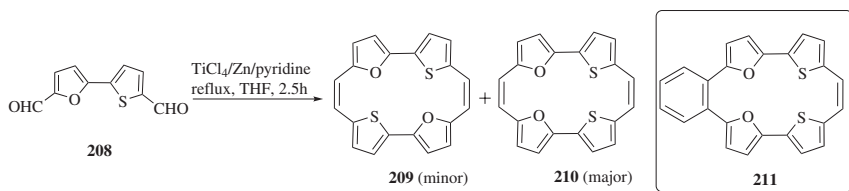
Scheme 83 Synthesis of tetraalkylated macrocycle.

On the contrary, neutral dithiaporphycene **207** (Scheme 84), with two thiophene units opposing each other could be obtained as a planar aromatic system much like the parent tetrapyrrolic porphycene **38**. Oxidation of precursor **206** proceeded easily (1993T6863).



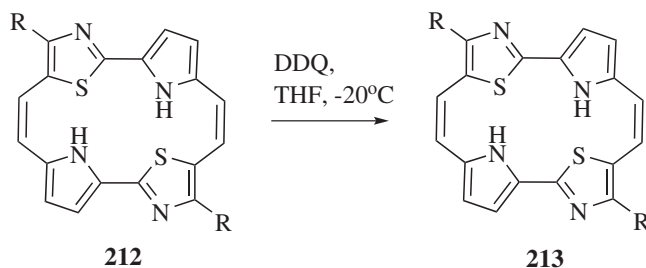
Scheme 84 Synthesis of neutral dithiaporphycene.

Similarly, mixed furan–thiophene porphycene derivatives **209**, **210**, and **211** (Scheme 85) have been reported, employing McMurry coupling of a dialdehyde such as **208** (00TL10277). Pd-chemistry (1982ACR178, 1985PAC1749, 1986PAC629, 1994PAC213) provided an exception to the traditional “2+2” McMurry coupling route to **211**.



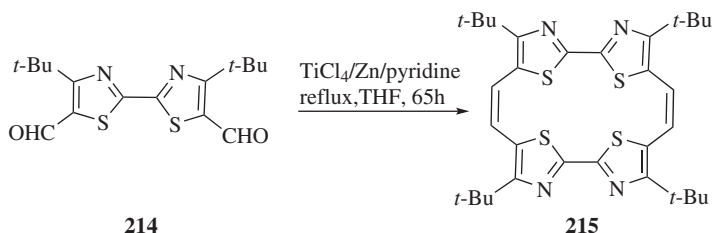
Scheme 85 Synthesis of mixed furan–thiophene porphycene.

The first porphycene containing a thiazole ring and nitrogen in the periphery, **213**, was obtained through the oxidation of reduced precursor **212** (Scheme 86) with DDQ (00EJOC2449).



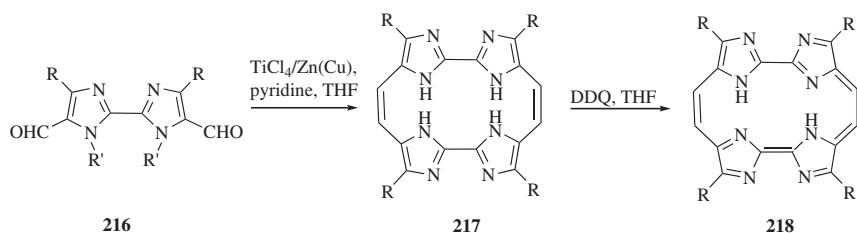
Scheme 86 Synthesis of a porphycene containing a thiazole ring and nitrogen in its periphery.

Subsequently, preparation of macrocycle **215** (Scheme 87), containing four thiazole units involved two steps. Diformylation of 4,4'-di(*tert*-butyl)-2,2'-bithiazole to obtain **214** and subsequent McMurry coupling furnished **215** (00HCA1161).



Scheme 87 Synthesis of porphycene containing four thiazole units.

Preparation of biimidazole containing tetraazaporphycenes referred to as “imidacenes” (03CEJ3065, 03EJOC1635) bear both alkyl and aryl substituents on the imidazole. The 2,2'-biimidazole (1858LA199) precursor (01CEJ721, 02JHC733) **216** ($R=Br$, $R^1=H$) (Scheme 88) was prepared from dimerization of iodoimidazole using a Pd-mediated Ullmann coupling followed by diformylation. The tetraimidazole macrocycle **217** was oxidized using DDQ. Appropriate use of Pd-coupling (00JPP441) allows appending aryl substituents ($R=Ar$) onto **216**.



Scheme 88 Synthesis of imidacenes.

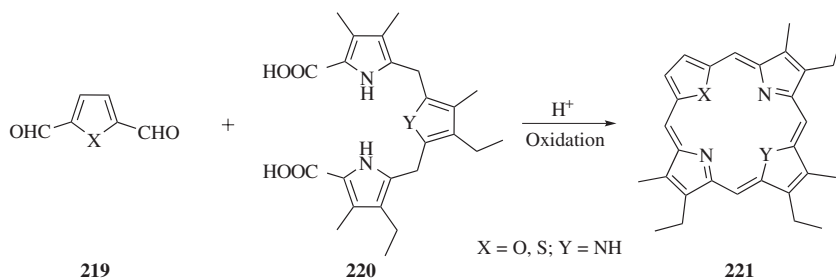
Like dioxaanulene **197** and unlike tetrathiaannulene **201**, the tetraimidazole derivative **217** as well as **218** exhibits unusual stability. The annulene **218** by virtue of [18]annulene-type aromatic structure is far more stable. The λ_{max} of **218** ($R=\text{alkyl}$) is red-shifted by 100 nm compared to the corresponding porphycene derivative **38** (06JPC(A)3480). This behavior has been attributed to the introduction of additional nitrogen atoms into the macrocycle core (00EJOC2449).

2.5.2. Core-modified porphyrins

Much like porphycenes, discussed in the preceding section, elegant methodologies have been developed over the years to synthesize heteroatom-substituted porphyrins. These have been discussed in detail in earlier reviews (00MI3, 06CCR468, 08CSR215). This review is intended to present outline on the synthetic methods available on the synthesis of mono-heteroatom (21- N_3X system) and diheteroatom-substituted porphyrins (21,23- N_2X_2 or 21,23- N_2XY , 21,22- N_2X_2 or 21,22- N_2XY systems). However, discussion on heteroatom-substituted corroles, carba porphyrins, chlorins, bacteriochlorins, and tetrabenzoporphyrin analogues has been excluded.

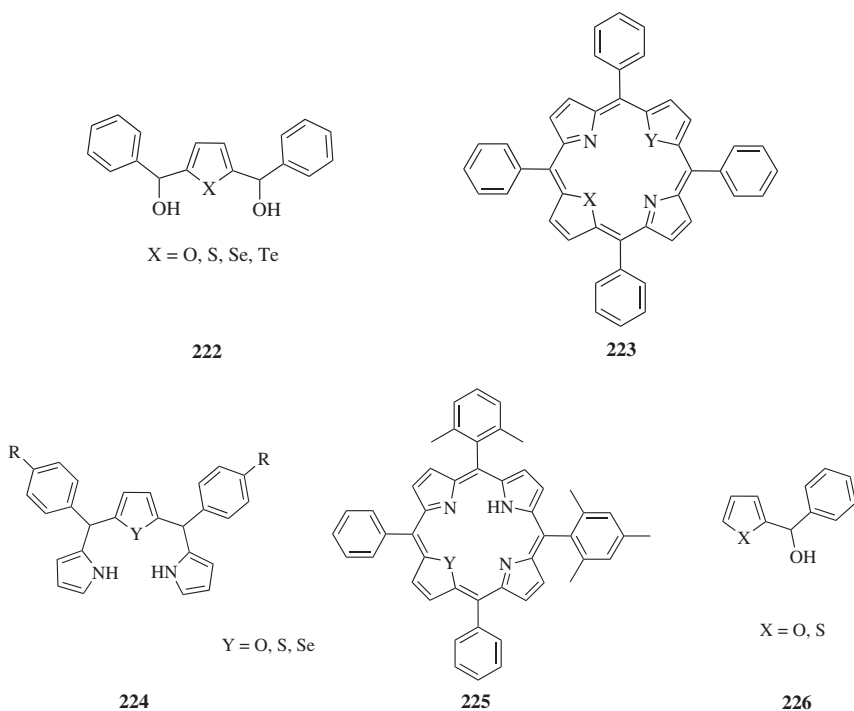
2.5.2.1. 21-Monoheteroatom-substituted porphyrins

The first synthetic approach to 21-monoheteroatom-substituted porphyrins involved a “3+1” condensation approach using 2,5-diformyl furan **219** ($X=O$) or thiophene **219** ($X=S$) and tripyrrane **220** ($Y=NH$), to obtain *meso*-unsubstituted 21-oxa **221** ($X=O$, $Y=NH$) or 21-thia **221** ($X=S$, $Y=NH$) porphyrins (Scheme 89) (1970JCS(D)807, 1971JCS(C)3681, 1969JCS(CC)1480).



Scheme 89 Synthesis of *meso*-unsubstituted 21-oxa or 21-thia porphyrins.

However, this approach was not suitable for *meso*-tetraphenyl derivatives. Alternatively diols **222** were employed (1987JA4428, 1997TL2383, (1975JA6540, 1978TL167, 1978TL1885, 1979JCSP(1)1066, 1996BKCS515, 1996TL197, 00BKCS97, 1997TL4149, 1998JPP69). One mole of **222** was condensed with 2 moles of arylaldehyde and 3 moles of pyrrole under porphyrin forming conditions to obtain 21-heteroatom-substituted porphyrins **223** ($X=S, Se, Te, Y=NH$), also prepared by condensing **222** ($X=O, S, Se$) with tripyrrane **224** (1996BKCS515, 1996TL197, 00BKCS97).



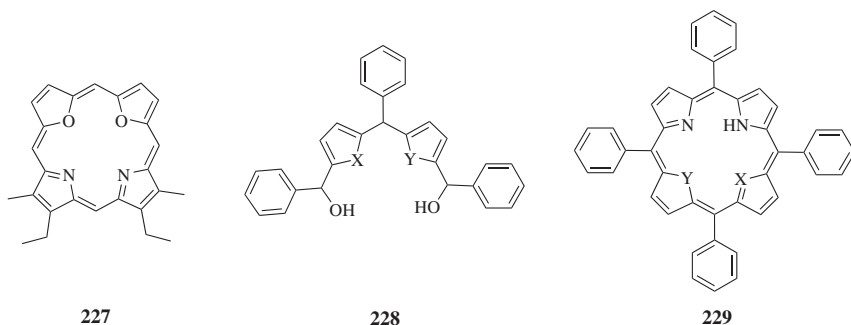
Chandrashekar et al. (1997TL4149, 1998JPP69) have prepared 21-oxa or 21-thia porphyrins **225** (X=O, S) by condensation of diols **222** (X=O, S) with dipyrromethanes. Likewise, mono-ol **226** (X=O, S) with benzaldehyde and pyrrole furnished **225** (04EJOC1693, 04JOC6796).

2.5.2.2. 21,23-Diheteroatom-substituted porphyrins

Reacting **219** (X=O, S) and a modified tripyrrane **220** (Y=O), β -substituted *meso*-unsubstituted 21,23-diheteroatom porphyrin **221** (X=O, S, Y=O) was obtained (1970JCS(D)807, 1971JCS(C)3681, 1969JCS(CC)1480). Condensing diol **222** (X=O, S, Se) with pyrrole under mild acidic condition followed by DDQ oxidation gave **223** (X=Y=O, S, Se) (1975JA6540, 1978TL167, 1978TL1885, 1979JCSP(1)1066). However, the mixed heteroatom systems **223** (X=S, Y=O; X=S, Y=Se; X=S, Y=Te) were prepared by condensing one equivalent of the diol **222** (X=O, S, Se, Te) with heteromodified tripyrrane **224** (R=H, Y=O, S; R=Me, Y=S, Se) (1978TL167, 1978TL1885, 1996BKCS515, 1996TL197, 1998JPP69).

2.5.2.3. 21,22-Diheteroatom-substituted porphyrins

The 21,22-dioxaporphyrin **227** was synthesized by “2+2” acid-catalyzed condensation of 5,5'-diformyldifurlylmethane and a dipyrromethane diacid (1969JCS(CC)1480). 21,22-Diheteroporphyrins **229** (X=Y=O, S; X=S, Y=O) containing S and O atoms have been obtained from **228** (X=Y=O; X=Y=S and X=S, Y=O) with 5-phenyl dipyrromethane derivative, followed by oxidation with DDQ (1998BKCS314, 1999TL8879).

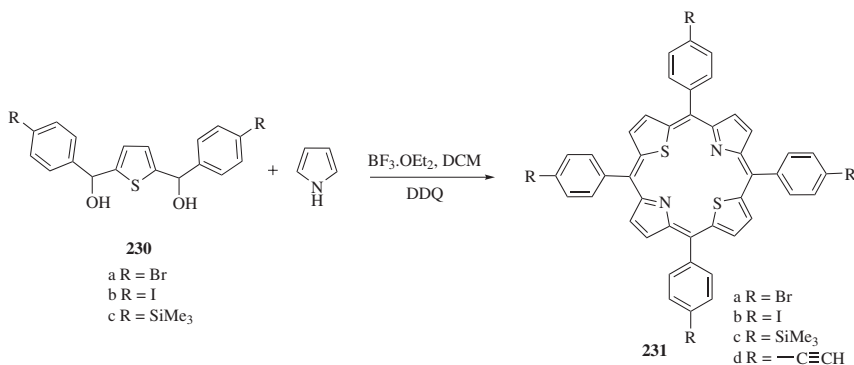


Like porphyrins, heteroporphyrins are aromatic and confirm the $[4n+2]$ π -electron Huckel rule (00MI3). Replacing N with O, S, Se, and Te perturbs π -delocalization and electronic properties. The alteration in π -delocalization is evidenced from downfield shifts in ^1H NMR spectra. The extent of shift in monoheteroatom is more than diheteroatom-substituted porphyrins (1979JA7055, 1984OMR561). The large heteroatoms

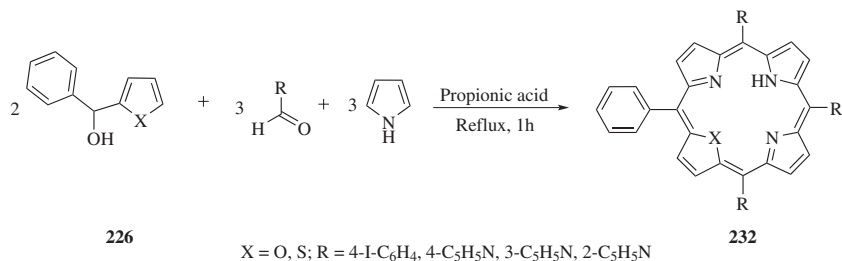
in diheteroatomic systems decrease the ring current arising from the π -delocalization. In their electronic absorption spectrum, heteroporphyrins show an intense Soret band and 3–4 Q-bands in 700–450 nm like N_4 -porphyrins. Both of these bands are red-shifted in the order of $S > Se > Te \gg O$ in heteroporphyrins. Further, the red shift in the diheteroatom porphyrins is more than the monohetero-substituted counterparts (1998JPP69, 1982IC1450). The emission bands of the heteroporphyrins (1998JPP69, 1982IC1450, 1990PIAS307, 1993JCS(FT)677) are also red-shifted with reduction in quantum yield. Compared to the N_4 -porphyrins, except oxaporphyrinoids, lifetime of the singlet excited state is comparable to those of N_4 -porphyrins, while that of other heteroatom-substituted porphyrin is generally low. Due to the inductive effect of heteroatom on the frontier orbital of the porphyrins, the heteroporphyrins are easy to reduce, difficult to oxidize (1998JPP69, 1981IC1987), and have strong ability to stabilize metals in uncommon oxidation states (00MI3). The core of the hetero-substituted porphyrins compared to the N_4 -porphyrin core shrinks owing to large heteroatoms as revealed by X-ray crystallographic analysis (00MI3).

Appending functional groups at the *meso*-position of heteroporphyrins renders structural complexity to these systems. Porphyrin cores N_2S_2 , N_3S , N_3O and N_2SO having 1–4 functional groups such as iodo, ethynyl, hydroxyl, aldehyde, etc. on *meso*-phenyl or pyridyl substituents have been reported (00BKCS97, 04EJOC1693, 04JOC6796, 1999JOC7890, 00TL3709, 01JCS(P1)1644, 01TL8547, 01SL1635, 02T5347, 03T2353, 04T8437, 05EJOC2500).

The diols **230a–c** with pyrrole using $BF_3 \cdot OEt_2$ in DCM, followed by DDQ oxidation furnished N_2S_2 heteroporphyrins **231a–d** (Scheme 90) (00TL3709, 01JCS(P1)1644). Acid-catalyzed condensation of thiophene or furan mono-ol **226** ($X=O, S$) (Scheme 91) with functionalized aryl aldehyde



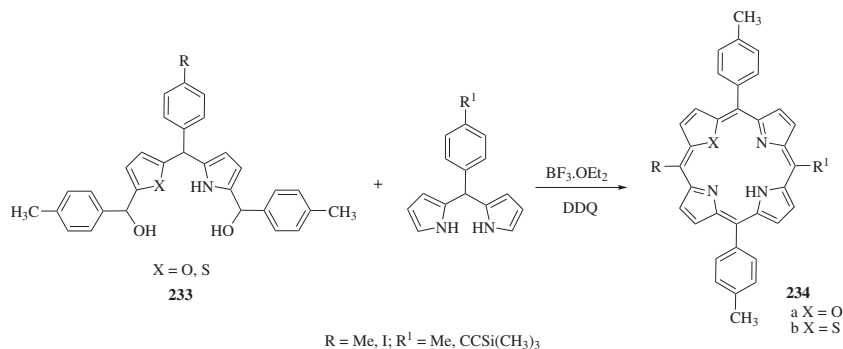
Scheme 90 Synthesis of N_2S_2 -type heteroporphyrins.



Scheme 91 Acid-catalyzed synthesis of *meso*-substituted 21-oxa or 21-thia porphyrins.

and pyrrole furnished 21-oxa **232** (X=O) or 21-thiaporphyrins **232** (X=S) containing three iodophenyl and pyridyl groups at *meso*-positions. These were used in making non-covalent unsymmetrical tetramers containing one N₃S and three N₄-porphyrin units (04EJOC1693, 04JOC6796).

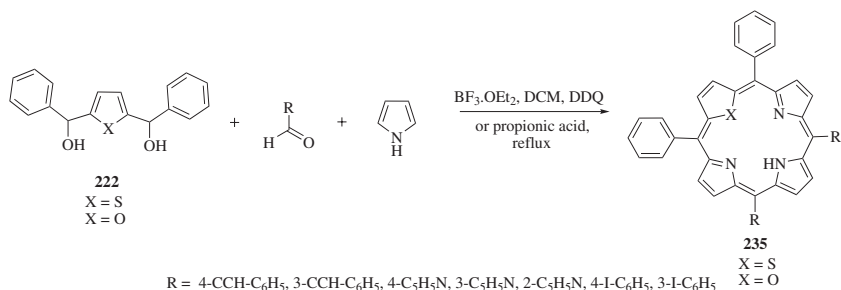
A heteroporphyrin containing two functional groups, *trans* 21-oxa **234a** and 21-thiaporphyrins **234b** (Scheme 92), have been obtained from **233** and a *meso*-aryl-substituted dipyrromethane (1999JOC7890).



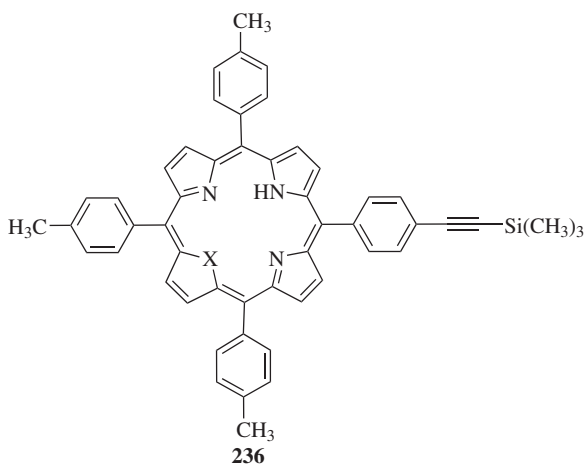
Scheme 92 Synthesis of *trans*-substituted 21-oxa and 21-thiaporphyrins.

A series of 21-thia **235** and 21-oxaporphyrins **235** (Scheme 93) with two functional groups at the *meso*-positions in *cis* position were synthesized by condensing diols **222** with pyrrole and an aldehyde. Such heteroporphyrins have been used to synthesize covalently linked or non-covalent complex porphyrins (01TL8547, 01SL1635, 02T5347, 03T2353).

Lindsey and coworkers have also synthesized heteroporphyrins bearing one functional group (1999JOC7890).



Scheme 93 Synthesis of *cis*-substituted 21-oxa and 21-thiaporphyrins.



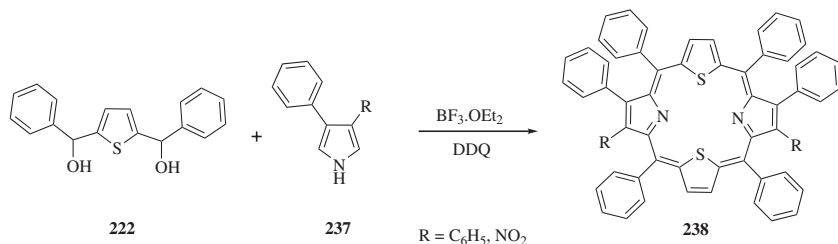
Condensation of dipyrromethanes with appropriate thienylpyrromethane or furylpyrromethane diols furnished monofunctionalized 21-thia **236** (X=S) and 21-oxaporphyrins **236** (X=O). Other methods used for synthesizing these compounds have also been reported ([00BKCS97](#), [04EJOC1693](#), [04JOC6796](#), [05EJOC2500](#)).

2.5.3. β -Substituted heteroporphyrins

The β -functionalization of porphyrins has gained considerable attention as β -substituents are in direct conjugation with the porphyrin ring, and small changes in the substituents at this position drastically alter electronic properties of the porphyrin. Porphyrins with electron releasing as well as electron-withdrawing substituents at β -pyrrole carbons are known ([1995SB105](#), [1998CSR31](#)). Porphyrins with electron-withdrawing substituents such as Br, NO₂ at β -pyrrole carbons of porphyrins are robust catalysts for alkene epoxidation and alkane hydroxylation ([1990CCR181](#), [1994SCI1311](#), [1997JA6442](#)). The β -substituted heteroporphyrins have been

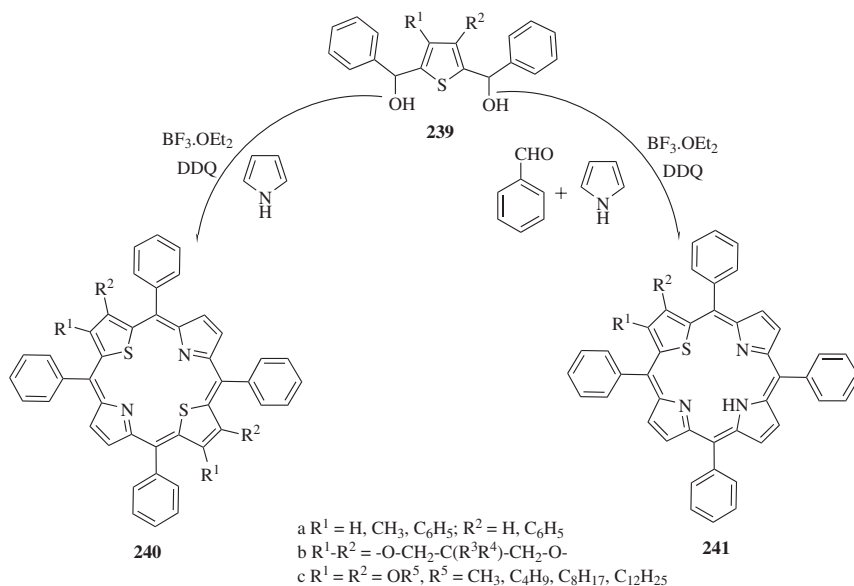
synthesized recently (00CL480, 02JCS(CC)2642, 03CL744, 04BCJ1173, 04T10671, 04T4739).

Ravikanth and coworkers have synthesized β -pyrrole-substituted 21,23-dithiaporphyrins by refluxing 21,23-dithiaporphyrin with NBS in chloroform. β -Aryl-substituted thiaporphyrin **238** (Scheme 94) has been obtained by condensing 3,4-disubstituted pyrroles **237** with thiophene diol **222** (X=S) under mild acid conditions (00CL480).



Scheme 94 Synthesis of β -pyrrole-substituted 21,23-dithiaporphyrins.

Same authors further synthesized β -thiophene-substituted 21,23-dithia and 21-thiaporphyrins. The 21,23-dithia **240a** and 21-thiaporphyrin **241a** having a methyl and phenyl group at β -positions of thiophene were synthesized by condensing the 3,4-disubstituted thiophene diols **239a** (Scheme 95) with



Scheme 95 Synthesis of β -thiophene-substituted 21,23-dithia and 21-monothiaporphyrin.

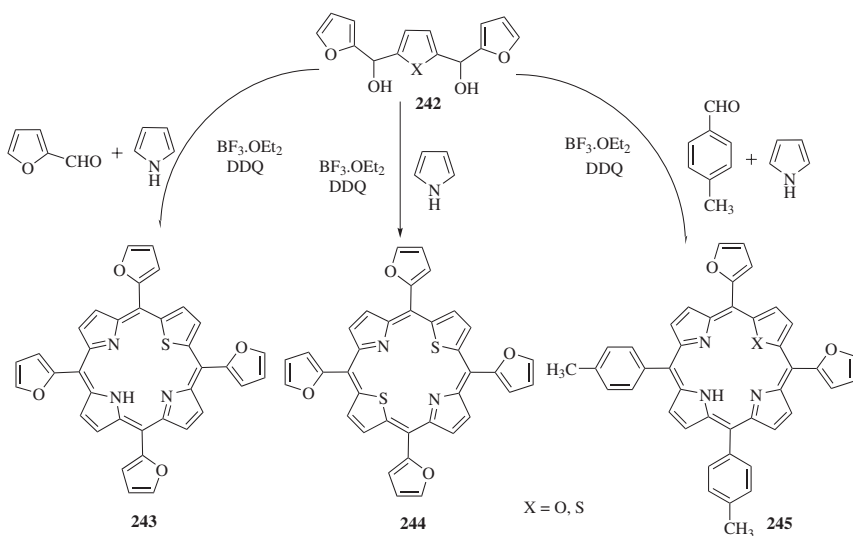
pyrrole alone or in combination with an aryl aldehyde, under acid-catalyzed reaction. Spectroscopic studies on β -thiophene-substituted thiaporphyrin show an upfield shift in the ^1H NMR spectrum, a red shift in absorption and emission bands compared to the β -unsubstituted thiaporphyrins (Scheme 94) (02JCS(CC)2642, 03CL744, 04BCJ1173, 04T10671).

The incorporation of cyclic substituents, such as propane-1,3-diylidioxy, its ethyl and benzyl derivatives substituted at the β -thiophene carbons of 21,23-dithiaporphyrins **240b** and 21-monothiaporphyrins **241b** (Scheme 95), has also been reported (04BCJ1173) by condensing the substituted thiophene diols **239b** with benzaldehyde and pyrrole. The cyclic substituents at the β -thiophene carbon atoms alter electronic properties of porphyrin.

A series of tetraalkoxy and dialkoxy-substituted 21,23-dithiaporphyrins **240c** and 21-monothiaporphyrins **241c** with methoxy, butoxy, octyloxy, and dodecyloxy substituents at β -thiophene carbon atoms were also synthesized (02JCS(CC)2642, 04T10671).

2.5.4. *meso*-Substituted heteroporphyrins

Synthesis of heteroporphyrins having 2-furyl, 2-thienyl, and 3-thienyl groups at the *meso*-positions has also been reported (02TL9453, 03T6131, 03EJC4392, 05JCS161). Like β -substitution, *meso*-substitution of heteroporphyrins also affects electronic properties. The heteroporphyrins having two and four furyl groups at the *meso*-position were synthesized using 2,5-bis(2-furylhydroxymethyl)thiophene **242** ($\text{X}=\text{S}$) or furan **242** ($\text{X}=\text{O}$) (Scheme 96). The tetrafuryl 21,23-dithiaporphyrin **244** was prepared by



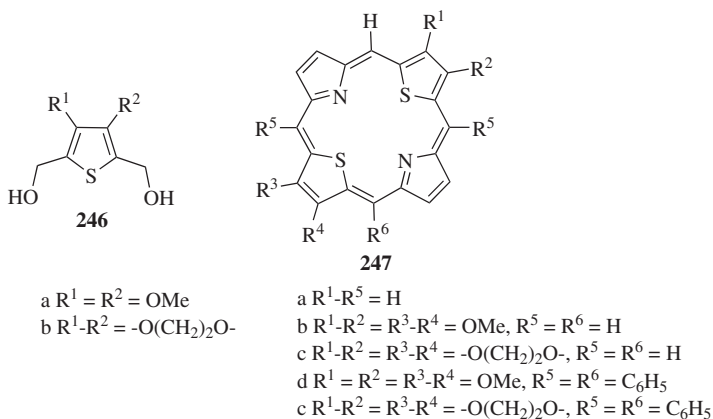
Scheme 96 Synthesis of *meso*-furyl-substituted heteroporphyrins.

condensing the diol **242** ($X=S$) with pyrrole and the 21-thiaporphyrin **243** was prepared by condensing diol **242** ($X=S$) and furan-2-carboxaldehyde and pyrrole (02TL9453). The difuryl 21-thiaporphyrin **245** ($X=S$) and 21-oxaporphyrin **245** ($X=O$) were also prepared from the reaction of **242** ($X=S$) and **242** ($X=O$), respectively, with *p*-tolylaldehyde and pyrrole under mild acidic conditions (Scheme 96) (02TL9453, 03T6131). Ravikanth et al. have reported the synthesis of *meso*-thienyl-substituted porphyrins with different cores, such as N_3S , N_3O , and N_2S_2 (03EJOC4392).

Porphyrins having bulky dendritic wedges at the *meso*-positions have received a lot of attention in recent years because of their importance as biomimic models (1998ACI1531, 1994ACI1739), for catalytic applications (1999JA262), and are attractive building blocks for the formation of supra-molecular architectures (1996SCI1095, 1999CR1665). Synthesis of 21-oxaporphyrin with a bulky phenyl ether-based second-generation dendron at two *meso*-positions in a *cis* fashion is also known (03CL1120).

2.5.5. *meso*-Unsubstituted heteroporphyrins

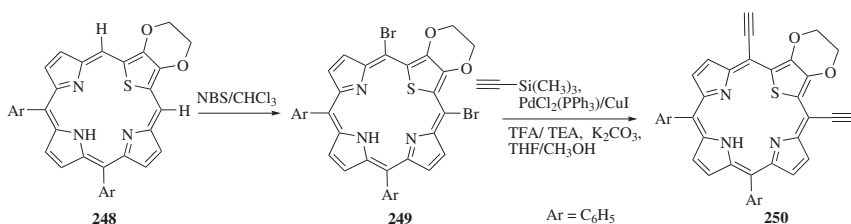
The high reactivity of the *meso*-unsubstituted porphyrins made these porphyrins ideal precursors for more complex systems with special physical and chemical properties. The β -unsubstituted *meso*-unsubstituted porphyrin or porphin has not been well studied because of its poor solubility. Broadhurst and coworkers (1969JCS(CC)1480) have synthesized 21-monoheteroporphyrins as well as 21,23-diheteroporphyrins with four *meso*-unsubstituted carbons.



Chmielewski et al. have reported the synthesis of 21-oxaporphyrin with one *meso*-unsubstituted carbon (1997CEJ268). Ravikanth et al. have reported the synthesis of a series of thiaporphyrin with four and two *meso*-unsubstituted carbons using thiophene diols (03EJOC3730). The

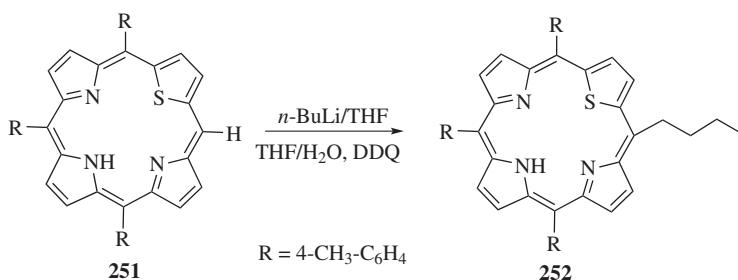
meso-unsubstituted β -substituted 21,23-dithiaporphyrin **247a–c** and *meso*-unsubstituted 21-thiaporphyrin are synthesized using thiophene diol **246**.

Synthesis of *meso*-unsubstituted heteroporphyrins with different cores, such as N_3S , N_3O , N_2S_2 , N_2O_2 , N_2SO , and N_2OS (**04EJOC2223**), has also been described. The reactivity of *meso*-unsubstituted heteroporphyrins was tested toward electrophilic and nucleophilic substitutions. The dibromo derivatives were synthesized by treating porphyrin **248** (**Scheme 97**) with NBS in $CHCl_3$ at room temperature (**03EJOC3730**). The diethynyl porphyrin **250** was synthesized by treating **249** with trimethylsilylacetylene in the presence of catalytic amounts of $PdCl_2(PPh_3)_2CuI$ in tetrahydrofuran (THF)/triethylamine, followed by deprotection of the trimethylsilyl group with K_2CO_3 in THF/ CH_3OH .



Scheme 97 Synthesis of *meso*-functionalized 21-thiaporphyrins.

The metallation behavior of *meso*-unsubstituted 21-thiaporphyrin **251** (**Scheme 98**) has been achieved using *n*-BuLi at $0^\circ C$. Subsequent oxidation with DDQ (**1998ACI1107**) resulted in the formation of *meso*-butyl porphyrin **252**.



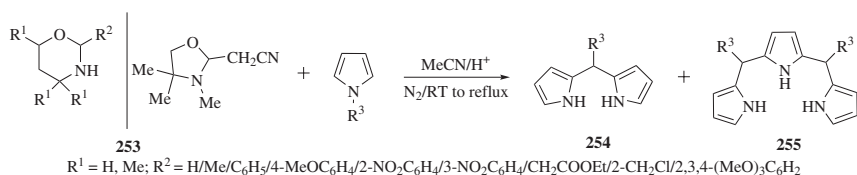
Scheme 98 Synthesis of a *meso*-butyl 21-thiaporphyrin.

Bis(heterocyclyl)methanes constitute highly valuable building blocks of natural and unnatural porphyrinoids (**00MI1**), which are of immense importance in biological, industrial, and material science applications

(00MI1, 1994JOC8071, 1994TL3493, 1994JCSP(1)2881, 08THC97, 06BMC225, 1998BMC2983, 06EJMC809, 07JMC4377, 00SM161, 03M5114, 1993JOC4376, 1999MI, 1996TL3571, 1998AM1013, 1999CM1915, 01JCS(CC)529, 03CL422, 1960T106, 1960T111, 1972TL3807, 1976JOC870, 08T2184, 06OL333, 08CJCU2545, 03CMC1891, 1970MI).

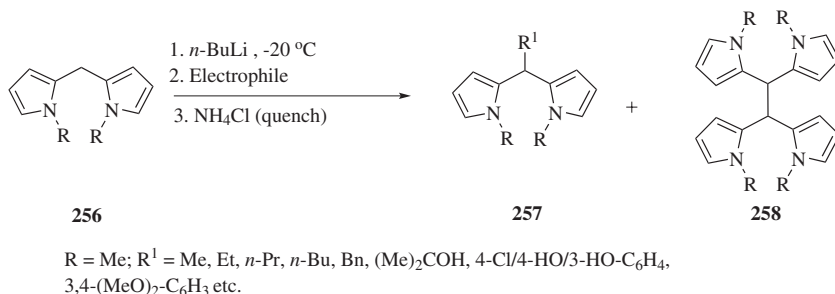
Condensation of heteroaryl species with aldehydes is a challenging task, as high reactivity and vulnerability of aliphatic counterparts toward both basic and acidic reagents lead to side reactions giving the required product in lower yield. Dipyrromethanes are important intermediates for the preparation of synthetic porphyrins and related compounds (dipyrins, calix[*n*]pyrroles, chlorins, corroles) (00MI1). Unlike naturally occurring porphyrins, which are β -substituted and *meso*-unsubstituted, synthetic porphyrins are *meso*-substituted and β -unsubstituted. Dipyrromethanes are used as precursors to dipyrromethenes, which are important ligands in the design of macromolecular structures. Difluoroboron complexes of dipyrromethenes (BODIPY) are used as fluorescent dyes for biological samples (06JA10). Access (10ACR300, 10CCR77, 01CR2751) to these building blocks relied mainly on one-pot condensations of pyrrole and aldehydes in acidified solvents: $\text{BF}_3/\text{OEt}_2/\text{DCM}$, acetic acid/DMF or THF, SnCl_4/DCM , *p*-toluenesulfonic acid/MeOH or toluene, or aqueous HCl/THF. A large pyrrole:aldehyde ratio (up to 400:1) employed to drive the reaction to completion leads to unwanted linear/cyclic oligomers. Further, the nonavailability of many functionalized aldehydes, the failure of aliphatic aldehydes to react, and their propensity to show side reactions limit the scope of this route.

Singh *et al.* have used perhydro1,3-heterocycle **253** as carbonyl equivalent for acid (TFA)-catalyzed dipyrromethane **254** synthesis (Scheme 99) using only stoichiometric amounts of pyrrole/*N*-methyl pyrrole and products were obtained in good yield with formation of tripyrromethanes **255** (05T6614, 05SC929).



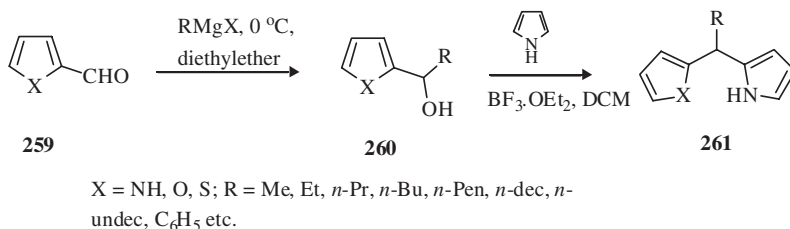
Scheme 99 Formation of di- and tripyrromethane from oxazinan-2-ones and oxazolidin-2-ones.

In 2007, Singh and coworkers developed lithiation–substitution methodology for *meso*-functionalized dipyrromethanes **257** (Scheme 100) (07TL227), free from all limitations.



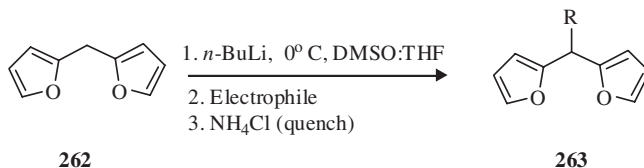
Scheme 100 Synthesis of *meso*-substituted dipyrromethanes.

In 2011, Singh et al. have reported the synthesis of *meso*-functionalized dipyrromethanes (**11SC3491**) **261** ($\text{X} = \text{NH}$) (**Scheme 101**) as well as unsymmetrical bis(heterocyclyl)methanes through Grignard addition of various aliphatic and aromatic halides on pyrrole-2-carboxaldehyde, followed by $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed condensation of pyrrole-2-carbinols with pyrrole, etc.



Scheme 101 Synthesis of *meso*-functionalized dipyrromethane through Grignard addition.

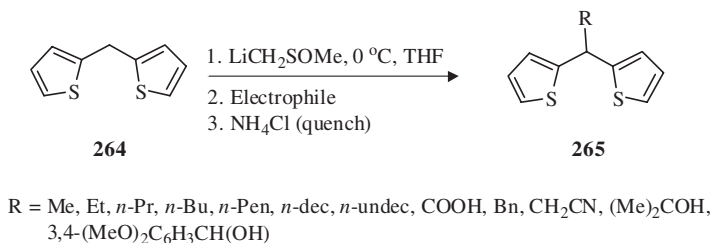
The lithiation–substitution methodology was further extended for *meso*-functionalization of other bis(furan-2-yl)methane **263**, using *n*-BuLi and dimethyl sulfoxide as solvent additives (**Scheme 102**). The approach was also extended for C-5 functionalization of bis(furan-2-yl)methane (**08TL6234**).



$\text{R} = \text{Et, } n\text{-Pr, } n\text{-Bu, Bn, (Me)}_2\text{COH, PhCMe(OH), PhCH(OH), 4-ClC}_6\text{H}_4\text{CH(OH), 3,4-(MeO)}_2\text{C}_6\text{H}_3\text{CH(OH), } \beta\text{-C}_{10}\text{H}_7\text{CH(OH), CONHPh etc.}$

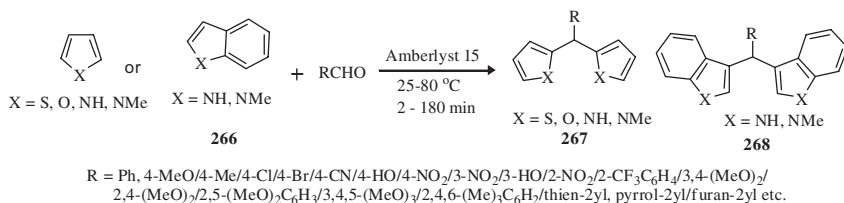
Scheme 102 Synthesis of *meso*-functionalized bis(furan-2-yl)methane.

Synthesis of *meso*-functionalized bis(thien-2-yl)methane **265** (Scheme 103) was reported (10T3682) through lithiation–substitution methodology using dimsyl anion as a base. This approach also furnished *meso*-linked bis(thien-2-yl)methane derivatives.

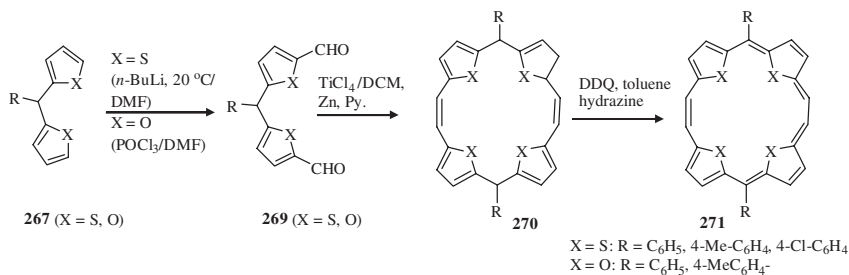


Scheme 103 Synthesis of *meso*-functionalized bis(thien-2-yl)methane.

Synthesis of **267** and **268** by condensation of electron-rich **266** with a variety of aldehydes using stoichiometric quantities in the presence of Amberlyst 15 catalyst, without using a solvent has also been reported (Scheme 104) (11JMCCF234).



Scheme 104 Synthesis of bis(heterocyclyl)methanes using Amberlyst 15.



Scheme 105 Synthesis of first neutral *meso*-functionalized tetrathia[22]annulene derivatives.

The *meso*-functionalized bis(thien-2-yl)methanes **267** (X=S) and bis(furan-2-yl)methanes **267** (X=O) were used for synthesizing the first neutral *meso*-functionalized tetrathia[22]annulene derivatives **271** (X=S) and tetraoxa[22]annulene derivatives **271** (X=O) (Scheme 105). The compounds were tested for organic field effect transistor (OFET) studies and have shown good mobilities with p-type semiconductor behavior (11JCS(CC)905, 12JCS(CC)121).

3. CONCLUSIONS

This overview on current developments of porphyrinoids delineates their structural diversity and provides an insight into the synthetic methods for making these macrocycles. The most general way to prepare porphycene and its analogues undoubtedly is Vogel's method employing McMurry-type coupling, while the synthesis of other derivatives of porphyrins use a building block approach employing bis(heterocycl) methane derivatives. Functional decoration of porphyrinoids especially at β -positions impacts their conformational flexibility and solubility, which has direct implication on their photophysical properties. While investigations at the *meso*-position are very limited, the synthetic potential does offer a chance to design new porphyrinoids.

LIST OF ABBREVIATIONS

AcOH	acetic acid
Ar	aryl
Bu	butyl
<i>n</i> -BuLi	<i>n</i> -butyllithium
CHCl ₃	chloroform
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	<i>N,N</i> -dimethylformamide
Et	ethyl
MRI	magnetic resonance imaging
MeOH	methanol
NLO	nonlinear optics
NaCN	sodium cyanide
NBS	<i>N</i> -bromosuccinimide
NCP	<i>N</i> -confused porphyrin
N ₂ CP	doubly confused porphyrin
NFP	<i>N</i> -fused porphyrin
OFET	organic field effect transistor

Ph	phenyl
PDT	photodynamic therapy
RF-ID	radio frequency identification
SEM	β -(trimethylsilyl)ethoxymethyl
TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
TBAF	tetra- <i>n</i> -butyl ammonium fluoride
TCNQF ₄	2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane
THF	tetrahydrofuran
<i>p</i> -TsOH	<i>p</i> -toluene sulfonic acid
TsNHNH ₂	tosylhydrazine
TEA	triethylamine
TFA	trifluoroacetic acid

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CHAPTER 3

Wine and Heterocycles

Heinrich Wamhoff^a and Gordon W. Gribble^b

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ABSTRACT

In this review an original and unique approach was undertaken to unite the notions “heterocycles” and “wine principles.” Indeed, it is astonishing that natural wines contain numerous heterocyclic principles in varying quantities (as low as nanograms!) that contribute to flavor, smell, taste, and aftertaste (“finish”) sensations, all of which are characteristic of the different grape types. During aging and maturation of the wines in barrels and bottles, manifold additional heterocycles are formed or extracted. The odor threshold plays an important role in all cases, which is ultimately dependent on the chirality centers of the isomers involved in aroma.

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These heterocyclic classes are manifold: *O*-heterocycles (lactones, furans, flavones, carbohydrates), *O*-glucosides of terpenes, tannins, flavones, procyanidins, heterocyclic polyphenols with significant benefits to human health, *S*-heterocycles stemming from yeast metabolism and possessing strong organoleptic properties, *N*-heterocycles (pyrroles, pyrimidines, pyrazines, the latter constituents having a typical green pepper flavor and aroma). Finally, the role of fungicides and pesticides in wine is discussed.

KEYWORDS

Lactones; Furans; Flavones; Anthocyanidins; Procyanidins; Carbohydrates; Glucosides; Resveratrol and di-, tri-, and tetrameric derivatives; Thiazoles; Fragrances; 1,3-Oxathians; Pyrroles; Pyrazines; Fungicides; Wine principles in treatment of human diseases.

1. PROLOG

One might regard it as a strange chance and a remarkable coincidence that two scientists in Germany and the USA, who are addicted to oenology, wine chemistry, and wine making, both experts in heterocyclic chemistry, meet in a joint project by invitation of A.R. Katritzky to write a chapter on wine and heterocycles.

2. INTRODUCTION

Heterocycles are ubiquitous in nature, with manifold industrial applications, and in all aspects of our life. In nature they occur in multiple forms, and they possess enormous biochemical significance – “the molecules of life.” The applications of heterocycles that are drawn from chemistry, biology, medicine, agriculture, and industry are legion.

A.F. Pozhorskii, A.T. Soldatenkov, and A.R. Katritzky have appreciated the importance of heterocycles in their monograph *“Heterocycles in Life and Society”* (2nd revised edition, John Wiley & Sons, West Sussex, UK 2011).

At first glance, a combination of “wine” and “heterocycles” seems not to be obvious. However, from a chemical viewpoint wine is a complex aqueous-alcoholic solution that contains more than 1200 different components (89MI1, 06MI1), the number of which is increasing as analytical techniques improve. Many of these components from the following classes of compounds possess extraordinary olfactory properties:

- alcohols and glycerol
- carboxylic acids

- esters
- terpenes
- anthocyanin
- polyphenols
- carbohydrates and polysaccharides
- tannins and gallic acid

The notion “heterocycles” in this context appears like a foreign word or a troublemaker, which could disturb the carefully tended harmony of the desirable odorants, the wine flavor, and taste bouquet characteristic of individual white wine varieties. In this review, we speak about quantities and odor thresholds between a few milligrams per liter and nanograms per liter, or even less.

However, on a second glance one finds that the world of manifold heterocyclic compounds has entered into one of the most ancient cultural drinks of the world. Besides numerous *O*-heterocycles, several *O,N*-, *N,S*- and *N*-heterocycles have been detected in wine that can impart organoleptic defects and off-flavors.

In addition to heterocycles in grape juice, there are also many acyclic precursors that are converted by fermentation, aging, and other modifications into heterocycles; for example, hydroxyl carboxylic acids, polyphenols, and amino acids.

The important classes of heterocycles in wine are:

- Lactones (formed from acids and alcohols)
- Carbohydrates, their derivatives, polysaccharides, and pectic substances
- *O*-Heterocycles formed by radical reactions of polyphenols
- *N*-Heterocycles stemming from amino acids
- Phenols, flavonoids, flavones, tannins, procyanidins, and anthocyanins
- Sulfur compounds produced by yeast metabolism (and residues of pesticide treatment)
- Heterocycles formed upon aging of wines and oxidation processes
- Non-desired heterocycles, contaminating residues of fungicides and pesticides.

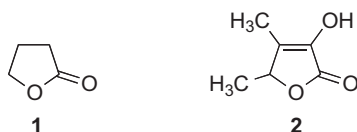
Of the volatile compounds in wine, alcohols represent a major component. Obviously, ethanol ($\text{C}_2\text{H}_5\text{OH}$) and glycerol ($\text{CH}_2\text{OH}-\text{CHOH}-\text{CH}_2\text{OH}$) are endpoints of the fermentation process – the important metamorphosis of glucose in grape juice into “wine” – the cultural drink that has been recognized for thousands of years and is the product of the world’s greatest biotechnological process.

Besides these simple fermentation alcohols, the yeast also forms higher alcohols as side products, “fusel oils,” that have intense odors and play a role in wine aroma. Other components are carboxylic acids, such as tartaric and malic acids, that are important as “life-insurance” during aging of the wine. Some of the aromas perceived in wines stem from esters

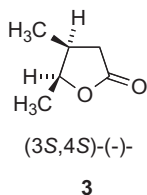
formed by the reaction of acids and alcohols, a process that occurs during fermentation, as influenced by yeast, or later during the process of aging. The inherent low pH of wine serves as a catalyst to impart one set of aromas early in the wine's life, and other aromas later as the wine ages.

3. OXYGEN HETEROCYCLES

Internal esterification between a carboxylic acid and an alcohol leads to the O-heterocycle lactone. Notably, butyrolactone **1**, an “oxo-derivative” of tetrahydrofuran (73AJEV5, 08MI1), but which is of minor organoleptic influence in wine. In contrast, infection of grapes by the noble fungus *Botrytis cinerea* gives rise to 4,5-dimethyl-2-hydroxy-2-furanone, called “sotolon” **2** (84ABC2207, 92JAF475, 03JAF4356, 04JAF6765), possessing a toasty, caramel, or walnut aroma. This often desirable compound is present in higher concentrations in Curry and Liebstöckel (*Levisticum officinale*), and has a threshold concentration of $\sim 5\mu\text{g/L}$, and is also found in aged Port wines.

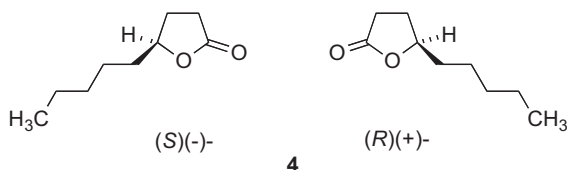


Another lactone, 3-methyl- γ -octalone known as “oak lactone” or “whiskey lactone” is released upon storing and aging wines in oak barrels (87LB35, 94PF1, 94JAF1971, 96FRI105, 99JC(A)239, 07MI1). This lactone, 4-butyl-3-methylbutan-4-olide, consists of four stereoisomers, namely (3*S*,4*S*)-(-)-, (3*R*,4*R*)-(+)-, (3*R*,4*S*)-(-)-, and (3*S*,4*R*)-(+)-4-butyl-3-methylbutan-4-olides, of which the (3*S*,4*S*)-(-)-isomer **3** has the lowest threshold: 20–24 ppb in white wine and 54–57 ppb in red wine.



These isomers possess coconut, walnut, and sweet wood notes and flavors reminiscent of hay or celery.

In addition, γ -nonalactone **4**, (*S*)-(-)- and (*R*)-(+)-4-pentylbutan-4-olide, shows weak to strong sweet coconut notes, as well as peach and apricot aromas.



This pair of enantiomers represents a good example for chirality and odor perception (89JAF413, 93PF1, 07MI2, 00MI1):

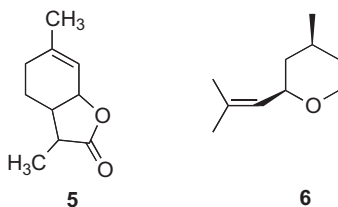
4 (S)(-)-4-pentylbutan-4-olide: fatty, moldy, weak, coconut nose, less intense than (R)(+)-4; odor threshold in red wine: 91 ppb;

4 (R)(+)-4-pentylbutan-4-olide: strong, sweet, soil, coconut with fatty-milky aspects; odor threshold in red wine: 285 ppb.

Higher molecular weight lactones, such as γ -decalactone, δ -dodecalactone, γ -jasmolactone, occur in fruit (peach and apricot aromas) but have been not found in wine, at least in very small traces by gas chromatography/mass spectrometry (GC-MS). If they are detected in higher quantities, then these lactones were undoubtedly added illegally, a case for prosecution (10MI3, 07MI27).

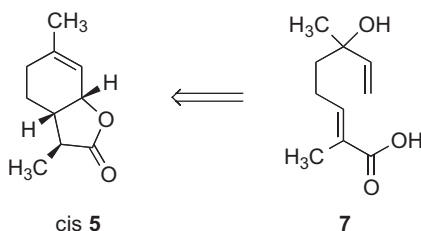
A very important lactone in wines is the so-called “wine lactone,” 3a,4,5,7a-tetrahydro-3,6-dimethyl-2(3H)-benzofuranone **5**, which exists in four enantiomeric pairs. This compound was first identified and isolated from the urine of Koala bears (75TL1885, 97JAF3027), from their diet of the leaves of the *Eucalyptus punctata* tree. And this shows that the wine lactone belongs to monoterpenoid flavoring ingredients, which have been converted into oxygenated forms.

Guth has isolated this intensely sweet and coconut-like odorant from different wine varieties, especially from Scheurebe and Gewürtztraminer (96HCA1159, 77JAF3022, 77JAF3027, 99MI39), along with *cis*-rose oxide **6**, a monoterpenoic pyran derivative (2*R*,4*S*)-tetrahydro-4-methyl-2(2-methylprop-1-enyl)-2,5-*cis*-2*H*-pyran. He used aromas to distinguish wine varieties on the basis of selected volatiles by the method of Rapp (90FJAC777, 99MI53).



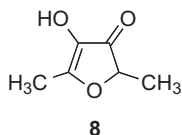
(-)-*Cis*- and (-)-*trans*-rose oxide **6** are industrially produced perfume additives from citronellol. Several comparative studies have dealt with fruit and Gewürtztraminer wine aroma (99JAF665, 08JAF1371). Guth

determined the configuration (96HCA1159, 77JAF3022, 77JAF3027, 99MI39) of the wine lactone, and in this study all eight possible stereoisomeric lactones were synthesized using 3-methylcyclohex-2-enone as starting material following the route of Hijfte and Vanderwall (84T4371). All eight isomers could be separated by capillary GC, and from these only (3*S*,3*aS*,7*aR*)-3*a*,4,5,7*a*-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one *cis*-5 is naturally occurring. This enantiomer has the remarkable low odor threshold of 0.00001–0.00004 ng/L in air (03TA1).

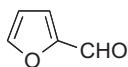
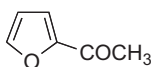
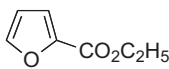
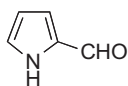
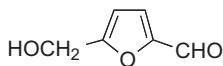


Wine lactone is formed by cyclization of a terpenoid pre-stage 7, *E*-2,6-dimethyl-6-hydroxyocta-2,7-dienoic acid, and this reaction mechanism has been investigated (06JAF30245). Winterhalter et al. isolated two novel terpenoid glucose esters from Riesling wine and transformed them in a biomimetic fashion into the wine lactone (98JAF30474). Moreover, the formation of wine lactone from grape-derived secondary metabolites has been reported (11JAF30660). Several synthetic approaches to enantiomerically pure (–)-wine lactone have been reported, *via* Pd-catalyzed enantioselective allylic substitution (00EJOC419), by FeCl₃/NaI-mediated iodolactonization of an α,γ,δ -unsaturated acid (01TA2985), and by a Diels–Alder approach (09EJOC4405).

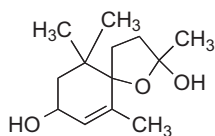
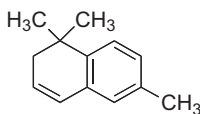
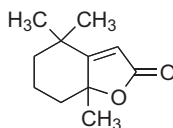
From the wine aromas of Pollux, Castor, and Riesling grapes, Rapp et al. and Schreier and Paroschy have isolated an undesirable strawberry aroma by GC–MS (80V13, 81MI112). This lactone was characterized as 2,5-dimethyl-4-hydroxy-2,3-dihydro-3-furanone 8 (“furaneol”) having an odor threshold of 50–100 ppb.



As a consequence of bottle aging, carbohydrate conversions can occur, although slowly at cellar temperature, to form the caramel-like 2-furfural aroma; for example, in aged Madeira wines. Rapp and Güntert (86MI141) have shown that such carbohydrate decomposition in Riesling wines leads to 2-furfural 9, 2-acetylfuran 10, ethyl furan-2-carboxylate 11, 2-formylpyrrole 12, and 5-hydroxymethylfurfural 13.

**9****10****11****12****13**

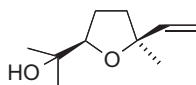
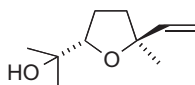
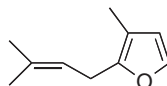
Such tertiary and quaternary aromas of wines occur upon storing, especially in Riesling wines, and these compounds are characteristic of the class of C-13-norisoprenoides. Thus, vitispiranes **14**, 2,6,10,10-1-oxaspiro[4,5]dec-6-ene-2,8-diol, having a herbal, resinous, and balsamic aroma, and accompanied by TDN, 1,1,6-trimethyl-1,2-dihydronaphthalene **15**, which is formed by a mechanism of carotinoid degradation, combine to give rise to a typical “kerosene” or “petrol” aroma ([85ZLUF109](#)). Precursor compounds might be 5,6-epoxy- β -ionone, 3-keto- α -ionone, and intermediates dihydroactindiolid and damascenone **16** (rose ketones) ([90AJEV277](#), [92V169](#)).

**14****15****16**

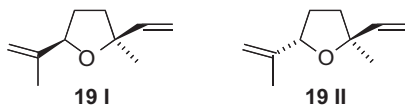
There are more than 550 identified volatile components in wine and most types of terpenoids contribute to wine aroma ([79MI59](#), [83SAJEV49](#), [89MI584](#)), the origin of which is divided into four classes:

- originating from grapes,
- produced during crushing of the grapes,
- produced during fermentation, and
- produced during maturation of wines.

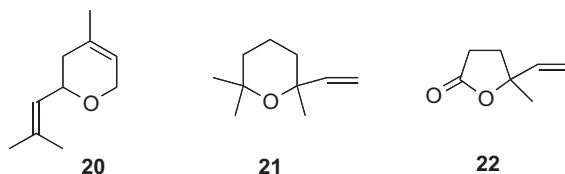
Cis- and *trans* 5-[2-hydroxyisopropyl]-2-methyl-2-vinyl-tetrahydrofuran (*cis/trans*-furan-linalool oxides) **17I/II** and rosefuran **18**:

**17 I****17 II****18**

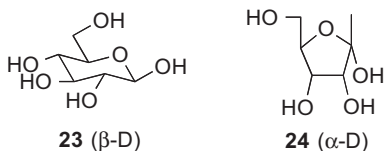
Cis- and *trans* 5-isopropyl-2-methyl-2-vinyl-tetrahydrofuran **19I/II** (*cis/trans*-anhydrofuran-linalool oxides) (80MI698, 77ZLUF98):



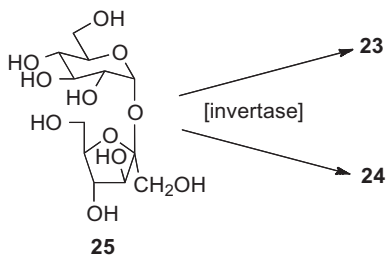
Further, neroloxide **20** (80MI698) and 2,6,6-trimethyl-2-vinyl-tetrahydropyran **21** (80JAF346), and 2-vinyl-2-methyl-tetrahydrofuran-5-on **22** (80MI698) have been isolated:



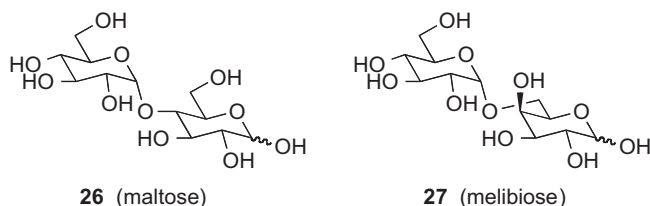
Another important group of heterocycles present in wine is the *Carbohydrates*, polysubstituted pyrans and furans, which can exist in both open-chain and cyclic structures. The most important of these sugars are glucose **23** and fructose **24**, and they represent the basis for the fermentation process giving the three main products: CO₂, glycerol, and ethanol:



Sucrose (saccharose) **25** is primarily produced by photosynthesis in grape leaves and then translocated into the grapes. During ripening the sucrose is hydrolyzed by the enzyme invertase into glucose and fructose, which constitute up to 15–25% of the grape juice. The proportion of these two sugars changes during the ripening process of the grapes. Due to the action of the enzyme epimerase the equilibrium glucose/fructose is shifted in favor of fructose (a good marker of grape ripening), to the ratio on the order of 1.5. Fructose tastes nearly twice as sweet as glucose. During the fermentation process, glucose is preferentially metabolized by the glucophilic yeasts (89MI502, 06MI66). Thus, the glucose/fructose ratio in grape must is decreased to 1:1, and the residual fructose maintains with other sugars the sweetness of the wine (the glucose content is about 1g/L).

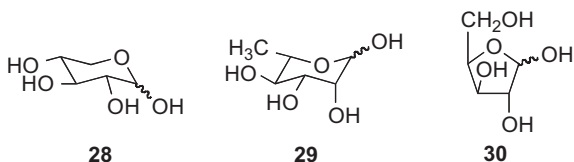


Wine contains traces of these disaccharides: saccharose **25**, maltose **26**, and melibiose **27**:



In cases of grape juice having a saccharose concentration greater than 2g/L, sugar must have been added to the juice to increase the alcohol content (“chaptalization”), which is illegal in southern Europe and California regions with warm climates. The illegal addition of saccharose is difficult to analyze, except by the D/H-isotope ratio of the ethanol ([82AC2380](#)) or of the residual sugar ([83V375](#), [09JC7296](#)). Higher free disaccharides in wine, for example, α,α -trehalose, cellobiose, sophorose, laminaribiose, and gentiobiose have been reported.

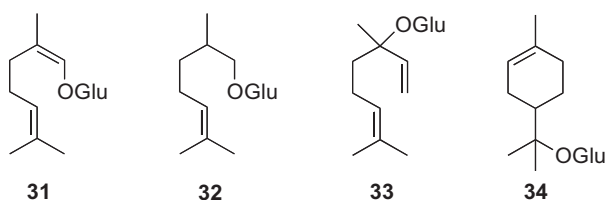
Other unfermented sugars in dry wines, “residual sugars,” are pentose sugars (below 1.5g/L): β -(L/D)-arabinose **28** (0.5–1.3g/L), α (L)-rhamnose **29** (0.3–0.4g/L), and α -D-xylose **30** (0.01–0.1g/L) ([76WW25](#), [78WW54](#)) shown in pyranose and furanose forms:



Furthermore, some trisaccharides, such as raffinose and mellibiose, and the tetrasaccharide stachyose have been identified in wines in quantities between 2 and 166mg/L ([76WW25](#), [78WW54](#), [78MI27](#), [79MI18](#)).

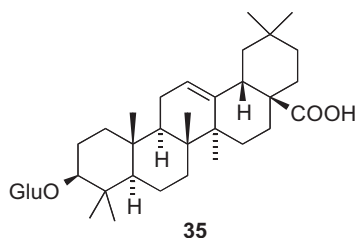
When carbohydrates are coupled with a non-carbohydrate *via* the semi-acetal functionality, *glycosides* are formed. These can exist as

O- and N-glycosides and are widespread in plants, and also in grapes. Thus, these carbohydrate–flavor conjugates play an important role in the flavor of wines (99MI283), being first recognized in 1974 by Cardonnier and Bayonore (74CRAS3387). Most of these glucoconjugates are of low molecular weight, and the grape berries accumulate them in the vacuoles of plant cells. In particular, monoterpenoids (geraniol and linalool, for muscat flavor), ketones (raspberry), and benzaldehyde (almonds) are present both as aglycones and glycosides. Indeed, there are hundreds of potential flavor-active compounds in grapes (85ZLUF109, 82P2013, 95JAF121, 98MI98, 95MI73, 92JC269, 80MI269, 93MI98, 86MI42), as e.g. 31–34:



In the glycosidic form they are almost odorless, but once the sugar moiety has been cleaved (e.g., by action of glycosidase enzymes) they regain the aromatic characteristics (95AJEV187). Also synthesis of glycosides has been reported (95JAF121).

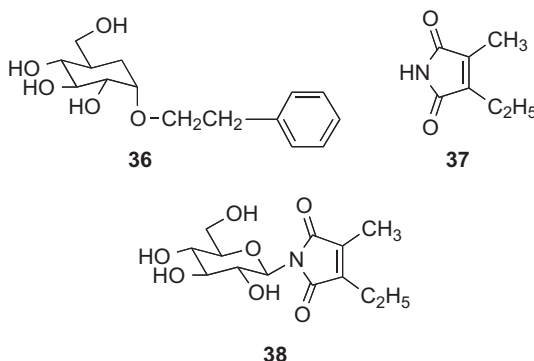
In addition, compounds with higher molecular weights occur as glycosides in wine; for example, the triterpenoid homosteroid oleanolic acid 35 is found in the cuticle (79AEM1069) and exhibits strong anti-inflammatory and potent anti-HIV activity (98JNP1090, 01BMCL3115):



Furthermore, flavones and anthocyanin glycosides in the hypoderm, which are responsible for the color in red grapes, are dealt with in the following section on phenolic compounds.

In the glycosidic fraction of Riesling wine phenylethyl- α -D-glucopyranoside 36 is found as a minor constituent (97NPL39). From Chardonnay grapes 2-ethyl-3-methylmaleinimide 37 has been identified as an aglycon following acid hydrolysis (93AJEV359). From Riesling wine

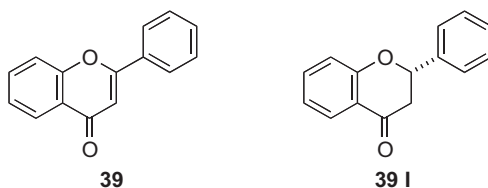
the corresponding *N*-glycoside **38** has been isolated, obviously both fragments from chlorophyll ([96P141](#), [97V159](#)).



4. PHENOLIC COMPOUNDS AND POLYPHENOLS

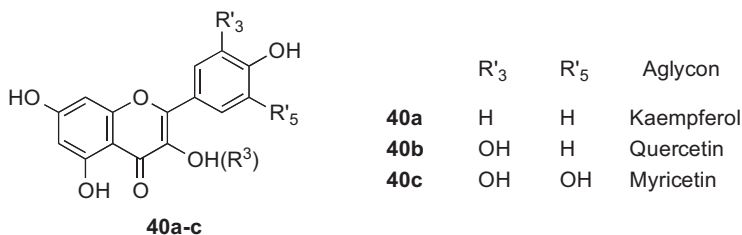
Another very important group of wine constituents that play a major beneficial role to human health are the *phenolic compounds* and *polyphenols*. These can be divided into *flavonoids* and *non-flavonoids*, and the heterocycles and glycosides derived from them ([01MI1](#), [06MI4](#), [06MI3](#), [89MI101](#), [89MI571](#), [11MI1](#), [10MI1](#), [06MI141](#)). Polyphenols are antioxidant compounds, which occur in the skin and seeds of grapes. They are extracted into the grape juice by the alcohols formed during fermentation. The proportion of phenols and polyphenols varies from the type of vinification, and red wine is normally richer in anthocyanins, proanthocyanidins, and flavonones.

Flavonoids are more or less intensely yellow colored pigments belonging either to the group of 2-phenyl-chromones **39** (flavones, flavonols) or 2-phenyl-chromanones **39I** (flavanones, flavanonols); both groups have a backbone of 2-phenyl-1,4-benzopyrones:



Fundamental investigations of these phenolics have been made by Ribéreau-Gayon ([64MI1](#), [68MI1](#)). Separations were achieved by thin-layer chromatography (TLC), GC ([73V226](#), [78WW54](#)), and high-performance

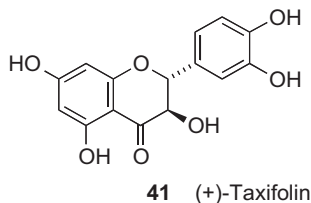
liquid chromatography (HPLC) (00JAF C2675, 02JFCA639). Some flavonols are shown here:



The concentration in wine is ca. 20–40mg/K (75MI1, 98JAF C368), and these flavonols are found as glycosides, as, for example, 3-*O*-rhamnosylquercetin with R³=rhamnose.

Kaempferol **40a** is a strong antioxidant that prevents the oxidative damage of cells; it prevents arteriosclerosis by inhibiting the oxidation of low-density lipoprotein (LDL) and the formation of platelets in the blood. It also acts as a chemopreventive agent (inhibition of cancer cell formation) (05MI107, 07MI924). Quercetin **40b** is the aglycon from flavonoid glycosides, such as rutin and quercitrin; it is found in red wines and contributes like kaempferol **40a** to beneficial health effects in humans (06MI765, 69MI659). Myricetin **40c** (NSC 407290) has similar properties, and it was found to act as an antagonist for the estrogen receptor in human breast cancer cells (05MI269). It is also a potent anticarcinogen and antimutagen due to its antioxidant action, it is an efficient protection of the heart (09MI531), and a novel natural inhibitor of neoplastic cell transformation and MEK 1 (07MI1918, 09MI17). In summary, polyphenols are highly suited for cancer prevention (08MI842) and cardiovascular health (11BBR743).

Flavonones and flavanonol are other heterocyclic pigments found in wine. Taxifolin **41** (2,3-dihydroquercetin) has only 50% of the antioxidative activity of quercetin, but it is both less mutagen and toxic (09MI451, 07MI1074):



As flavonoids and flavanones contribute to the yellow color in both white and red wines, anthocyanins **42** and their mono- and diglucosides are the bright red pigments in grapes, mainly in the skin, but in autumn also in the leaves. These components contribute only slightly to the taste; but as

they readily polymerize with tannins, they play an important role in tannin retention and aging:

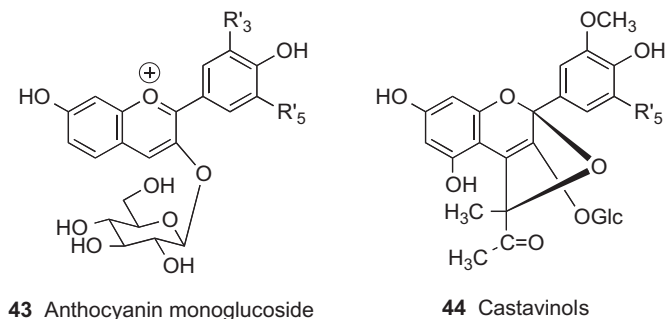
Anthocyanidins 42 a-c			
	R' ₃	R' ₅	aglycon
42 a	OH	H	Cyanidin
42 b	OCH ₃	H	Peonidin (20-60 mg/K)
42 c	OH	OH	Delphinidin (2-20 mg/K)
42 d	OH	OCH ₃	Petunidin (3-7 mg/K)
42 e	OCH ₃	OCH ₃	Malvidin (200-600 mg/K)

The amount of anthocyanins in purple grapes varies with the grape varieties ([75MI1](#), [98JAF368](#), [73WW181](#)):

Grape variety	Quantity (mg/K)
Alicante Bouchet	5200
Shiraz	2200
Cabernet Sauvignon	1700
Pinot Noir	825

From their structure anthocyanins are flavylium cations, and their formation seems to be a function of day and night temperatures ([72AJEV71](#), [76MI1](#)). They act as a natural “sunscreen,” protecting cells from light damage by absorbing blue-green and UV light ([98MI1](#)). Thus, anthocyanins have found use in dye-sensitized solar cells ([97JPC\(B\)9342](#), [09MI145](#)), and they were the focus of research presented at a 2007 symposium on health benefits, including the topics of cancer, aging, neurological diseases, inflammation, diabetes, and bacterial infections ([08MI2](#)).

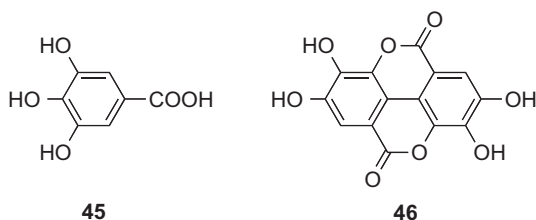
The color of anthocyanins depends on pH. Low pH induces a bathochromic shift (toward violet), while glucose fixation **43** and acylation shift the absorption in the opposite direction (toward orange) ([93MI1](#)):



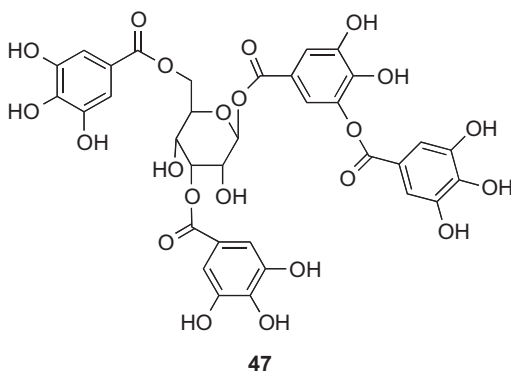
With α -dicarbonyl compounds, such as diacetyl, colorless castavinols **44** are formed; these are not present in grapes but form rapidly in wine ([96TL7739](#), [97MI19](#)).

5. TANNINS

Tannins: Gallic acid **45** is a phenolic compound found mainly in grape seeds and stems, but also it can be leached from oak barrels, occurring generally in amounts of 10–100mg/L. Two molecules of gallic acid in a head-to-tail fashion are the dilactone ellagic acid **46**:

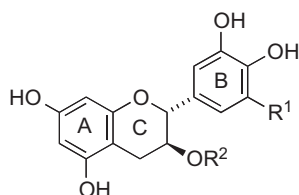


By oligomerization with glucose tannic acids **47** are formed with molecular weights from 600 to 3500:

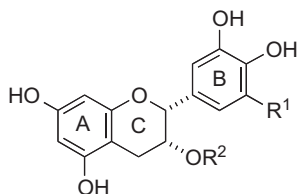


This scheme shows a condensation product from two molecules of gallic acid and one of ellagic acid with glucose, which is hydrolyzable into its components. Some C-glycosidic ellagitannins ([96AJEV103](#), [06JAF7349](#), [99JAF72060](#), [09MI1](#)) in wine, such as (–)-vescalagin and castalagin, target human topoisomerase ([05MI6503](#)).

Polymeric tannins are complex molecules comprising flavan-3-ols or catechins, and called “procyanidins” **48**, **49a–d**:

**48 a-d** (2*R*,3*S*)-Catechins

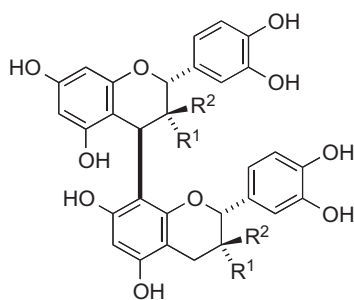
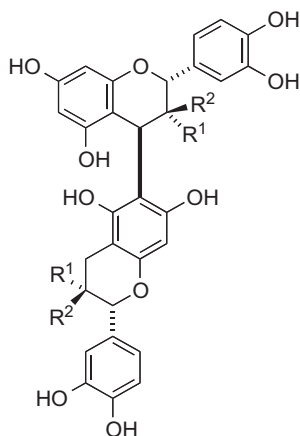
	R ¹	R ²
48 a	H	H (+)-catechin (2 <i>R</i> ,3 <i>S</i>)
48 b	H	H (-)-catechin (2 <i>S</i> ,3 <i>R</i>)
48 c	OH	H gallo catechin
48 d	H	gall.acid galloylcatechin

**49 a-d** (2*R*,3*R*)-Epicatechins

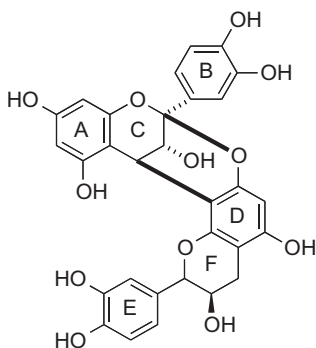
	R ¹	R ²
49 a	H	H (+)-epicatechin (2 <i>S</i> ,3 <i>S</i>)
49 b	H	H (-)-epicatechin (2 <i>R</i> ,3 <i>R</i>)
49 c	OH	H gallo catechin
49 d	H	gall.acid galloylepicatechin

When these polymers are heated in acidic solution intermediate unstable cations are formed, which are converted into brown condensation products consisting of “red cyanidin.” Several di-, tri-, and oligomeric procyanidins have been isolated and characterized ([90T5733](#), [00TL485](#), [06AJEV298](#), [06AJEV289](#), [11MI489](#)). Smaller catechin polymers contribute more to the astringency and bitter taste than the larger complexes, which are simply too large to fit into the taste receptors. The concentrations of catechin and epicatechin in red wines have been determined ([98AJEV23](#)). Interestingly, catechin induces longevity in the nematode *Caenorhabditis elegans* ([09MI477](#)).

Dimeric procyanidins exist in two different structural species (4β → 8) **50** and (4β → 6) **51**:

**50** Procyanidin (4β→8)-dimer**51** Procyanidin (4β→6)-dimer

These are called type -B procyanidins, and in wine there occur about 50 dimers, eight of which have been identified to date (95MI1). The type A ($4\beta \rightarrow 6$) dimer **51** was presented earlier involving condensation with diacetyl (96AJEV103, 06JAF C7349, 99JAF C2060, 09MI1). The antioxidant activity of wine catechins, procyanidins, anthocyanins, and proanthocyanins has been measured (07MI797). Corder et al. reported on the red wine procyanidins and vascular health (06NAT56).



52 type A procyanidin

Red wines contain about 20 times the procyanidin content of white wines (08MI284), and, furthermore, branched flavan-3-ol procyanidin oligomers are known (03AJGWR15, 03AJGWR110, 99JAF C2719, 03AJGWR211). Pinot Noir grapes do not have condensed tannins in the skin (92MI1), and, as any wine connoisseur knows, these red wines are less colored than, for example, Cabernet Sauvignon.

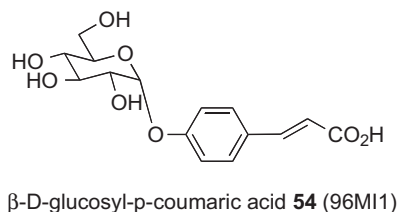
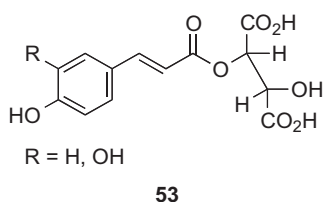
Anthocyanins and tannins show manifold chemical properties, pH-dependence, protein interactions, and polymerization reactions (68MI1, 08MI1579, 11MI2). But, of general interest are oxidation reactions (95MI1, 91JAF C1047, 97AJEV370). With regard to polymerization, procyanidin trimers (epicatechin-($4\beta \rightarrow 8$)-epicatechin ($4\beta \rightarrow 8$)-catechin) were quantified for the first time in white wines (Grenache and Mueller-Thurgau) (93AJEV168, 79AJEV289).

6. NON-FLAVONOID POLYPHENOLS AS PRECURSORS FOR O-HETEROCYCLES

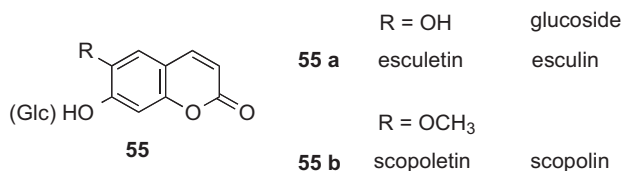
There are two groups of non-flavonoid polyphenols having lower molecular weights, which are themselves not heterocyclic compounds, but nevertheless are precursors to oxygen heterocycles:

- (a) phenolic (cinnamic) acids \rightarrow coumarins
- (b) *trans*-resveratrol \rightarrow viniferines

Several cinnamic acids **53** are found in grapes and wine, but they are invariably esterified (e.g., with tartaric acid) or as simple glycosides **54** (65BSF2649, 98JAF4203, 00JAF2681, 09MI515, 07MI101):

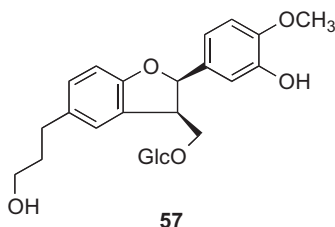
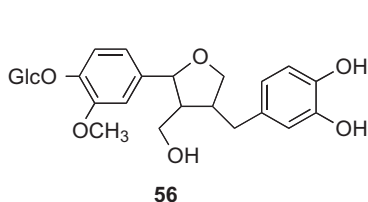


By intramolecular esterification coumarins **55** are formed:



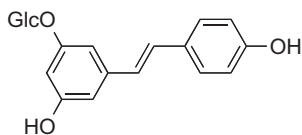
These non-flavonoid phenolic compounds are easily oxidized (89JC428, 89JAF41069) and show anticancer activities (04MI3707).

Additional oxygen heterocycles with a furan ring are lignans **56** and neolignans **57**, which have been isolated from Riesling wine (01JAF2788):



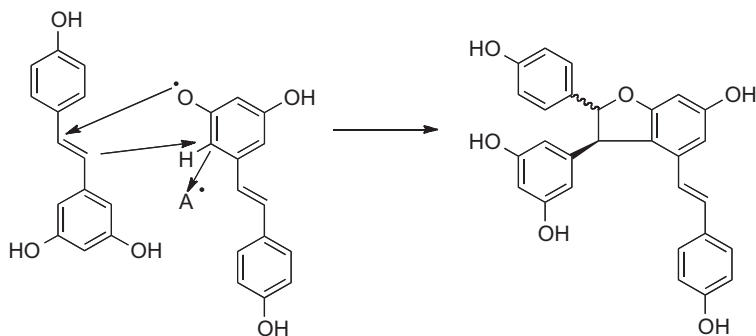
The second group of non-flavonoid polyphenols, which is a precursor for various oxygen heterocycles, is the *trans*-resveratrol **58**, a trishydroxystilbene derivative that occurs in wine (and also in peanuts) as the glucoside *trans*-piceid (10MI227, 95AJEV159, 99MI505, 96AJEV415, 97MI44, 98MI87, 99JAF3223, 96AJEV57, 06MI2). Resveratrol can be extracted from Japanese knotweed (*Polygonum cuspidatum*) but was first identified in 1939 by Takaoka (39MI1090) as being in *Veratrum grandiflorum*; hence

the name: “res” from resorcinols, “vera” from veratrum, and “ol” from hydroxyl groups:



58 Piceid

Resveratrol has molecular dimensions similar to the steroid scaffold, which explains its special hormonal character (“phytoestrogen”) with regard to steroid receptors. It is a phytoalexin produced naturally under environmental stress or insect/animal attack by gene-directed rapid metabolism (88MI161). Over the last decade resveratrol has been shown to possess a fascinating spectrum of pharmacological properties. In comparison to the proanthocyanidins, resveratrol plays only a limited role in the so-called “French Paradox” (06NAT56, 92MI1523, 93MI27, 94MI3118, 99MI1865, 98MI184, 79MI1017, 92AJEV49). As an antioxidant and antimutagen it is responsible for cancer chemoprevention and anticancer activity. Indeed, resveratrol interferes with all three phases of carcinogenesis: initiation, promotion, and progression (97MI218, 06MI493). One study shows that resveratrol stops the growth of breast cancer cells by blocking the effects of estrogen (11MI3695). One special property of resveratrol is as an inactivator and co-reductant of COX-1 peroxidase, thus acting as a radical scavenger (05JNP36, 01JNP136, 03JAF5488). Resveratrol also inhibits COX-2- transcription and activity (98MI21875). As by-products of this radical scavenging process several stereoisomers of the furan derivative viniferin 59¹ have been isolated in wine (05JNP36, 01JNP136, 03JAF5488, 77MI151, 00JAF6103) in quantities of about 10mg/L.



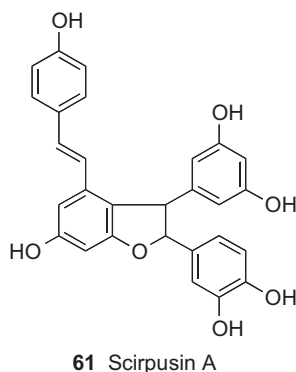
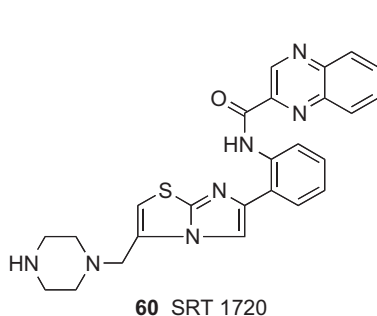
59 ϵ -viniferin (cis/trans)

¹Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cyclic adenosine monophosphate (cAMP) phosphodiesterases (12CE421)

Viniferins show interesting properties: they display at levels of 10–100 μmol , a more potent effect on the human P 450 enzyme than resveratrol (03MI1199), and they inhibit at levels of 5–200 μmol monoaminoxidase (06MI54). Likewise, in coronary heart disease ϵ -viniferin is more effective than resveratrol (11MI1259).

Resveratrol shows a direct inhibitory activity on heart fibroblasts and suppresses the spreading of heart fibrose (05MI1131). The vasoconstrictor peptide endothelin (ET-1) is controlled in its biosynthesis by polyphenols, and especially by resveratrol. Only 5 μmol causes an endothelin-dependent vasodilatation and lowers blood pressure (88NAT411, 01MI152, 01NAT863, 06NAT566).

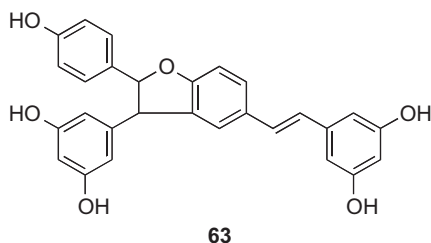
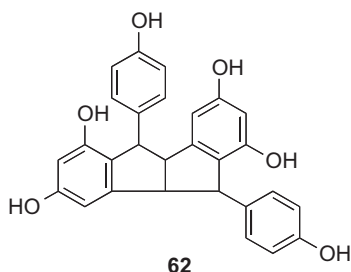
Sinclair and his group showed in 2003 that resveratrol significantly extends the lifespan of yeast (*Saccharomyces cerevisiae*) (03NAT191). Subsequently, they demonstrated similar life extensions of vertebrates (*Nothobranchius furzeri*), fruit flies (*Drosophila melanogaster*) (07MI546), and worms (*C. elegans*) (04NAT686, 07ANY530, 07NI546, 06MI296, 05MI473, 06NAT868). Health and survival of mice on a high-caloric diet is improved by resveratrol (06NAT337). Mechanistically, resveratrol activates Sir 2 of the sirtuin gene family (in mammals SIRT 1, SIR 2-1, SIR 2a of NAD⁺-dependent deacetylases are responsible for lifespan-extending effects of caloric restriction by influencing the production of glucose and insulin) (06MI48, 10MI261). In this regard small molecule activators of SIRT 1 have been developed as therapeutics for the treatment of type 2 diabetes (07NAT712), such as SRT 1720 60:



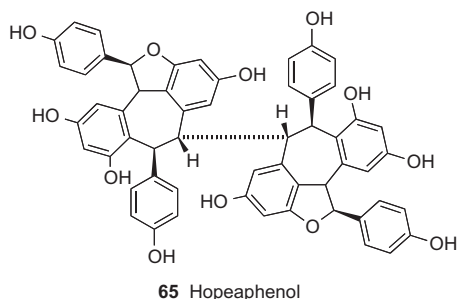
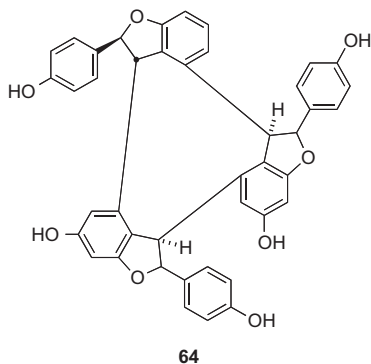
In Alzheimer's disease resveratrol could be of importance as it inhibits the aggregation of the amyloid- β -peptide (07BMC1160, 08MI6, 11ANY103). In addition, stilbene dimers, such as scirpusin A 61 and ϵ -viniferin glucoside, which were isolated from wine grapes in Xinjiang province, China, demonstrate a strong inhibition of this fatal aggregation process (10BMCL3441, 10JSFA823, 11FC727, 06MI495). Resveratrol might

also be useful in protecting against brain damage following cerebral ischemia, as has been shown in rats and mice (02MI655, 01MI1057, 08MI709, 10MI375, 10MI325).

Pallidol **62** is another dimer of resveratrol that is found in (red) wine stems and macerated wines in quantities ranging between 0.38 and 2.22mg/L that has both antioxidant and antifungal activity (98JAF4203, 02JAF42046, 01JNP136, 08MI25, 11MI3).

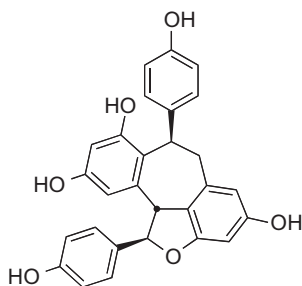


δ-Viniferin **63** is another resveratrol dehydrotetramer. Compared to ε-viniferin, **63** lacks one hydroxyl group on the benzofuran ring. Along with other stilbenes it was first isolated from Brazilian wines (03JAF5488, 05JAF5664) in quantities of ~1.2mg/L. α-Viniferin **64** is a stilbene dehydrotrimer that functions as a phytoalexin (a stress metabolite) in leaves. The production of **64** by *Vitis vinifera* grapes can be induced by infection or injury (76MI77, 81MI213, 77P1452, 77E151), or by UV light, obviously *via* enhanced formation of peroxidase (94MI133).



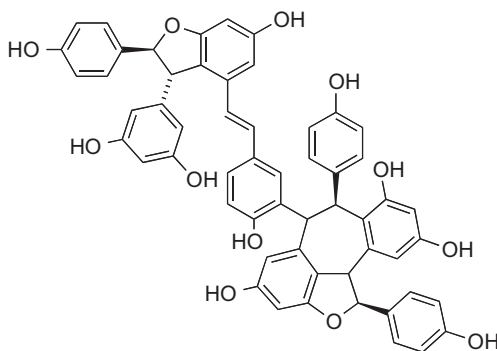
Hopeaphenol **65** is a resveratrol dehydrotetramer found in wines, initially in North African wines (02JAF42046, 01JNP136, 08MI25, 11MI3, 06JAF9559, 10PR357) in quantities from 0.3 to 3.8mg/L.

Ampelopsin A **66** can be viewed as the monomer of hopeaphenol isolated by Oshima et al. ([90T5121](#), [95T11979](#)). The quantity in wine is ca. 2–16mg/L ([00MI591](#)); on the cytotoxicity against cancer cells, cf. ([99JOC6976](#), [99PAC1611](#)).

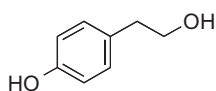


66 Ampelopsin A

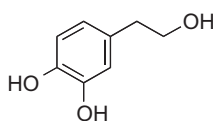
Seya et al. describe the isolation of additional resveratrol tetramers, as Vitisin A **67** with cardiomyocyte apoptosis activity ([09MI90](#)); for more dimeric resveratrols, cf. ([08MI507](#)).



67 Vitisin A



68



69

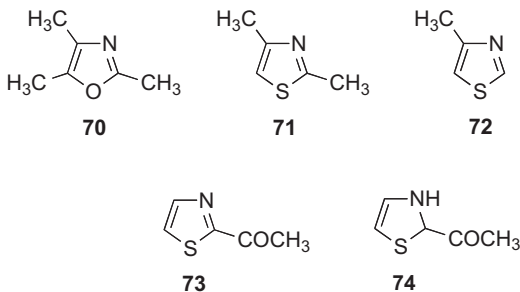
Recent investigations have shown that white wine also contains natural phenolic antioxidants with cardioprotective abilities: tyrosol **68** and hydroxytyrosol **69** (*p*-hydroxyphenylethanol) ([65CRAS1915](#)). In particular, cardioprotective abilities were reported for myocardial ischemia reperfusion ([08JAF692](#)), and white wines are rich in active components, such as **68** and **69** ([08JAF6733](#), [09MI573](#)).

Finally it should be noted that similar to vitamin C (ascorbate) ([08PNA11105](#)), resveratrol in pharmacological concentrations and in the presence of Cu-ions can act as a prooxidant leading to cytotoxicity and apoptosis induction ([09JMC1963](#), [01MI1111](#)).

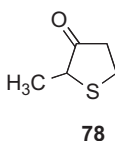
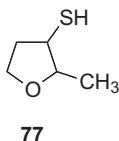
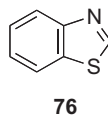
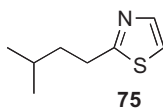
7. SULFUR HETEROCYCLES

Besides the open-chain sulfur compounds involved in the characteristic aroma of wines ([98JAF1044](#), [98JAF5215](#), [00AJEV178](#), [11MI1325](#)), some S-heterocycles have been identified in wines having odor thresholds less than 0.8 ng. Sulfur compounds are formed during fermentation from S-containing amino acids, such as cysteine, cystine, and methionine, and display pleasant and specific aromas (black currant, grapefruit) but also rather unpleasant odors ([75TL1885](#), [97JAF3027](#), [02AJEV144](#), [02JAF4076](#), [03MI9](#)) being intensely malodorous compounds.

Thiazoles are in many foods, and are industrially produced fragrances (e.g., sulfurol), and 2-isobutylthiazole has been identified in wine with a 3 µg/K threshold ([09MI367](#)). Thiazoles belong to the Maillard-type aroma compounds ([04MI353](#), [11MIC861](#)) **70–72**.

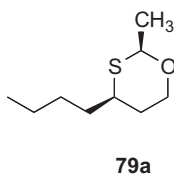


The following heterocycles in wine have been determined by GC–nitrogen phosphorus detector (NPD) ([02JAF5803](#)): **73** and **74**. Especially in Sauvignon Blanc wines isobutylthiazole **75** is responsible for herbaceous green character (tomato spice) with a threshold of 2–3.5 ppb ([82SAJEV53](#)). Benzothiazole **76** is also found in Sauvignon Blanc wines, and imparts a green grassy note with a 50 µg threshold ([76JAF331](#)).



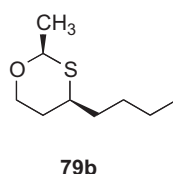
By an improved solid-phase extraction procedure, 2-methyl-tetrahydrofuran-3-thiol **77** could be measured in wine at levels of 0.2 ng/L ([01MI533](#), [08JC\(A\)9](#)). This compound smells like strongly cooked meat, described as roasted meaty. From grape cultivars of the Vinho Verde region in Portugal 2-methyl-tetrahydrothiophen-3-one **78** was isolated ([02ACA157](#)).

The impact of commercial yeast strains on wine fermentation leads to the formation of metabolites of yellow passion fruit (*Passiflora edulis Sims*): 2-methyl-4-propyl-1,3-oxathian **79** ([10MI282](#), [98JAF1076](#), [98MI53](#)). This oxathian exists in four enantiomeric forms, **79a–d**, and there are pronounced sensory differences between them ([06CRV4099](#)); for their enantioselective synthesis, cf. ([84HCA947](#), [85LA1185](#)). It should be mentioned that most of the aforementioned sulfur heterocycles are sold worldwide as fragrances and flavors.



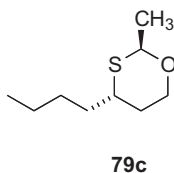
(2*S*,4*R*)-(+)-cis
2-methyl-4-propyl-1,3-oxathian

odor threshold 2 ppb
sulfury note of tropical fruits



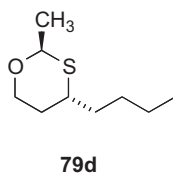
(2*R*,4*S*)-(-)-cis...

odor threshold 4 ppb
fresh, floral, less sulfury



(2*S*,4*S*)-(+)-trans...

sulfurons, slight bloomy sweet

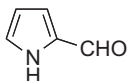
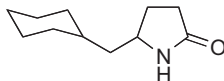


(2*R*,4*R*)-(-)-trans...

green grass, root earthy,
red radish

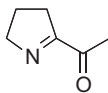
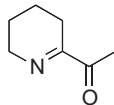
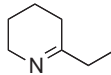
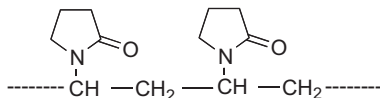
8. N-HETEROCYCLES: PYRROLES, PYRIMIDINES, PYRAZINES

Drawert reports on biogenic amines in wine, among them pyrrolidine **80** (65V127). In a yeast extract pyrrole **81** could be characterized with GC–MS as a biosynthetic metabolite of yeast (85MI125). For a discussion of the maleimides in Chardonnay and Riesling wines, cf. (93AJEV359, 96P141, 97V159, 96P141).

**80****81****82****83**

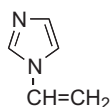
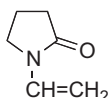
From Spanish oak wood (*Quercus petraea*, *Quercus pyrenaica*) 1H-pyrrole-2-carbaldehyde **82** was extracted and characterized by GC–MS, showing that the oak wood quality has a great influence on wine's sensory properties (07AJEV163). Similarly, Canadian ice wines have been investigated by GC–MS, and 5-(cyclohexylmethyl)-2-pyrrolidinone **83** could be characterized (02AJEV46, 04MI1675).

Mousy taint has been established as a microbiological defect of wine due to three species of *Brettanomyces* and two species of *Lactobacillus*. *Brettanomyces* have been frequently found in wooden casks (86AJEV127, 02JAF7079, 03MI243, 08SAJEV128), and the amino acid L-lysine is essential for the formation of the pyrroline **84** and the tetrahydropyridines **85** and **86**. Isolation and characterization of these amines have utilized GC–MS (00AJGWR255, 06JAF6465, 10MI268).

**84****85****86****87**

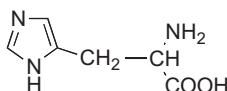
It should be mentioned that polyvinylpyrrolidone (PVP) **87** and polyvinylpyrrolidone–polyvinylimidazole (PVP/PVI) copolymers are used

for “blue fining,” especially of white wines (60AJEV170, 76MI51). PVP is a FDA approved water-soluble polymer with a strong affinity for polyphenols. These are precipitated and the content of the phenols and their astringency reduced. PVP is also used for the removal of metals from wine instead of the “classical” potassium hexacyanoferrate(II) (92WW8, 07V138). Residual PVP has been analyzed in wine (69AJEV152). The use of PVP has furthermore led to the development of HPLC–MS methods for the detection of monomers *N*-vinylimidazole **88**, *N*-vinylpyrrolidinone **89**, imidazole **90**, and 2-pyrrolidinone **91** (10JAF8300, 95MI31):

**88****89****90****91**

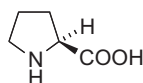
Recently, the FDA has warned about the chemical caramel colorings as food additives that are produced with ammonia, as they may contain the carcinogens 2- and 4-methylimidazole (11MI2).

Finally it should be mentioned that several *heterocyclic amino acids* are found in wine: histidine **92**, proline **93**, 3-hydroxyproline **94**, and tryptophan **95**. The amounts of these and other amino acids can be both increased and decreased during fermentation (65MI1); thus, the amino acid content in different wine species is rather variable (71V299, 75WW188, 74AJEF7, 85AJEV43, 05MI315, 95JC(A)373).

**92**

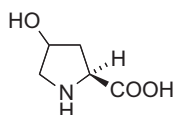
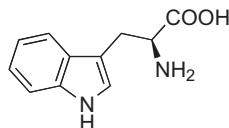
Must: 21-59 mg/L

Wine: 6-7 mg/L

**93**

Must: 115-409 mg/L

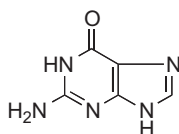
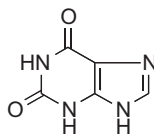
Wine: 208-280 mg/L

**94****95**

Wine: 38.3 mg/L

Ultra-performance liquid chromatography (UPLC) analysis of free amino acids of “on-lees” aged wines gave time- and yeast-dependent amounts of histidine, 11.1–21.1mg/L, and proline 769.7–895.7mg/L (11JC(B)1361).

Upon analysis of the non-flavonoid fraction of wine, *pyrimidines* have been found (65MI307, 79AJEV98) by chromatography on Sephadex 6-25 and phenol assayed by colorimetry. Of the nucleic acids (mainly guanine **96** and xanthine **97**) less than 5mg/L can be assumed to be present.

**96** Guanine**97** Xanthine

Pyrazines represent an important group of heterocyclic flavor compounds in several wine species (92MI479, 89MI61). Notably, methoxy-pyrazines **98a–d** have been found in many wines; they possess a typical smell of green bell pepper (*Capsicum annuum*). Due to their relatively high concentration, pyrazines especially contribute to the typical aroma of Cabernet Sauvignon, Cabernet Franc, Merlot, and Sauvignon Blanc (75CRAS(D)75, 98MI31, 82SAJEV53, 86JAF C268, 91AJEV109, 00JAF C4830, 04MI172), at levels of 1–40 ng/L. Their impact in the resulting wine is strongly and systematically influenced by viticultural conditions (temperature during ripening, berry maturity, fruit exposure to sunlight). These pyrazines are mainly localized in the berry skin (02AJEV1).

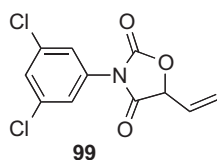
	2-methoxy	taste	[ng/L] odor threshold (69JAF C1322)
	98 a 3-isobutyl	green pepper	2
	98 b 3-isopropyl	green pepper + soil	2
	98 c 3-sec.butyl	green pepper	1
	98 d 3-ethyl	green pepper + soil	400

The desirable concentration for the aroma is small, 8.15 ng/L; levels of 30 ng/L are perceived as unharmonic (69JAF1322, 03MI8). The methoxy-pyrazines form in the grapes from glycine, leucine, isoleucine, and valine *via* diketopiperazine intermediates. After enolization, *O*-methylation, and dehydration the pyrazines are formed (01MI329, 10MI77, 11JAF17310).

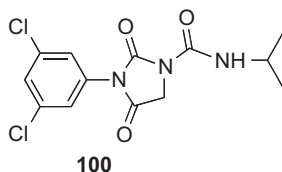
9. NON-DESIRED HETEROCYCLES IN WINE

As wine is always grown in monocultures with a single crop over a wide area, this can lead to the quicker spread of diseases. Thus, fungal diseases can play an important role in destroying an entire vineyard. Such fungi are *Peronospora* (*Plasmopara viticola*), *Oidium* (*Uncinula necator*), *B. cinerea* (gray mold), a high-risk pathogen, *Pseudopeziza tracheiphila*, and *Phomopsis viticola*. Furthermore, manifold insects can diminish or devastate the harvest, as e.g., *Lobesia botrana*, *Eupoecilia ambiguella*, or *Panonychus ulmi* (78MI91, 94MI120); in the United States the Willamette spider mite (*Eotetranychus willamette*) and the Pacific spider mite (*Tetranychus pacificus*) are grape pests. In some cases pheromone traps can control these diseases. However, in many cases plant protection in the vineyards is essential, once infection has occurred, to avoid a rapid and uncontrollable spreading of the diseases. On the other hand, resistance phenomena of *B. cinerea*, especially in vineyards have restricted the use of many fungicides (08MI214, 11MI63).

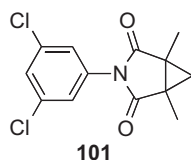
While the fungicides Folpet[®], Captan[®], and Captafol[®] are forbidden in German vineyards, against *B. cinerea*, vinclozolin (Ronilan) **99**, iprodione (Rovral) **100**, and procymidone (Sumislex) **101** are considered safe to use (89MI220); triadimefon (Bayleton) **102** is used against *Oidium*.



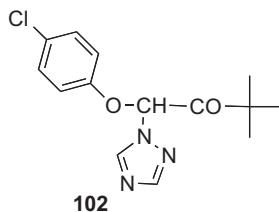
Vinclozolin
(allowed until 2004)



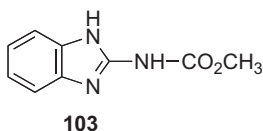
Iprodione
(resistance observed)



Procymidone
(allowed tolerance 5 ppm)



Triadimefon
(Bayleton®)



Carbendazim

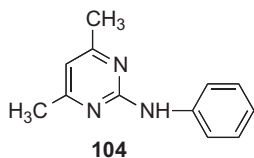
While the use of carbendazim **103** in vineyards could not find agreement by the European Union (EU), it can be used on corn and grain. Many pesticides applied before the harvest may concentrate in the grape skins or seeds, partly due to their oil solubility. Early on, agricultural authorities (BATF, EU) determined pesticide residues in wine in order to ensure consumer's safety. This has been performed by solid-phase extraction and capillary GC (03J AFC1148), rapid HPLC method (92J AFC817, 00J AFC967), or GC-MS. The limits of detection were less than 0.005mg/L (03J AFC1148) and 0.006–0.020ppm (92J AFC817, 00J AFC967).

Azole fungicides were determined (05JC(A)90, 05JC(A)113) with GC-mass selective detection, and 17 pesticides were found with quantitation limits of 2–10µg/L (00JC(A)205). For the fate of fungicide and insecticide residues in Australian wine grapes, cf. (09FC634). Azoxystrobin was found in several nanograms per milliliter (10JC(A)7484).

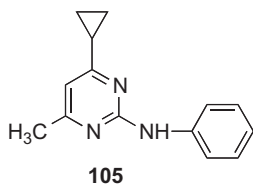
We want to emphasize that pesticide residues in food and wines are something to be concerned about. As a direct result of pesticide treatments carried out in viticulture there are three possible resulting impacts of their use:

- residues in grapes, must, and wines;
- influence on fermentation and organoleptic characteristics of wine; and
- health and hygienic quality and toxicological effects on the consumer (10MI421).

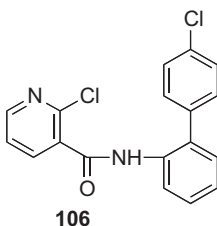
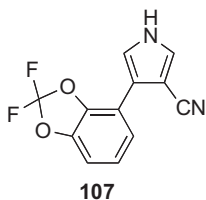
Due to the phenomenon of pesticide resistance, the search for novel fungicides and insecticides continues. While the standard pesticides pyrimethanil **104** and cyprodinil **105** are still in use against *Botrytis*, boscalid **106**, fludioxonil **107**, and azoxystrobin **108** are new principles for fighting pests:



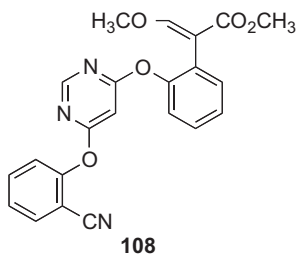
Pyrimethanil



Cyprodinil

Boscalid
(Nicobifen)

Fludioxonil

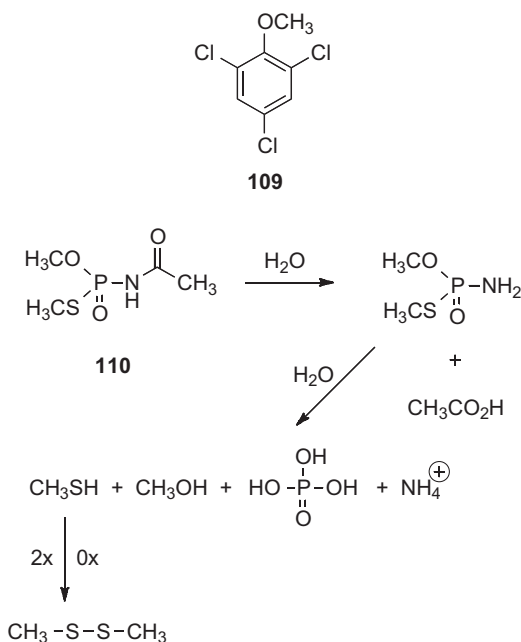


Azoxystrobin

Similar concerns involve the plasticizers in plastic wine corks, due to the presence of phthalates; however, any such concern seems to have been negated by the use of screw caps or glass stoppers. In any event, with these new closures one can avoid the unpredictable moldy off-flavor cork taint characterized by a set of undesirable smells and tastes, called “corked” or “corky,” that can arise in any wine with traditional corks, irrespective of price and quality level.

The chief cause of cork taint is the presence of 2,4,6-trichloroanisole (TCA) (and/or the tribromo analog) **109** (81MI97, 82JAF359, 81MI48, 86E873, 92MI273). Its generation is a biochemical masterpiece of *Streptomyces* microorganisms within the cork, transforming glucose in a multistep process (shikimic acid pathway) into the chlorinated benzene derivative (85MI55).

Finally, it should be mentioned the vintages 1982, 1983, and 1985 in most German wineries were nearly destroyed during bottle storing by using the insecticide Orthen® (Acephat) **110** (86MI872, 98MI87, 09MI596). Due to a slow hydrolysis of the phosphorus thioamide a cheese-like stink from the combination of methylmercaptan and dimethyl disulfide made these wines treated with Orthen® nasty and undrinkable.



10. CONCLUSION

As this brief excursion into the world of wine principles demonstrates, there are manifold heterocycles that have been detected, isolated, and characterized. Many of them play a decisive role for taste, flavor, smell, and color of wine; others play a significant beneficial role to the human health. Due to their antioxidant activity these latter components display cardioprotective abilities and are chemopreventive in antitumor and anticancer activities. Heterocycles are one class of compounds in a much

larger collection of constituents now numbering more than 1200 detected and identified compounds in wine. In some cases, heterocycles are responsible for off-flavors and off-odors, very often in minute quantities down to few nanograms per liter. This all was made possible by modern analytical techniques that allow the chemist to detect traces of compounds at ppb or ppt levels. Heterocycles are in fact ubiquitous in our environment, as predicted by the monograph of Katritzky et al.

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