OXAZOLES: SYNTHESIS, REACTIONS, AND SPECTROSCOPY

Part A

Edited by

David C. Palmer

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Raritan, New Jersey

AN INTERSCIENCE PUBLICATION

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SYNTHESIS, REACTIONS, AND SPECTROSCOPY, PART A

This is the sixtieth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR AND PETER WIPF, *Editors*

ARNOLD WEISSBERGER, *Founding Editor*

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To my wife, Vicki, with love

The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

The Chemistry of Heterocyclic Compounds has been published since 1950 under the initial editorship of Arnold Weissberger, and later, until his death in 1984, under the joint editorship of Arnold Weissberger and Edward C. Taylor. In 1997, Peter Wipf joined Prof. Taylor as editor. This series attempts to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has traditionally dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry, and biochemistry, and for this reason we initiated several years ago a parallel series entitled General Heterocyclic Chemistry, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal, and biochemically oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

The chemistry and synthetic applications of oxazoles were first covered in 1986 in an comprehensive volume edited by I. J. Turchi (Volume 45 of *The Chemistry of Heterocyclic Compounds* series). In the meantime, the number of synthetic strategies directed toward oxazole assembly as well as the use of these versatile heterocycles as intermediates, catalytic ligands, and pharmaceutical building blocks has vastly increased. We felt that a supplement and update of oxazole chemistry would be welcomed by the international chemistry community, and we are delighted that Dr. Palmer and his colleagues have accomplished this onerous mission. This volume represents another outstanding service to the organic and

heterocyclic chemistry literature that we are pleased to publish within *The Chemistry of Heterocyclic Compounds* series.

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PETER WIPF

Foreword

The subject of heterocyclic chemistry, prior to 1950, had been viewed as the domain of a small group of organic chemists. The perception prevailed that these individuals simply added ingredients together to make a witch's brew, heated it to 150°–250° C, and ultimately isolated a heterocyclic compound. This may be a somewhat exaggerated description of the subject but nevertheless makes the point that up to that time, it was assumed that one needed special training and knowledge to engage in this subject. However, in spite of this, a large number of molecularly distinct heterocyclic compounds were prepared and subsequently found to have highly important uses in medicine, polymers, dyes, and a number of other areas. As biology and biochemistry matured into a true science during the past 50 years, more and more biological phenomena were found to involve heterocyclic systems. This led to an increased appreciation of heterocycles, their chemical properties, and the reactions they undergo. As a result, these ring systems were subsequently regarded as more than a narrow field of chemistry. There is now little need to convince the informed scientific community of the incredible value of heterocyclic compounds.

As organic chemistry entered a new level of sophistication in the 1950s and understanding of chemical reactions was actively pursued, heterocyclic compounds were also included in this exploration and found to play a major role in many important chemical reactions, both as intermediates and as final products.

As this writer predicted in 1974 in a monograph entitled ''Heterocycles in Synthesis,'' these ring systems will not only be crucial to the scientific areas already mentioned above but will also find great importance in the synthesis of all types of organic compounds. In fact, in the current climate, heterocycles and their properties are so well accepted that they pervade all areas of medicine and biology, as well as chemistry.

The present updated volumes relating to oxazoles, oxazolines, and oxazolones are very timely works since these simple five-membered ring heterocycles have contributed much to the knowledge we have acquired in various fields of biological and chemical sciences. For example, we may envision oxazolones as tautomeric derivatives of the old and well-known azlactones, first reported in 1883. They may also be viewed as ''cyclized'' amino acid derivatives or their dehydro analogs and therefore would be expected as constituents of many biologically active natural products. In addition, these ring systems have shown their versatility in the synthesis of a variety of ligands for metal catalysts, as well as precursors or vehicles to reach many types of functionalized compounds. Furthermore, their chiral counterparts—oxazoles, oxazolines, and oxazolones containing a stereogenic center—have been major players in a very large number of asymmetric syntheses. Hardly a day passes that some journal does not describe the involvement of these chiral, non-racemic heterocycles for preparing an organic compound in very high

enantiomeric excess. Thus, oxazoles and their derivatives, whose synthesis, properties, and reactivity are described in the following two volumes, represent an immensely versatile family of heterocyclic compounds for future exploitation by both synthetic and medicinal chemists.

Fort Collins, Colorado
November, 2002

A. I. MEYERS

Preface

By far the most comprehensive review of the synthesis and reactions of mononuclear oxazoles and derivatives is *The Chemistry of Heterocyclic Compounds, Volume 45*, edited by I. J. Turchi and published in 1986. This work is the definitive reference for oxazole chemistry through 1983. Subsequently, literally tens of thousands of references appeared in the period 1983–2001 pertaining to this remarkable small ring heterocycle. Oxazoles and derivatives continue to be of great interest and importance in all aspects of synthetic chemistry with applications in medicinal and agricultural chemistry, material sciences, photographic dyes, peptide chemistry, asymmetric catalysis, and polymer chemistry. Indeed, more than 250 reviews focusing on specific aspects of the chemistry and biology of oxazoles, oxazolones, oxazolines, and chiral bis-oxazolines have been published from 1983 to 2001. The continuing interest in oxazoles together with the wealth of new information warrants a second review of this exciting area.

It would require a Herculean effort to prepare a complete discussion and review of every report related to the synthesis, reaction, or application of an oxazole while tabulating every oxazole, oxazolone, oxazoline, and chiral bis-oxazoline prepared and evaluated during the period of 1983–2001. Such an undertaking is beyond the scope of this review. Furthermore, the ease with which electronic databases, including the patent literature, can be searched, the data retrieved, and the information tabulated would render such a project somewhat redundant.

Rather, the intent of the current project is to provide the reader with a discussion and leading examples of significant advances made in the synthesis, reactions, and applications of mononuclear oxazoles, oxazolones, oxazolines, and chiral bis-oxazolines during this time frame. The material focuses on the more recent literature, although an update of the older synthetic literature is included wherever possible. In an effort to be selective, references to relevant reviews of material, not discussed in a chapter, are provided. Completely reduced oxazoles, i.e. oxazolidines as well as benzo-fused derivatives, are outside the scope of this review.

The coverage is similar to that of Volume 45, although the presentation has been changed and the scope has been expanded to include a chapter devoted to the exciting area of chiral bis-oxazolines. The material is presented in nine chapters and two volumes. In some cases, the organization of the individual chapter contents is different from that in Volume 45 to reflect the changing emphasis on newer methodologies and synthetic targets. For example, in Part A, Chapter One contains an expanded section that deals specifically with the synthesis of selected naturally occurring mono-, bis-, and tris-oxazoles to reflect the significant synthetic challenges therein. In addition, the discussion of cycloaddition and Diels-Alder reactions of oxazoles is introduced in Chapter One but is covered in detail in Chapter Three. In Part B, oxazolones are defined by the structure of the individual

regioisomer and discussed in Chapters Five, Six, and Seven, respectively. Chapter Eight describes the syntheses and reactions of oxazolines including asymmetric methodogy employing monooxazoline ligands. A new chapter, Chapter Nine, was added to include the recent developments in asymmetric synthesis utilizing chiral bis-oxazolines. Discussion of material from the patent literature has been included as an integral part of the volumes. Primary emphasis has been given to general syntheses and reactions. However, reactions that are more limited in scope and yet are singularly unique may also be described.

Tables are included in every chapter. Wherever possible, these contain a variety of selected examples to provide the reader with the scope and limitations of synthetic methods and reactions. However, in some cases a table will contain only the examples reported. No attempt has been made to provide an exhaustive compilation of every oxazole, oxazolone, or oxazoline prepared since 1983.

Part A is devoted specifically to the synthesis, reactions, and spectroscopic properties of oxazoles and encompasses four chapters: Chapter 1—Synthesis and Reactions of Oxazoles; Chapter 2—Spectroscopic Properties of Oxazoles; Chapter 3—Diels-Alder and Cycloaddition Reactions of Oxazoles; and Chapter 4—Synthesis and Reactions of Mesoionic Oxazoles.

Part B is comprised of the following five chapters: Chapter 5—Synthesis and Reactions of 2(3*H*)-Oxazolones and 2(5*H*)-Oxazolones; Chapter 6—Synthesis and Reactions of 4(5*H*)-Oxazolones; Chapter 7—Synthesis and Reactions of 5(2*H*)-Oxazolones and 5(4*H*)-Oxazolones; Chapter 8—Synthesis and Reactions of Oxazolines; and Chapter 9—Synthesis and Reactions of Chiral bis-Oxazolines.

Acknowledgments: I thank the authors for their individual contributions and patience through several iterations of the chapters. I am indebted to the library staff at Johnson & Johnson Pharmaceutical Research & Development who secured even the most obscure references in a timely manner. A very special acknowledgment and thanks are due to Dr. Fuqiang Liu for his critical insights, suggestions, comments, and review of individual chapters during preparation of these volumes. The series editors, particularly Professor Ted Taylor, offered many helpful suggestions and guidance. I thank Dr. Darla Henderson and Ms. Amy Romano at John Wiley & Sons for their constant encouragement and support. Special thanks are due to Ms. Shirley Thomas and her staff at John Wiley & Sons for their patience and understanding during preparation of these volumes. Finally, I am deeply thankful to my wife, Vicki, for her continual support, patience, and understanding during this entire project.

The reader may well encounter errors in a work of this magnitude, particularly in one with several thousand structures. I hope such errors will not detract from the overall intent of the volumes. Nonetheless, any errors are the responsibility of the editor.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. DAVID C. PALMER
Raritan, New Jersey

Contents - Part A

Abbreviations

2-MI	2-methylimidazole
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
Acm	acetamidomethyl
AHMHA	4-amino-3-hydroxy-6-methylheptanoic acid
AHPBA	3-amino-2-hydroxy-4-phenylbutyric acid
AIBN	2,2′-azobisisobutyronitrile
Alloc or AOC	allyloxycarbonyl
AMNT	aminomalononitrile *p*-toluenesulfonate
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BDMS	biphenyldimethylsilyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	[1,1′]binaphthalenyl-2,2′-diol
BINOL-box	3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc-Ox	2-oxo-3(2*H*)-oxazolecarboxylic acid *tert*-butyl ester
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
BOP-Cl	*N,N*-bis-(2-oxo-3-oxazolidinyl)phosphonic chloride
BPA	L-4-boronophenylalanine
BPO	dibenzoyl peroxide
Bt	benzotriazol-1-yl or 1-benzotriazolyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
Cbz-Ox	2-oxo-3(2*H*)-oxazolecarboxylic acid benzyl ester
CDI	1,1′-carbonyldiimidazole
CIP	2-chloro-1,3-dimethylimidazolium hexafluorophosphate
cod	cyclooctadiene
Cp	cyclopentadiene
CPTS	collidine *p*-toluenesulfonate
CSA	camphorsulfonic acid
CSI	chlorosulfonylisocyanate
DAST	diaminosulfur trifluoride
dba	dibenzylideneacetone
DBF-box	2,2′-(4,6-dibenzofurandiyl)bis[4,5-dihydro-4-phenyloxazole
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-dicyclohexylcarbodiimide

DCE	1,2-dichloroethane
DDQ	2,3-dichloro-4,5-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DECP or DEPC	diethylcyanophosphonate, diethylphosphoryl cyanide
Deoxo-fluor	bis(2-methoxyethyl)aminosulfur trifluoride
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAC	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMTO	dimethoxytrityl
DOPA	3,4-dihydroxyphenylalanine
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenylphosphino)butane
DPPC	diphenylphosphoryl chloride, diphenyl phosphochloridate
dppe	1,4-bis(diphenylphosphino)ethane
dppf	1,4-bis(diphenylphosphino)ferrocene
DPPOx	diphenyl-(2-oxo-3(2*H*)-oxazolyl)phosphonate
dppp	1,4-bis(diphenylphosphino)propane
EDCI or EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ETHP	2-ethyl-1,4,5,6-tetrahydropyrimidine
ETMG	2-ethyl-1,1,3,3-tetramethylguanidine
EVL	ethoxyvinyllithium
FMO	frontier molecular orbital
Fmoc	9-fluorenylmethoxycarbonyl
HATU	*O*-(7-Azobenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HBTU	*O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoric triamide
HMTA	hexamethylenetetraamine
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HydrOx	hydroxy-oxazoline
IBCF	isobutyl chloroformate
Im	Imidazole
KHMDS	potassium hexamethyldisilazane, potassium bis(trimethylsilyl)amide

L-(+)-DET	L-(+)-diethyl L-tartrate
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LDEA	lithium diethylamide
LiHMDS	lithium hexamethyldisilazane, lithium bis(trimethylsilyl)amide (LHMDS)
LTMP	lithium 2,2,6,6-tetramethylpiperidide
LUMO	lowest unoccupied molecular orbital
m-CPBA	*m*-chloroperoxybenzoic acid (MCPBA)
MeBmt	(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid
MEK	methyl ethyl ketone
MIBK	methyl isobutyl ketone
MOM	methoxymethyl
morphoCDI	*N*-cyclohexyl-*N*′-2-(*N*-methylmorpholinio)ethylcarbodiimide *p*-toluenesulfonate
Ms	methanesulfonyl (mesyl)
NaHMDS	sodium hexamethyldisilazane, sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMM	4-methylmorpholine (*N*-methylmorpholine)
NMO	4-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NOE	nuclear Overhauser effect
Nos	*p*-nitrobenzenesulfonyl (nosyl)
NPM	*N*-phenylmaleimide
PB	Probase
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PEG	poly(ethylene)glycol
PET	positron emission tomography
PhosOx	phosphine-oxazoline
Phth	Phthaloyl
Piv	Pivaloyl
PMB	*p*-methoxybenzyl
PPA	poly(phosphoric acid)
PPE	polyphosphate ester
PPL	porcine pancreatic lipase
PPTS	pyridinium *p*-toluenesulfonate
PyBOP	benzotriazol-1-yl-*N*-oxytris(pyrrolidino)phosphonium hexafluorophosphate
PyBroP	bromotris(pyrrolidino)phosphonium hexafluorophosphate
PyrOx	pyridine-oxazoline
RaNi	raney nickel

SelOx	selenide-oxazoline
SEM	2-(trimethylsilyl)ethoxymethyl
SES	2-(trimethylsilyl)ethanesulfonyl
SulfOx	sulfide-oxazoline
TADDOL	α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetra *n*-butylammonium fluoride
TBDMS or TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBTU	*O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
TCNE	tetracyanoethylene
TEAHC	tetraethylammonium hydrogen carbonate
TEAP	tetraethylammonium perchlorate
TECM	tandem Erlenmeyer condensation macrolactamization
TEMPO	2,2,6,6-tetramethyl-1-piperidinyl *N*-oxide
TEOF	triethyl orthoformate
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIA	*N,N,N′*-triisopropylacetamidine
TIG	1,2,3-triisopropylguanidine
TIPS	triisopropylsilyl
TMANO	trimethylamine *N*-oxide
TMEDA	*N,N,N′,N′*-tetramethyl-1,2-ethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Tol-BINAP	2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TosMIC	tosylmethyl isocyanide, [(*p*-toluenesulfonyl)methyl] isocyanide
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Troc	2,2,2-trichloroethoxycarbonyl
Ts or Tos	*p*-toluenesulfonyl (tosyl)

OXAZOLES:
SYNTHESIS, REACTIONS, AND SPECTROSCOPY, PART A

This is the sixtieth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

CHAPTER 1

Synthesis and Reactions of Oxazoles

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1.1. INTRODUCTION

Oxazoles continue to hold a center stage in organic synthesis, although the structure of the first oxazole was reported over a century ago. This is evidenced by the continued growth in the number of research publications and reviews.[1–18] The field of oxazoles is extensive and includes natural products, medicinal chemistry, and materials science. This chapter describes the major developments in this field from 1983 to 2001.

The chapter is divided into the following sections: ''Introduction,'' ''Synthesis of Oxazoles,'' ''Reactions of Oxazoles,'' and ''Oxazole Natural Products.'' The introduction is a brief discussion of the numbering and lists the major ^{1}H, ^{13}C, and ^{15}N resonances of a few selected examples. The reader should consult Chapter 2 for a complete discussion of the spectroscopic properties of oxazoles.

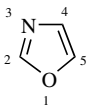
The second section describes the common methods of synthesis. It is important to note that no attempt has been made to describe every monocyclic oxazole synthesized or all synthetic methods. Rather, the most common and useful synthetic methods and some particularly novel methods have been included together with tables of some representative examples. The reader should consult the primary literature for further examples. In addition, this section and the reactions of oxazoles are not necessarily organized in the same manner as in the first volume edited by Turchi. This reflects the changing emphasis on new methods applicable to complex natural product synthesis.

The third section presents important reactions of oxazoles but again no attempt has been made to describe every reaction of an oxazole or every derivative prepared. Here, the aim is to convey the wealth of chemistry available by the selected examples.

The last section includes syntheses of some naturally occurring oxazoles. The choice of these natural products is arbitrary and selected from the recent literature to demonstrate the versatility of oxazoles in synthesis. For more complete discussions of oxazole natural products the reader is referred to specialized reviews.[19–22]

1.2. GENERAL PROPERTIES OF OXAZOLES

Oxazoles are numbered around the ring starting at the oxygen atom (Fig. 1.1) and are designated as 1,3-oxazoles to indicate the position of heteroatoms in the ring.



1

Figure 1.1. Oxazole.

The proton acidities of oxazoles have been theoretically calculated and determined experimentally. The reactivity of oxazoles indicates that the acidity of a hydrogen atom decreases in the order C(2) > C(5) > C(4). This is true in most cases; however, exceptions are well documented and depend on the substitution. The acidity of the hydrogen at C(2) was estimated to be $pK_a \sim 20$ while for oxazole itself the pK_b is reported to be $pK_b \sim 1$.[17,18]

Oxazoles exhibit characteristic resonances in both ^1H NMR and ^{13}C NMR spectra. The parent compound displays resonances (δ) between 7.00 and 8.00 in the ^1H NMR spectrum, and the presence of substituents can change the chemical shift by up to 1 ppm. The ^{13}C NMR of oxazole displays typical aromatic resonances (Fig. 1.2). The shielding or deshielding effect of C(2) substitution on the C(4) and C(5) resonances is typically < 2 ppm. The ^1H, ^{13}C, and ^{15}N chemical shifts of a few selected examples are shown in Figure 1.2.[23–26]

The IR spectrum of oxazole displays absorbances at 1537, 1498, 1326 (ring stretch), 1257 (C-H in plane deformation), 1143, 1080 (ring breathing), and 1045 cm^{-1}.[23–26] In the UV, the λ_{max} of oxazoles depend highly on the substitution pattern. In methanol, the parent ring system has an absorption maximum at $\lambda_{max} = 205$ nm.[17,18]

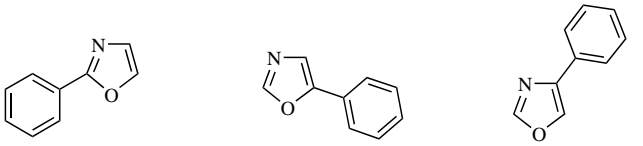
^{1}H NMR resonances of selected oxazoles (δ, ppm)

1 $H_2 = 7.95$, $H_4 = 7.09$, $H_5 = 7.69$

2 $H_4 = 6.94$, $H_5 = 7.49$

3 $H_2 = 7.70$, $H_5 = 7.32$

4 $H_2 = 7.75$, $H_4 = 6.77$

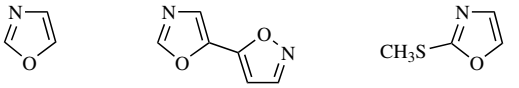


5 $H_4 = 7.26$, $H_5 = 7.71$

6 $H_2 = 7.87$, $H_4 = 7.33$

7 $H_2 = 7.95$, $H_5 = 7.95$

^{13}C NMR resonances of selected oxazoles (δ, ppm)

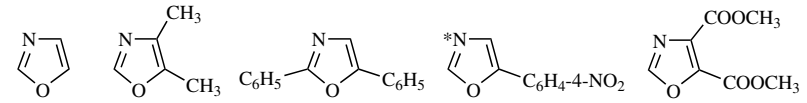


1 $C_2 = 150.6$, $C_4 = 125.4$, $C_5 = 138.1$

8 $C_2 = 151.5$, $C_4 = 126.0$, $C_5 = 141.1$

9 $C_2 = 161.1$, $C_4 = 128.1$, $C_5 = 139.8$

^{15}N NMR resonances of selected oxazoles (δ, ppm, d_6–DMSO)



1 N = −123.7

10 N = −121.9

11 N = −122

12 N* = −117.7

13 N = −119.2

Figure 1.2. ^{1}H, ^{13}C, and ^{15}N NMR resonances of selected oxazoles.

1.3. SYNTHESIS OF OXAZOLES

1.3.1. Oxidation of Oxazolines

The structural diversity and complexity of naturally occurring oxazoles (see Section 1.5) has fueled a continuing search for mild, efficient methods of oxazole

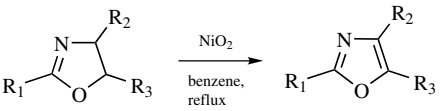
ring construction. One method that has become particularly useful in this context is the oxidation of oxazolines.

The dehydration of β-hydroxyamides is the most widely used method for the synthesis of oxazolines, and the various reagents used for this conversion will not be discussed further in this section. Instead, the reader should consult Chapter 8 and Chapter 9 in Part B for the synthesis and reactions of oxazolines and chiral bis-oxazolines for detailed discussions and leading examples.

A variety of reagents have been evaluated in the search for the direct oxidation of oxazolines to oxazoles. Even though a number of reagents efficiently oxidize activated oxazolines (i.e., oxazolines containing an electron-withdrawing group at the 4 or 5 position), a general, high-yielding method to effect oxidation of unactivated oxazolines has not been described.

1.3.1.1. Nickel Peroxide

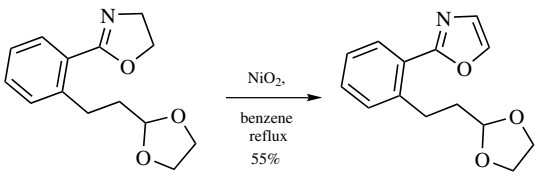
Although new methods have been developed recently for the oxidation of oxazolines, oxidation with NiO_2 is one of the oldest and still widely used methods. It was originally reported by Meyers and Evans (Scheme 1.1).[27]



14 **15**

Scheme 1.1

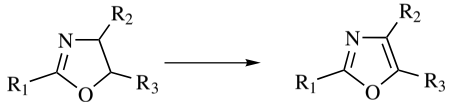
Nickel peroxide[28] is an efficient reagent for the oxidation of activated oxazolines that contain an electron-withdrawing group (R_2 or $R_3 = COOC_2H_5$ or other electron-withdrawing groups), but it is less useful for the oxidation of unactivated oxazolines (R_2 or R_3 = alkyl, H). The heterogeneous reaction is conducted by refluxing an excess of NiO_2 in benzene, and a radical reaction mechanism has been proposed. The application of NiO_2 in the synthesis of eupolauramine[29] is a noteworthy example in which one of the key steps involves the oxidation of the unactivated oxazoline **16** to the 2-aryloxazole **17** in 55% yield (Scheme 1.2).



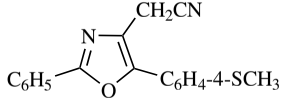
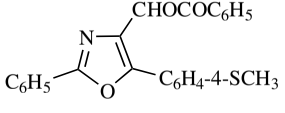
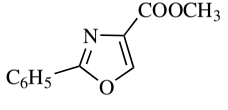
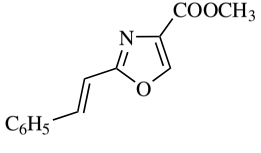
16 **17**

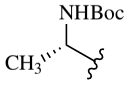
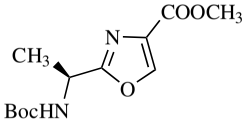
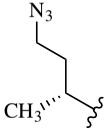
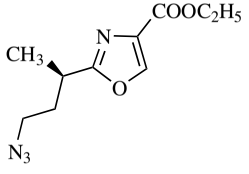
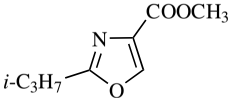
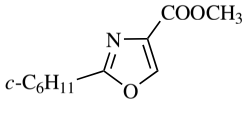
Scheme 1.2

TABLE 1.1. 2,4-DISUBSTITUTED- AND 2,4,5-TRISUBSTITUTED OXAZOLES VIA OXIDATION OF OXAZOLINES



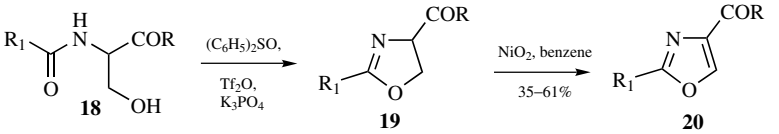
14 **15** **Figure 1.3**

Entry	R_3	R_2	R_1	Product	Yield[a] (%)	References
1	4-CH_3S-C_6H_4	CH_2CN	C_6H_5		54 (A)	34
2	4-CH_3S-C_6H_4	$CH_2OCOC_6H_5$	C_6H_5		40 (A)	34
3	H	$COOCH_3$	C_6H_5		55 (B)	32, 33
4	H	$COOCH_3$	$C_6H_5CH{=}CH$		61 (B)	32, 33

5	H	$COOCH_3$			51 (C)	35, 36
6	H	$COOC_2H_5$			56 (C)	35, 36
7	H	$COOCH_3$	i-C_3H_7		1/76[b] (D)	35, 36
8	H	$COOCH_3$	c-C_6H_{11}		1/66[b] (D)	35, 36

[a] *A*, $CuBr_2/LiBr/CaCO_3$; *B*, nickel peroxide; *C*, $CuBr/Cu(OAc)_2/C_6H_5C(O)OOtBu$; *D*, *N*-Bromosuccinimide.
[b] Ratio refers to the ratio of **65:66** (see Scheme 1.20).

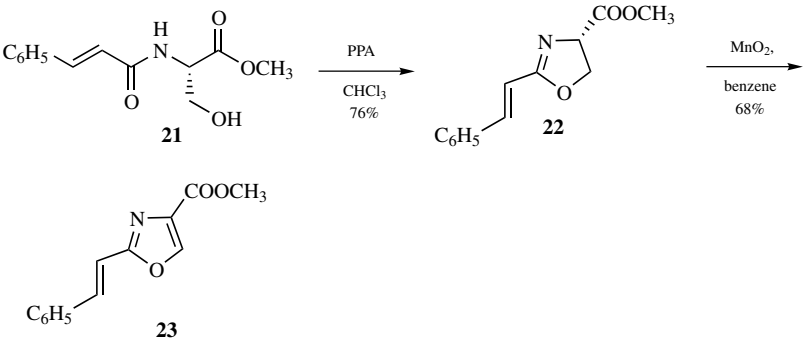
Pattenden and co-workers[30,31] successfully used nickel peroxide oxidation in the synthesis of the naturally occurring oxazole thiangazole (described in Section 1.5.2). Shioiri's group [32,33] developed a versatile method for the cyclodehydration of β-hydroxyamides that, in combination with NiO_2 oxidation, results in a general synthesis of 2-alkyl(aryl)-4-oxazolecarboxylic acid esters **20** (Scheme 1.3). For example, reaction of **18** ($R = OCH_3$) with diphenylsulfoxonium triflate, generated in situ, yields oxazolines **19** ($R = OCH_3$), which are converted to 2-aryl-4-oxazolecarboxylic acid esters **20** ($R = OCH_3$) using NiO_2. Representative examples of this methodology are shown in Table 1.1, entries 3 and 4.



Scheme 1.3

1.3.1.2. Manganese Dioxide

Activated manganese dioxide is a closely related oxidant to NiO_2 but less commonly used. Meguro, Fujita, and co-workers[37] described oxidation of oxazolines using MnO_2 in their synthesis of antidiabetic agents. For example, the serine-derived β-hydroxyamide **21** was cyclized to the oxazoline **22** with polyphosphoric acid. Oxidation of **22** with activated manganese dioxide afforded 2-styryl-4-oxazolecarboxylic acid methyl ester, **23** (Scheme 1.4).



Scheme 1.4

Oxidation of oxazolines using MnO_2 was also employed in the synthesis of a berninamycin A fragment by Shin and co-workers[38–40] and in the preparation of the naturally occurring 2,4-disubstituted oxazole, phenoxan **28**, by Yamamura's group[41] (Scheme 1.5). For berninamycin, the oxazoline **25** was synthesized in 61% yield by Mitsunobu[42] dehydration of the serine-derived amide **24**.